COMPREHENSIVE ORGANIC SYNTHESIS

Selectivity, Strategy & Efficiency in Modern Organic Chemistry

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Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

Techniques

CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
CT	charge transfer
GLC	gas–liquid chromatography
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORD	optical rotatory dispersion
PE	photoelectron
SCF	self-consistent field
TLC	thin layer chromatography
UV	ultraviolet

***Reagents, solvents,* etc.**

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BHT	2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene)
bipy	2,2′-bipyridyl
Bn	benzyl
t-BOC	*t*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl
CAN	ceric ammonium nitrate
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or –)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or –)
DMA	dimethylacetamide
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	*N,N'*-dimethylimidazolone
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
E^+	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EWG	electron-withdrawing group
HMPA	hexamethylphosphoric triamide
HOBT	hydroxybenzotriazole
$IpcBH_2$	isopinocampheylborane
Ipc_2BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri-*s*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LITMP	lithium tetramethylpiperidide
L-selectride	lithium tri-*s*-butylborohydride
LTA	lead tetraacetate
MCPBA	*m*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MEM-Cl	β-methoxyethoxymethyl chloride
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl
Ms	methanesulfonyl
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
Nu^-	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SEM	β-trimethylsilylethoxymethyl
Sia_2BH	disiamylborane
TAS	tris(diethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDMS-Cl	*t*-butyldimethylsilyl chloride
TBHP	*t*-butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBS-Cl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPS-Cl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMS-Cl	trimethylsilyl chloride
TMS-CN	trimethylsilyl cyanide
Tol	tolyl
TosMIC	tosylmethyl isocyanide
TPP	*meso*-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTFA	thallium trifluoroacetate
TTN	thallium(III) nitrate

1.1
Ene Reactions with Alkenes as Enophiles

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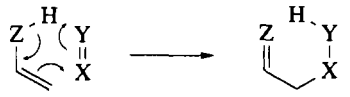
1.1.1 INTRODUCTION

The thermal reaction of an alkene having an allylic hydrogen (an 'ene') with a compound containing a double or triple bond (enophile) to form a new bond with migration of the ene double bond and 1,5-hydrogen shift is referred to as the ene reaction (equation 1). The ene reaction is mechanistically related to the much better known Diels–Alder reaction since both reactions can be concerted, proceeding through cyclic transition states involving six electrons.[1–5] Stepwise ene reactions proceeding through either a diradical or zwitterionic intermediate are also known. Ene reactions proceed most readily when the enophile, like the dienophile in a Diels–Alder reaction, is electron deficient. Similarly, the ene, like the diene in the Diels–Alder reaction, should be electron rich. Although the exact order depends upon the enophile and reaction conditions, the relative reactivity of alkenes as ene components has typically been found to be 1,1-di- > tri- > tetra- >> mono- > 1,2-disubstituted. Unfortunately, ene reactions typically occur at higher temperatures than related Diels–Alder reactions, limiting the synthetic utility of the ene reaction.

As in the Diels–Alder reaction, Lewis acid catalysis dramatically increases the rates of some ene reactions. Complexation of a Lewis acid to an α,β-unsaturated ketone, aldehyde or ester makes the double

bond more electron deficient, thereby accelerating the ene reaction and making these reactions more synthetically useful.[6,7] Recent investigations suggest that at least some of these Lewis acid catalyzed ene reactions are stepwise rather than concerted but that the intermediate bears more resemblance to a π-complex than to an open zwitterionic intermediate.[8–11]



(1)

Coverage in this chapter is restricted to the use of alkenes or alkynes as enophiles (equation 1; X = Y = C) and to the use of ene components in which a hydrogen is transferred. Coverage in Sections 1.2 and 1.3 is restricted to ene components in which all three heavy atoms are carbon (equation 1; Z = C). Thermal intramolecular ene reactions of enols (equation 1; Z = O) with unactivated alkenes are presented in Section 1.4. Metallo-ene reactions are covered in the following chapter. Use of carbonyl compounds as enophiles, which can be considered as a subset of the Prins reaction, is covered in depth in Volume 2, Chapter 2.1. Addition of enophiles to vinylsilanes and allylsilanes is covered in Volume 2, Chapter 2.2, while addition of enophiles to enol ethers is covered in Volume 2, Chapters 2.3–2.5. Addition of imines and iminium compounds to alkenes is presented in Volume 2, Part 4. Use of alkenes, aldehydes and acetals as initiators for polyene cyclizations is covered in Volume 3, Chapter 1.9. Coverage of singlet oxygen, azo, nitroso, S=N, S=O, Se=N or Se=O enophiles are excluded since these reactions do not result in the formation of a carbon–carbon bond.

Intermolecular reactions will be presented first, followed by intramolecular reactions. Coverage will be organized by the nature of the enophile, The emphasis will be on material published since the field has been reviewed,[1–7,19,141] and on examples demonstrating the stereo-, regio- and chemo-selectivity of these reactions.

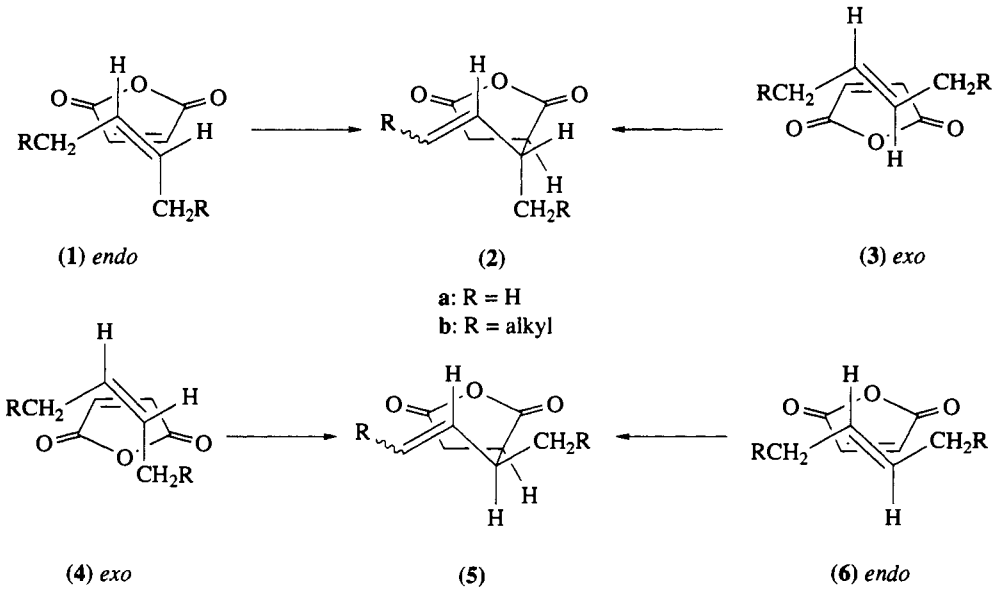
1.1.2 INTERMOLECULAR REACTIONS

1.1.2.1 Electron Deficient Alkenes as Enophiles

1.1.2.1.1 Thermal reactions

Alkenes are relatively unreactive as enophiles in thermal ene reactions.[1] Maleic anhydride is the most generally used enophile of this class. Arnold and Showell showed that β-pinene reacts at 140 °C with maleic anhydride, dimethyl maleate, dimethyl fumarate and methylenemalonic esters to form mixtures of ene adducts.[12] Berson and coworkers found that maleic anhydride reacts with *cis*-2-butene to give an 85:15 mixture of (**2a**) and (**5a**).[13] The major product (**2a**) is formed from *endo* transition state (**1a**) with the carbonyl groups toward the ene component. The minor product (**5a**) is formed from *exo* transition state (**4a**) with the carbonyl groups away from the ene component. Similar results are obtained with cyclopentene. On the other hand, *trans*-2-butene reacts with maleic anhydride to give a 57:43 mixture of (**5a**), formed from *endo* transition state (**6a**), and (**2a**) formed from *exo* transition state (**3a**). Hill and Rabinowitz demonstrated that ene reaction of an optically active ene component with maleic anhydride leads to optically active products, suggesting that the reaction is concerted.[14] Friedrich *et al.* established that the ene reaction of deuterated 2,3,3-trimethyl-1-butene with maleic anhydride proceeds through *cis* addition of the 'ene' component and deuterium to the maleic anhydride double bond.[15] Hill and coworkers found that a hydrogen is abstracted exclusively from the face opposite the *gem*-dimethyl bridge and that a 3:1 mixture of *endo* and *exo* isomers is formed in the thermal ene reaction of β-pinene with maleic anhydride.[16] The effect of substituents on maleic anhydride on the scope of the ene reaction has been examined,[17] and competing free-radical pathways have been proposed for ene reactions of maleic anhydrides with monounsaturated fatty acids.[18] As part of a comprehensive study of ene and retro-ene reactions of organosilanes and organogermanes, Dubac and Laporterie found that maleic anhydride undergoes thermal ene reactions with allyltrimethyl-silane or -germane at 200 °C to give vinyl-silanes or -germanes.[19]

Dwyer *et al.* have determined rates of reactions and energy and entropy of activation for the ene reactions of maleic anhydride with a series of terminal alkenes and *cis*- and *trans*-5-decene.[20] Nahm and



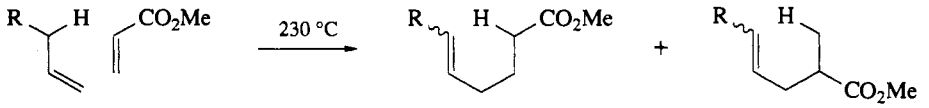
(1) *endo* (2) (3) *exo*

a: R = H
b: R = alkyl

(4) *exo* (5) (6) *endo*

Cheng have used ^{13}C NMR to determine the regioselectivity, *endo*/*exo* selectivity and *cis*/*trans* selectivity of the thermal ene reaction (200 °C, 16 h) of maleic anhydride with all nine decenes.[21] Their results, which are consistent with those of Berson described above,[13] can be summarized as follows: (1) maleic anhydride adds preferentially, but with only modest selectivity, to the less-hindered end of the double bond; (2) starting from a *cis*-alkene there is a > 6:1 preference for the *endo* transition state (**1b**) leading to the *threo* isomer (**2b**) with a *trans* double bond exclusively; (3) starting from a *trans*-alkene there is only a ~1.5:1 preference for the *endo* transition state (**6b**) leading to the *eyrthro* isomer (**5b**) as a 4.2:1 mixture of *trans* and *cis* isomers. Despite its reactivity, tetracyanoethylene has only rarely been used as an enophile.[22]

Alkenes containing only a single electron-withdrawing group have seen little use as enophiles in thermal reactions. A DuPont group demonstrated that thermal ene reactions occur between enophiles such as methyl vinyl ketone, methyl acrylate, methyl methacrylate and acrylonitrile and simple alkenes on heating at 200–300 °C for 0.15–9 h.[23] Reaction of methyl acrylate with isobutene gives the ene adduct in 46% yield, while reaction of methyl acrylate with 1-butene affords the ene adduct in only 8.5% yield. Under some conditions the initially formed ene adduct reacts as the ene component with a second molecule of enophile to give a 2:1 adduct. Alder and von Brachel found that reaction of excess propene with methyl acrylate at 230 °C for 40–50 h gives a 7:1 mixture of regioisomeric ene adducts (**7a**) and (**8a**) in 30% yield.[24] Similar reaction with 1-heptene provides a 3:1 mixture of ene adducts (**7b**) and (**8b**) in 35% yield. Monoactivated enophiles not only are relatively unreactive but give mixtures of regioisomers in thermal ene reactions.

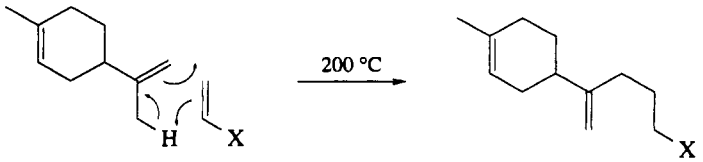


a: R = H
b: R = n-C_4H_9
c: R = n-C_3H_7
d: R = n-C_5H_{11}

(7) (8)

More recently, Wolinsky has shown that acryloyl chloride reacts with β-pinene at only 70 °C for 2 d to give ene adduct (**9a**) in 84% yield.[25] These atypically mild conditions for a thermal ene reaction result from the powerfully electron-withdrawing chlorocarbonyl group making acryloyl chloride a reactive enophile and the strained electron-rich exomethylene double bond making β-pinene the most reactive readily available ene component. β-Pinene reacts with acrolein on heating at 140 °C to give ene adduct (**9b**) in 30% yield.[26] Nitroethylene polymerizes very readily but does undergo an ene reaction with β-pinene in low yield on heating at reflux in benzene for 16 h.[27] Mehta and Reddy report that limonene reacts with acrylonitrile and methyl acrylate at 200 °C for 12–24 h to give the ene adducts (**10a**) and (**10b**) in 25 and 45% yield, respectively.[28] Vinyltrichlorosilane reacts as an enophile with terminal alkenes and cycloalkenes at 250 °C for 48 h to give ene adducts in 60% yield.[19]

(**9a**) X = Cl
(**9b**) X = H

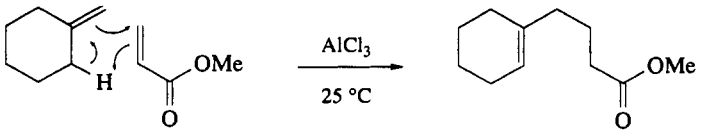


(**10a**) X = CN
(**10b**) X = CO_2Me

1.1.2.1.2 Lewis acid catalyzed reactions

(i) Acrylate esters

Inukai[29] and Snider[30] first demonstrated that Lewis acids could be used to catalyze ene reactions of non-aldehyde enophiles. Inukai reported that reaction of 1-hexene, methyl acrylate and $AlCl_3$ for 3.5 h at 150 °C gives ene adduct (**7c**) in 39% yield.[29] Snider found that reaction of methylenecyclohexane than methyl acrylate in benzene in the presence of 0.1 equiv. of $AlCl_3$ for 48 h at 25 °C gives ene adduct (**11**) in 70% yield.[30] Ene adducts could be obtained from the $AlCl_3$ catalyzed reaction of methyl acrylate and reactive 1,1-disubstituted alkenes, although 2:1 adducts were also formed in some cases. Two groups[31,32] reexamined these Lewis acid catalyzed ene reactions in response to Sands' erroneous report that alkenes and methyl acrylate undergo Lewis acid catalyzed [2 + 2] cycloadditions.[33] Beckwith found that $AlCl_3$ catalyzed reaction of isobutene or 2,3-dimethyl-2-butene with methyl acrylate in benzene gives only the expected ene adducts.[32] In dichloroethane–nitromethane the initial products undergo isomerization or rearrangement. Greuter and Bellus obtained ene adducts from $AlCl_3$ catalyzed reaction of methyl acrylate with isobutene, 2-methyl-2-butene or 2,3-dimethyl-2-butene in dichloroethane–nitromethane with careful control of reaction conditions to prevent isomerization of the double bond in the initially formed products.[31] Åkermark and Ljungqvist found that ene reaction of 1-octene with methyl acrylate could be catalyzed by a $AlCl_3$/NaCl/KCl eutectic at 100 °C for 16 h to give the expected ene adduct (**7d**) in 40% yield as an 86:14 (*E*):(*Z*) mixture.[34]



(**11**)

Lewis acid catalyzed ene reactions of methyl acrylate with alkenes are regiospecific, giving only adduct (**7**), in marked contrast to the thermal reactions which give mixtures of adducts (**7**) and (**8**). Complexation of a Lewis acid to the acrylate ester makes the double bond electron deficient and polarizes it so that reaction with the alkene occurs only at the more electron deficient β-carbon of methyl acrylate.

More highly functionalized products can be obtained, often in better yield, by the ene reaction of α-substituted acrylate esters.[35–37] $EtAlCl_2$ is a more effective catalyst than $AlCl_3$ for these reactions because it is a Brønsted base as well as a Lewis acid.[7] The $EtAlCl_2$ catalyzed reactions of methyl α-bromo- and α-chloro-acrylate with *trans*-1,2-disubstituted and trisubstituted alkenes are both regio- and stereo-specific.[35,36] The major product (**13a**; 85–95%) is formed *via* transition state (**12a**) in which the methoxycarbonyl group is *endo*.[35,36] The stereochemistry of the major adduct was established by the stereospecific conversion of (**13a**) to both diastereomers of (±)-2-amino-4-methyl-5-hexenoic acid[38] and confirmed by X-ray crystallographic analysis in a related system.[39]

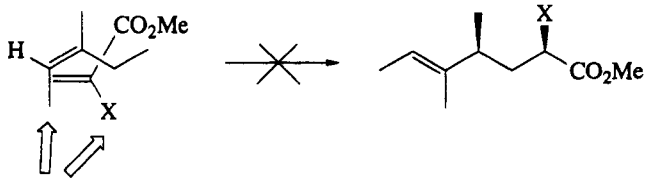
(12a) R = H
(12b) R = Et

X = Br, Cl

(13a) R = H
(13b) R = Et

The selective formation of the ene adduct with the methoxycarbonyl group *endo* is analogous to the *endo* selectivity usually observed in the Diels–Alder reaction, probably for similar electronic reasons. With 1,2-disubstituted and trisubstituted alkenes the *endo* selectivity of this ene reaction controls the relative stereochemistry of two centers in a 1,3-relationship. Since attempted thermal ene reactions of methyl α-haloacrylates give only polymer, the effect of the Lewis acid on the stereochemistry cannot be determined.

The ene reactions of α-haloacrylate esters with trisubstituted alkenes are also regiospecific. Transfer of a hydrogen occurs predominantly (90–100%) from the alkyl group *syn* to the vinylic hydrogen to give (**13b**). This appears to be due to steric interaction of the *exo* substituent on the acrylate with the substituent on the less-substituted end of the ene component, which is minimized if the substituent is hydrogen (**12b**) rather than carbon (**14**). This steric interaction is responsible for the failure of this ene reaction with *cis*-1,2-di- and tetra-substituted alkenes. This regioselectivity is general, although there is also a competing preference for the formation of the more stable, more highly substituted double bond.[35,36]



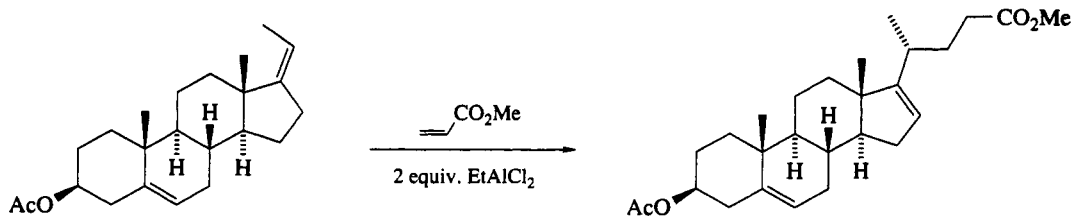
(14) **(15)**

Similar results are obtained with methyl methacrylate, methyl α-acetamidoacrylate, methyl α-bromomethylacrylate and dimethyl itaconate.[36] Those acrylates with electron-withdrawing α-substituents such as chloro or bromo are somewhat more reactive than methyl acrylate, while those with electron-releasing α-substituents such as methyl are less reactive with methyl acrylate. In an attempt to extend the scope of the ene reaction, acrylates containing a strongly electron-withdrawing α-substituent were examined. Trimethyl α-phosphonoacrylate undergoes $EtAlCl_2$ catalyzed ene reactions in high yield at 0 °C with most classes of alkenes.[40] The adducts are useful reagents for the phosphonate modification of the Wittig reaction. On the other hand, methyl α-cyanoacrylate undergoes Me_2AlCl catalyzed reactions to give a zwitterion which reacts further to give a complex mixture of ene adducts, cyclobutanes, dihydropyrans and 2:1 adducts.[41]

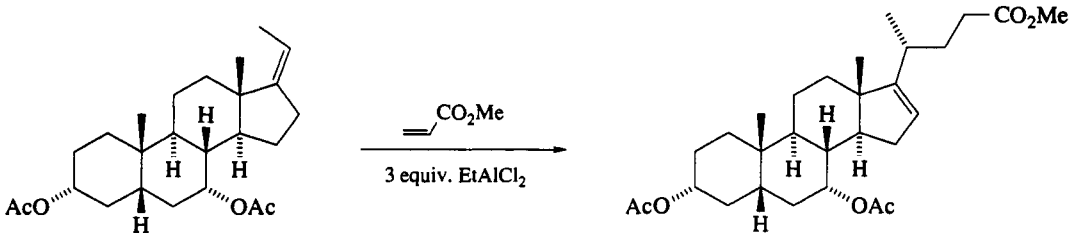
A particularly elegant application of these ene reactions is the elaboration of functionalized steroid side chains with the natural stereochemistry at C-20 from (*Z*)-$\Delta^{17(20)}$-pregnenes (**16**) and (**18**) by Uskokovic and coworkers.[39,42] $EtAlCl_2$ catalyzed ene reaction of (**16**) with methyl acrylate occurs selectively from the α face to give 25-hydroxycholesterol precursor (**17**) with the natural stereochemistry at C-20.[39] An additional equivalent of $EtAlCl_2$ must be used to complex any basic functional groups, *e.g.* acetate, on the steroid nucleus. For instance, reaction of (**18**) with methyl acrylate and 3 equiv. of $EtAlCl_2$ in CH_2Cl_2 for 3 d at 25 °C gives chenodeoxycholic acid precursor (**19**) in 72% yield.[42] Lewis acid catalyzed ene reactions of methyl propiolate can also be used to introduced functionalized steroid side chains.[43,44] Reaction of methyl propiolate with (*E*)-$\Delta^{17(20)}$-pregnenes gives an ene adduct with the unnatural stereochemistry at C-20.[45]

(ii) α,β-Unsaturated ketones and aldehydes

$ZnCl_2$ catalyzed ene reaction of methyl vinyl ketone and acrolein with β-pinene in ether at 25 °C gives the expected ene adducts in 62% and 32% yields, respectively.[30] Methyl vinyl ketone is reported to undergo $AlCl_3$ catalyzed ene reactions with limonene, carvone and perillaldehyde.[28] Although Lewis acid catalyzed ene reactions of acrolein and methyl vinyl ketone with alkenes are probably general, the initial products often cannot be isolated since the unsaturated carbonyl compound undergoes an intramolecular Lewis acid catalyzed type II ene reaction.[46,47]

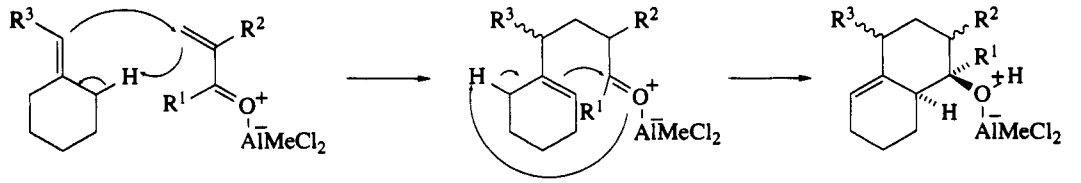


(16) (17)



(18) (19)

Reaction of alkylidenecyclohexanes with acrolein derivatives and Me_2AlCl generates unsaturated aldehydes (**20**; R^1 = H) which cannot be isolated but undergo type II intramolecular ene reactions to give (**21**; R^1 = H).[46] Reaction of alkylidenecyclohexanes with methyl vinyl ketone derivatives gives (**20**; R^1 = Me) which can be isolated if the reaction is carried out at –20 °C but cyclize at 25 °C to give (**21**; R^1 = Me).[46,47] Similar results have been obtained with alkylidenecyclopentanes[46] and 2- and 3-substituted methylenecycloalkanes.[47] 24-Oxocholesteryl acetate has been synthesized from (*Z*)-5,17(20)-pregnadienyl-3β-acetate by reaction with isopropyl vinyl ketone and 2 equiv. of Me_2AlCl at 25 °C to give the ene adduct in 46% yield followed by hydrogenation of the C(16)—C(17) double bond over Pt/C.[46] In this case a type II intramolecular ene reaction is precluded by the absence of allylic ring hydrogens.



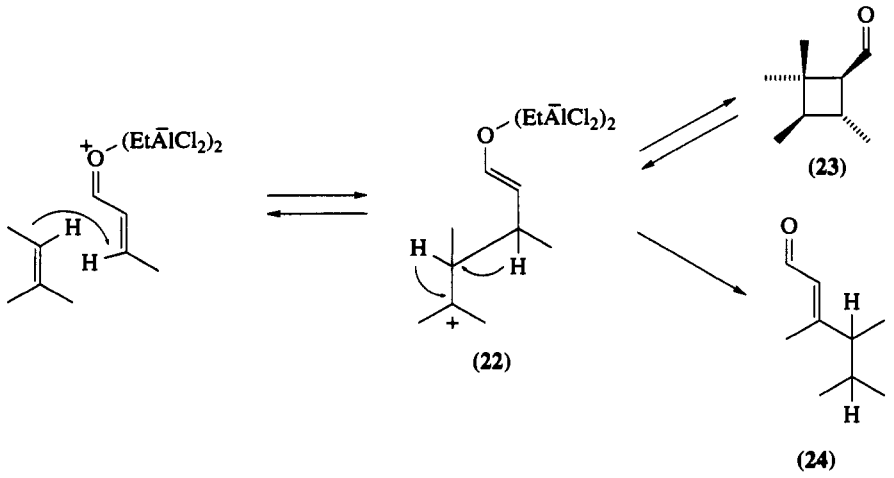
(20) (21)

Lewis acid complexes of β-substituted α,β-unsaturated ketones and aldehydes are unreactive toward alkenes. Crotonaldehyde and 3-penten-2-one cannot be induced to undergo ene reactions like acrolein and methyl vinyl ketone. The presence of a substituent on the β-carbon stabilizes the enal– or enone–Lewis acid complex and sterically retards the approach of an alkene to the β-carbon. However, Snider *et al.* have found that a complex of these ketones and aldehydes with 2 equiv. of $EtAlCl_2$ reacts reversibly with alkenes to give a zwitterion (**22**).[48] This zwitterion, which is formed in the absence of a nucleophile, reacts reversibly to give a cyclobutane (**23**) or undergoes two 1,2-hydride or alkyl shifts to generate irreversibly a β,β-disubstituted-α,β-unsaturated carbon compound (**24**).

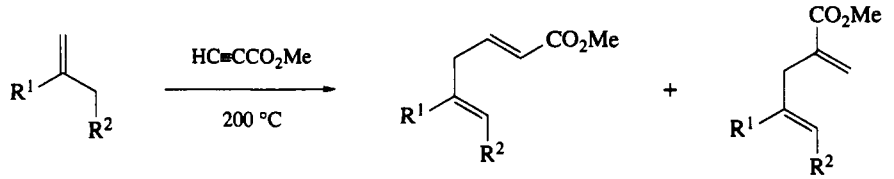
1.1.2.2 Electron Deficient Alkynes as Enophiles

1.1.2.2.1 Thermal reactions

Acetylenedicarboxylic ester, propiolic esters and dicyanoacetylene react with unactivated ene components below 200 °C.[1,24] Isobutene undergoes ene reactions with dimethyl acetylenedicarboxylate



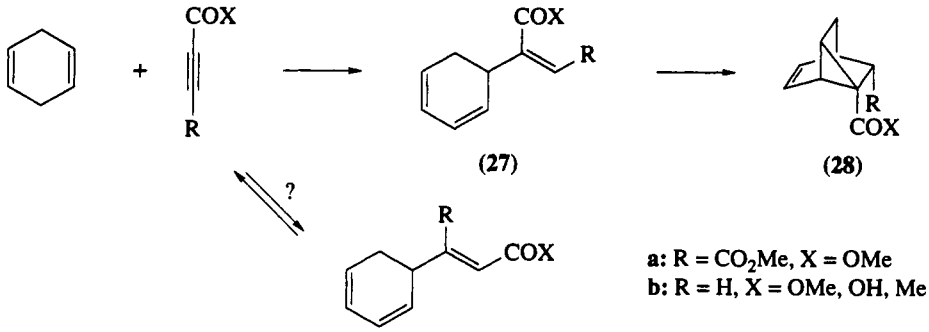
(DMAD), methyl propiolate or 1,1,1-trifluoropropyne or hexafluoro-2-butyne at 145–250 °C.[49] Ene reactions with DMAD give only one product, while reactions with methyl propiolate give mixtures of regioisomers.[24] Reaction of methyl propiolate with 1-heptene for 30 h at 200 °C gives a 4:1 mixture of (**25a**) and (**26a**) in 30% yield. Similar reaction with isobutene gives a 94:6 mixture of (**25b**) and (**26b**) in 50% yield.[24] Reaction of limonene with methyl propiolate for 24 h at 160 °C gives the ene adduct in 70–80% yield.[28]



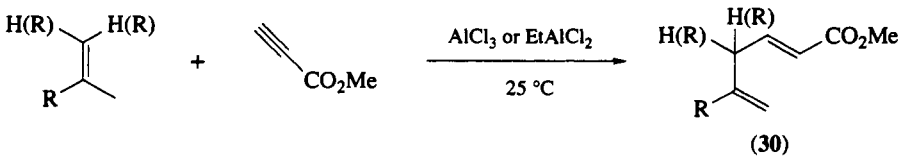
Alder and Bong discovered a tandem ene/intramolecular Diels–Alder reaction in which 1,4-cyclohexadiene reacts with DMAD at 185 °C to give ene adduct (**27a**), which reacts further to give intramolecular Diels–Alder adduct (**28a**).[50,51] Recent studies by Giguere optimized the conditions for this reaction and extended it to monoactivated alkynes.[51] 1,4-Cyclohexadiene reacts with methyl propiolate, propiolic acid or 3-butyn-2-one at 350 °C (or at 220 °C in the presence of $ZnCl_2$) to give (**28b**) in 30–70% yield. The formation of (**28b**) indicates that ene adduct (**27b**), rather than the expected ene adduct (**29b**), is formed. This surprising result may be due to the formation of both ene adducts and competing retro-ene and Diels–Alder reactions. Alternatively, the selective formation of (**27b**) may result from a change in mechanism of the ene reaction. The second double bond of a diene does not lower the activation energy in a 'normal' concerted ene reaction, leading to (**29b**) in which carbon–carbon bond formation is more advanced than hydrogen transfer in the transition state. The second double bond of the diene will lower the activation energy for an 'abnormal' ene reaction in which hydrogen transfer is more advanced than carbon–carbon bond formation in the transition state. Adduct (**27b**) is the expected product of such an 'abnormal' ene reaction. Similar factors may be responsible for the selective formation of the unexpected regioisomer in the ene reaction of acrylonitrile with ergosteryl acetate.[52]

1.1.2.2.2 Lewis acid catalyzed reactions

Snider demonstrated that $AlCl_3$ catalyzed reactions of methyl propiolate with a wide variety of alkenes give good yields of 1:1 adducts.[53–55] 1,1-Disubstituted, trisubstituted and tetrasubstituted alkenes give exclusively ene adducts (**30**) (equation 2). 1,2-Diubstituted alkenes give exclusively cyclobutenes formed by stereospecific [2 + 2] cycloaddition (equation 3). Monosubstituted alkenes give mixtures of ene adducts and cyclobutenes. $EtAlCl_2$ in CH_2Cl_2 was found to be a more effective catalyst for this reaction since it can act as a proton scavenger as well as a Lewis acid.[54] Optimal yields are usually obtained with



close to 1 equiv. of catalyst since the product α,β-unsaturated ester is more basic than methyl propiolate and complexes preferentially to the Lewis acid. Functionalized alkenes containing nonbasic functional groups are suitable substrates. Alkenes containing more basic functional groups are suitable substrates if an additional equivalent of Lewis acid is used for every basic site.[54] Similar results are obtained in $ZnCl_2$ catalyzed reactions of 3-butyn-2-one,[56] and $EtAlCl_2$ catalyzed reactions of ethynyl *p*-tolyl sulfone[57] with alkenes.



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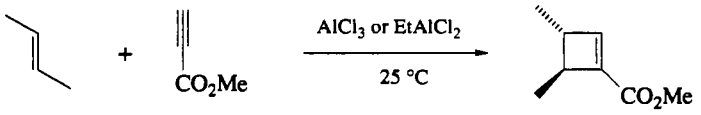
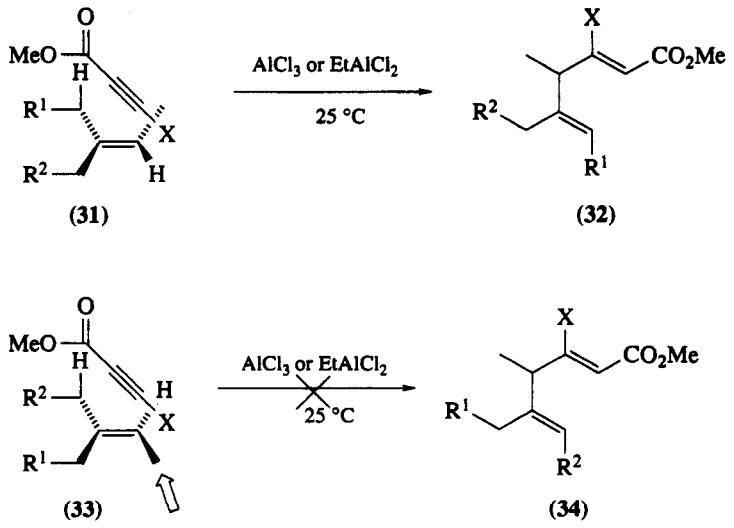


(3)

Lewis acid catalyzed ene reactions with methyl propiolate have been used for the construction of steroid side chains,[43–45] and for the synthesis of the A1 component of the female sex pheromone of the California red scale.[58] $AlCl_3$ catalyzed [2 + 2] cycloadditions of methyl propiolate have been used for the synthesis of inside-inside bicyclics and [10]paracyclophanes.[59] An intramolecular version of this cycloaddition has been used in the construction of coronofacic acid.[60]

Good yields of 1:1 adducts have also been obtained from Lewis acid catalyzed reactions of methyl chloropropiolate or DMAD with alkenes.[61–64] With methyl chloropropiolate, cyclobutenes are obtained exclusively from mono- and 1,2-di-substituted alkenes and mixtures of ene adducts and cyclobutenes are obtained with 1,1-di-, tri- and tetra-substituted alkenes.[61,62] With DMAD, ene adducts are obtained exclusively from 1,1-di-, tri- and tetra-substituted alkenes and mixtures of ene adducts and cyclobutenes are obtained from 1,2-disubstituted alkenes.[61–64] $EtAlCl_2$ is a more effective catalyst than $AlCl_3$ since it is a proton scavenger as well as a Lewis acid. With $AlCl_3$, lactone byproducts are also formed.[63,64] The relative reactivity of alkenes in these Lewis acid catalyzed reactions was found to be 1,1-di- > tri- > tetra- >> mono- > 1,2-di-substituted. With reactive ene components such as methylenecyclohexane, ethylidenecyclohexane and β-pinene, good yields of ene adducts can be obtained with DMAD by thermal reaction at 110–130 °C for 0.25–6 d.[64]

With trisubstituted alkenes the ene reaction with DMAD or methyl chloropropiolate, but not methyl propiolate, is regiospecific.[61,62] A hydrogen is transferred from the alkyl group *trans* to the alkenyl hydrogen to give (**32**). An examination of possible transition states indicates severe steric interactions between R and X (Cl or CO_2Me) in (**33**) leading to (**34**), while transition state (**31**) leading to the observed product (**32**) has no significant steric interactions.



1.1.2.3 Allenes as Enes or Enophiles

Surprisingly few examples of the use of allenes as the ene components in ene reactions have been reported. In a series of papers, Taylor and coworkers reported that alkylallenes undergo thermal ene reactions with DMAD, hexafluoro-2-butyne and 3,3,3-trifluoropropyne to give cross-conjugated trienes.[65,66] Similar reactions occur between allenes and hexafluoroacetone and electron-deficient azo compounds.[67–69]

Lewis acid catalyzed reactions of allenes with alkenes generally give cyclobutanes rather than ene adducts. $AlCl_3$ catalyzed reactions of alkylallenes with alkenes give alkylidenecyclobutanes.[70] Similarly, $AlCl_3$ catalyzed reactions of alkynes with alkenes give cyclobutenes.[71] These reactions are believed to occur by stereospecific cycloaddition of the alkene with the vinyl cation formed by complexation of $AlCl_3$ to the allene or alkyne.

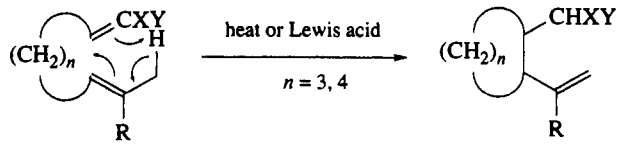
2,3-Butadienoate esters undergo $AlCl_3$ and $EtAlCl_2$ catalyzed stereospecific [2 + 2] cycloadditions with a wide variety of alkenes to give alkyl cyclobutylideneacetates in good yield.[72,73] The stereospecificity and ratios of (*E*)- and (*Z*)-isomers suggest a [$_{\pi}2_s$ + $_{\pi}2_a$] cycloaddition of the ester–Lewis acid complex to the alkene analogous to the cycloaddition of ketenes with alkenes. Similar results are obtained with methyl 2,3-pentadienoate, methyl 4-methyl-2,3-pentadienoate and methyl 2-methyl-2,3-butadienoate.[74]

1.1.3 INTRAMOLECULAR REACTIONS: ALKENES AS THE ENE COMPONENT

Intramolecular ene reactions are much more facile than their intermolecular counterparts due to the less negative entropy of activation for the intramolecular reaction. Even simple alkenes and alkynes are suitable enophiles in intramolecular reactions. Formation of cyclopentanes from 1,6-dienes or 1,6-enynes is a very facile process, providing some of the most impressive synthetic applications of the ene reaction. Formation of cyclohexanes from 1,7-dienes or 1,7-enynes is much less facile since the entropy of activation becomes more negative with the longer tether connecting the ene and enophile. For similar reasons, formation of larger rings by intramolecular ene reactions is rarely a synthetically useful reaction. Two comprehensive reviews of intramolecular ene reactions by Oppolzer and Snieckus[3] and by Taber[5] provide more complete coverage than is possible here.

Oppolzer has classified intramolecular ene reactions into type I, II and III depending on whether the tether is attached to carbon 1, 2 or 3 of the ene component (see equations 4, 5 and 6). Type IV reactions, which are a variation of type I in which the tether is attached to the terminal rather than internal end of the enophile, are occasionally observed (see equation 7). Type I reactions with alkenes or alkynes as enophiles have been extensively studied. Only a few examples of type II, III and IV reactions with alkenes or alkynes as enophiles are known. Numerous examples of intramolecular type I, II and III reactions with carbonyl compounds as enophiles are discussed in Volume 2, Chapter 2.1.

Type I



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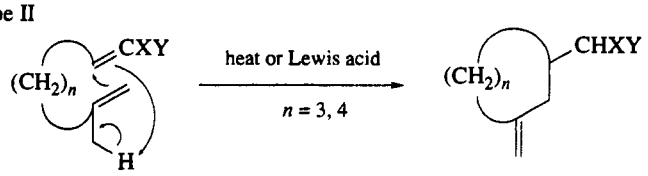
Type II



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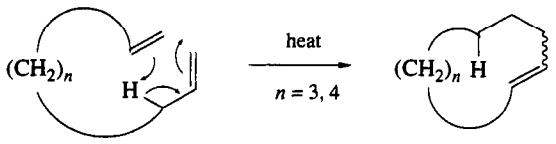
Type III



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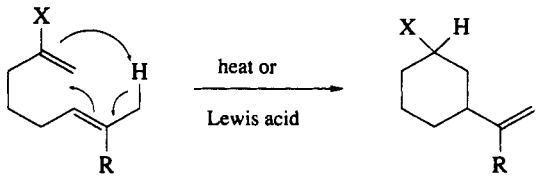
Type IV



(7)

Type I intramolecular ene reactions give mixtures of *cis*- and *trans*-1,2-disubstituted cycloalkanes depending on whether the ene reaction proceeds through an *endo* or *exo* transition state. In general, steric rather than electronic effects determine which transition state is preferred. The reaction is often very selective, as indicated below.

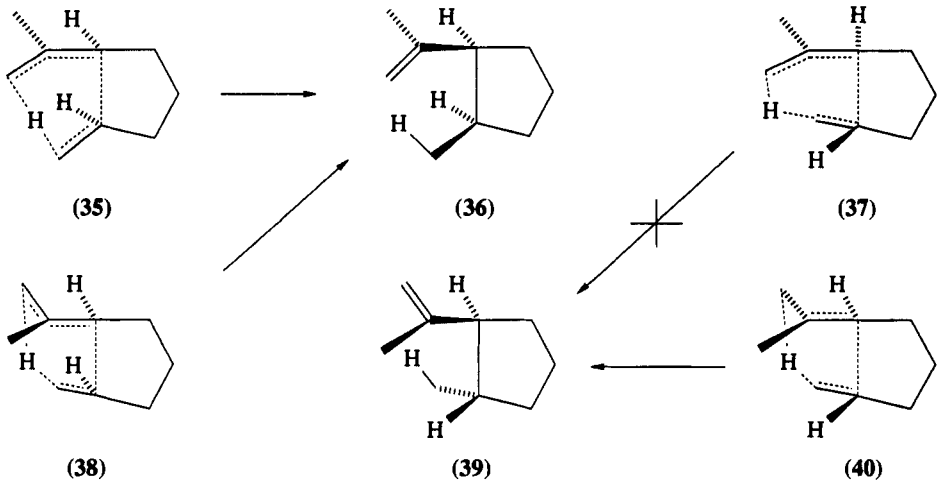
1.1.3.1 Formation of 1-Vinyl-2-alkylcyclopentanes from 1,6-Dienes

1.1.3.1.1 Unactivated enophiles

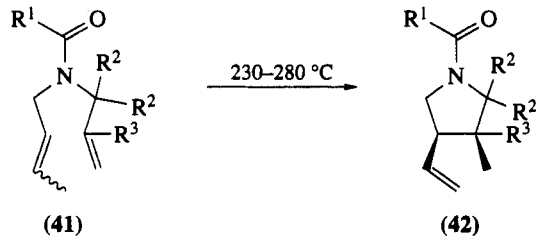
Pioneering studies by Huntsman,[75] Ohloff[76] and others[77,78] demonstrated that cyclization of unactivated 1,6-dienes occurs in a flow system at 400–500 °C or on heating for longer times at 250–350 °C. Despite the apparently harsh conditions, good yields of product are usually obtained if no thermally sensitive functional groups are present. Lewis acid catalysis of these reactions is not possible since there is no basic site on the enophile.

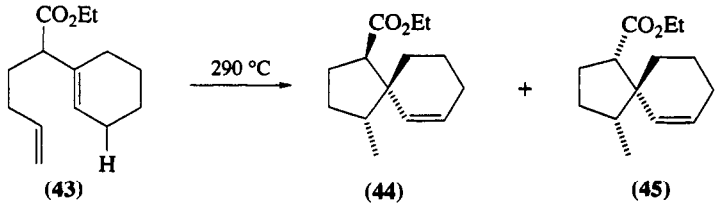
A characteristic feature of these reactions is the selective or exclusive formation of *cis*-2-alkyl-1-vinylcyclopentanes (**36**). Intramolecular ene reaction with hydrogen transfer from an alkyl group *cis* to the tether containing the enophile must occur through *exo* transition state (**35**) to give (**36**) since the *endo* transition state (**37**), which would give (**39**), is too hindered. Intramolecular ene reaction with hydrogen transfer from an alkyl group *trans* to the tether containing the enophile occurs through *endo* transition state (**38**) to give (**36**) and through *exo* transition state (**40**) to give (**39**). The formation of (**36**) is usually strongly preferred in thermal ene reactions despite the possible formation of (**39**) from (**40**).

More recent studies have utilized more highly functionalized substrates to prepare synthetic intermediates. Oppolzer has shown that intramolecular ene reactions provide an efficient approach to substituted pyrrolidines.[79] Thermolysis of (**41**; R^1 = Me, OMe; R^2 = H, Me; R^3 = H, Ph) at 230–280 °C for 7–63 h gives pyrrolidine (**42**) in 55–90% yield. The *cis* isomer of (**41**) gives exclusively the *cis*-substituted pyrrolidine (**42**). The *trans* isomer of (**41**) affords 75–90% of *cis*-substituted (**42**). Oppolzer *et al.* have



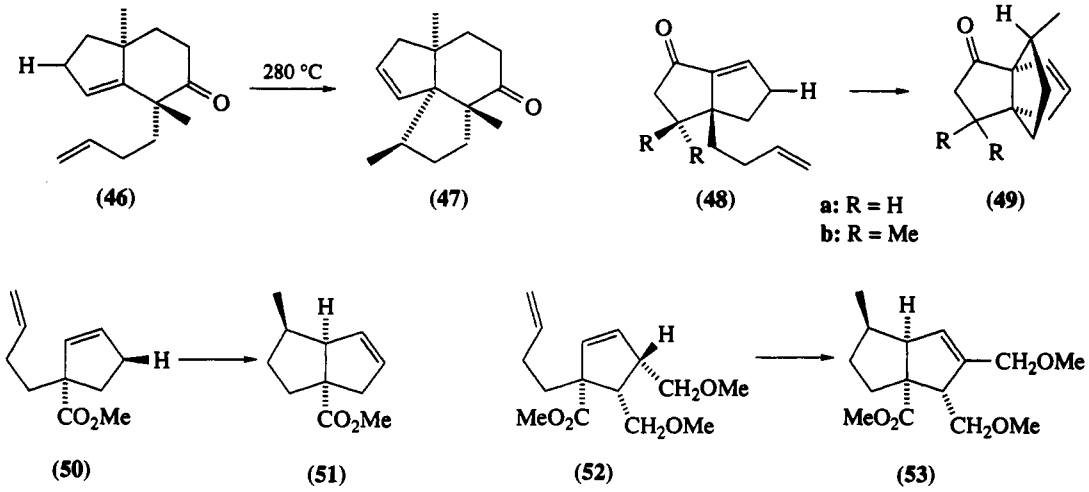
used an intramolecular ene reaction to prepare a spirocyclic precursor to β-acorenol, β-acoradiene, acorenone-B and acorenone.[80] Thermolysis of (**43**) in toluene at 290 °C for 72 h provides a 1.7:1 mixture of (**44**) and (**45**) in 68% yield. The methyl and vinyl are *cis* on the five-membered ring in both isomers. Adduct (**44**) was converted to β-acorenol and β-acorenone and adduct (**45**) was converted to acorenone-B and acorenone.



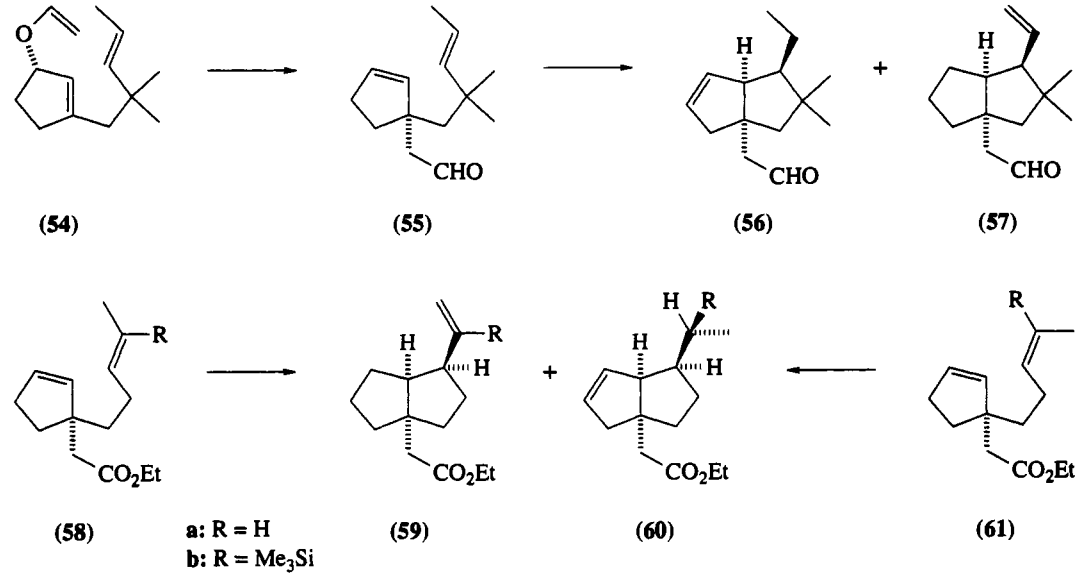


Oppolzer used an intramolecular ene reaction as the key step in a synthesis of isocomene.[81] Thermolysis of (**46**) in toluene at 280 °C for 24 h gives tricyclic ene adduct (**47**) in 17% yield. As required for the synthesis of isocomene, the methyl and vinyl substituents on the newly formed cyclopentane are *cis*. Oppolzer and coworkers developed two approaches to modhephene using intramolecular ene reactions to construct the [3.3.3]propellane system.[82,83] Pyrolysis of (**48a**) in toluene for 12 h at 250 °C gives (**49a**) in 73% yield. Pyrolysis of (**48b**) in toluene for 16 h at 250 °C gives a 76% yield of (**49b**) containing the *gem*-dimethyl group needed for the synthesis of modhephene. Once again, the methyl and vinyl substituents on the newly formed cyclopentane are *cis*. In model studies for the synthesis of pentalenolactone, Plavec and Heathcock developed routes to diquinanes based on intramolecular ene reactions.[84] Flash vacuum pyrolysis of (**50**) at 500 °C gives (**51**) in 93% yield. Thermolysis of (**52**) for 40 min at 345 °C gives the highly functionalized diquinane (**53**) in 71% yield.

Ziegler and Mencel have described tandem Claisen–ene rearrangements.[85] Thermolysis of vinyl ether (**54**) for 2 h at 330 °C gives a 1:1 mixture of aldehydes (**56**) and (**57**) in 75% yield. Claisen rearrangement gives (**55**), which undergoes intramolecular ene reactions with the side-chain double bond acting as the enophile to give (**56**) and the cyclopentene double bond acting as enophile to give (**57**). Ziegler and Mikami then introduced a trimethylsilyl group on to the side-chain double bond in an attempt to control the orientation of the ene reaction.[86] Pyrolysis of either (**58a**) or (**58b**) in benzene at 300 °C for 15 h pro-



vides a 1:1 mixture of (**59**) and (**60**), indicating that in this case the trimethylsilyl group does not perturb the orientation of the ene reaction. On the other hand, pyrolysis of (**61b**) at 300 °C gives only (**59b**), while pyrolysis of (**61a**) gives a 3:1 mixture of (**59a**) and (**60a**). Therefore steric interactions caused by the trimethylsilyl group in (**61b**) prevent the side-chain double bond from acting as the enophile.



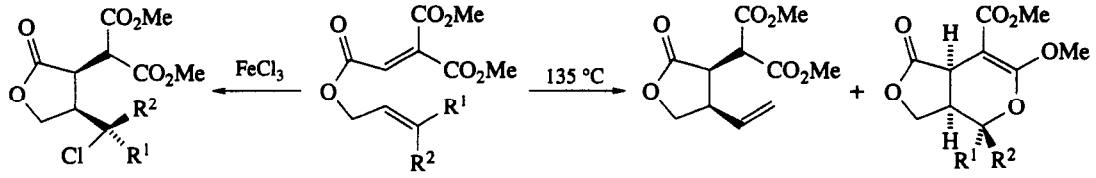
1.1.3.1.2 Activated enophiles

As in intermolecular ene reactions, the presence of electron-withdrawing substituents, such as alkoxycarbonyl groups, on the enophile lowers the activation energy, permitting the ene reaction to occur under milder conditions. Type I intramolecular ene reactions with enophiles bearing two electron-withdrawing substituents on the terminal carbon occur under very mild conditions. Intramolecular ene reactions with enophiles bearing a single electron-withdrawing group on the terminal carbon sometimes proceed under mild conditions but, somewhat surprisingly, often proceed only at the elevated temperatures required for unactivated enophiles. Complexation of a Lewis acid to the electron-withdrawing group further activates the enophile, permitting these reactions to be carried out at or below room temperature.

Kelly found that intramolecular ene reaction of triester (**62**) occurs rapidly at room temperature to give (**63**).[87] Snider and coworkers investigated the scope of this reaction and found that 1-allylic 2,2-dimethyl ethylenetricarboxylates undergo intramolecular cyclization reactions at 80–140 °C to give mixtures of ene adducts and dihydropyrans resulting from inverse electron Diels–Alder reactions in which the α,β-unsaturated ester functions as the diene.[88] The *trans*-crotyl triester (**64a**) reacts at 135 °C for 200 h giving

a 1:1 mixture of the *cis*-substituted ene adduct (**65**) and the Diels–Alder adduct (**66a**). The *cis*-crotyl triester (**64b**) reacts similarly giving a 9:1 mixture of (**65**) and (**66b**). Different products are formed with Lewis acid catalysis.[89] Treatment of (**64a**) with $FeCl_3$ in CH_2Cl_2 for 30 min at 25 °C gives chlorolactone (**67**), resulting from stereospecific *trans* addition of carbon and chlorine to the double bond in 85% yield. Similar treatment of (**64b**) gives chlorolactone (**68**) in 75% yield.

(**62**) (**63**)



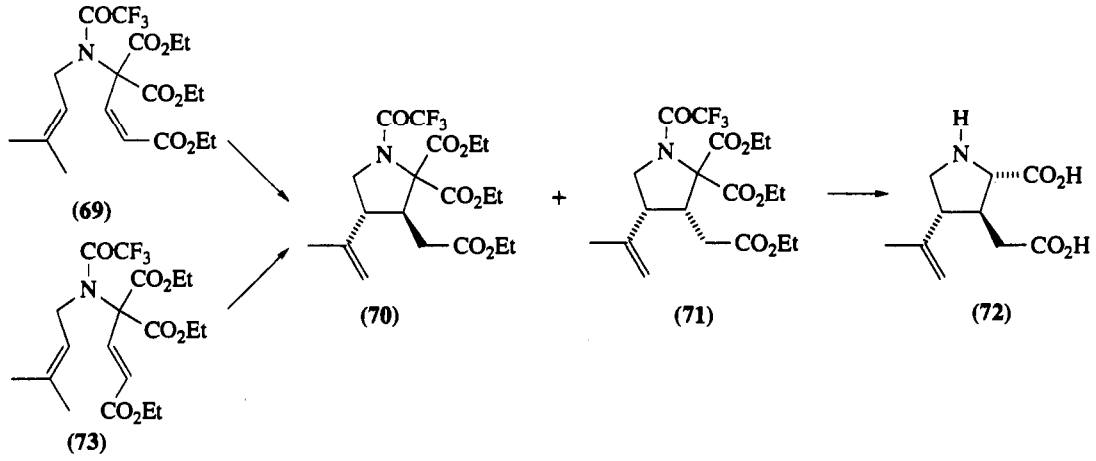
(**67**) R^1 = Me, R^2 = H
(**68**) R^1 = H, R^2 = Me

(**64**)

a: R^1 = Me, R^2 = H
b: R^1 = H, R^2 = Me

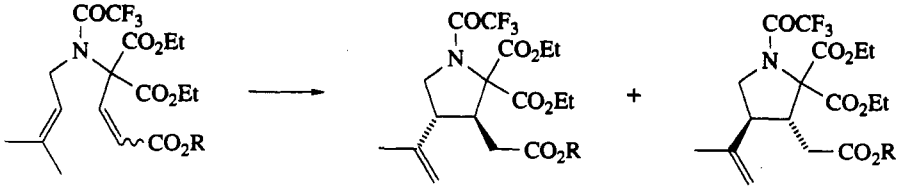
(**65**) (**66**)

Oppolzer and Sammes independently developed a route to α-allokainic acid (**72**) based on the thermal ene reactions of (*Z*)-alkene (**69**) and (*E*)-alkene (**73**).[90–92] Pyrolysis of (**69**) for 5 min at 180 °C or 80 h at 70 °C gives a 3:1 mixture of (**70**) and (**71**). Reaction of (**73**) under similar conditions gives a 1:1 mixture of (**70**) and (**71**). The *trans* isomer (**70**) was converted to α-allokainic acid (**72**) by hydrolysis and decarboxylation. Oppolzer found that $EtAlCl_2$ catalyzed ene reactions of these esters proceed at very low temperature with improved selectivity for the desired *trans* isomer (**70**).[91] Treatment of (**69**) at –78 °C with 3 equiv. of $EtAlCl_2$ for 8 h or 20 equiv. of $EtAlCl_2$ for 5 min gives only (**70**). Treatment of (**73**) at –35 °C with $EtAlCl_2$ gives a 89:11 mixture of (**70**) and (**71**). At least three equiv. of $EtAlCl_2$ are needed to complex fully the ester groups in (**69**) and (**73**). The ene reactions of (**69**) and (**73**) differ from most ene reactions of 1,6-dienes in that *trans*-pyrrolidines are the exclusive or major products.



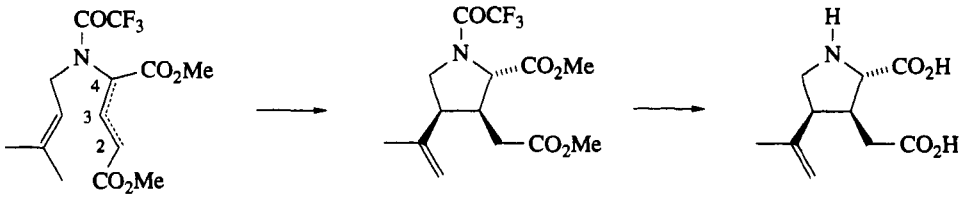
(**69**) (**73**) (**70**) (**71**) (**72**)

Oppolzer and coworkers have developed an enantioselective version of this reaction which permits the synthesis of (+)- and (–)-α-allokainic acid from (**76**) and (**77**), respectively.[93,94] Treatment of (–)-8-phenylmenthyl ester (**74**) with $EtAlCl_2$ at –78 °C gives a 95:5 mixture of (**76**) and (**77**). Treatment of (–)-8-phenylmenthyl ester (**75**) with $EtAlCl_2$ at –35 °C gives an 11:89 mixture of (**76**) and (**77**). Oppolzer and Mirza used ^{13}C labeling to establish that the hydrogen is transferred exclusively from the *trans*-methyl group of (**69**).[95] This result precludes a stepwise mechanism with a free cationic intermediate which should transfer hydrogen equally from both methyl groups.

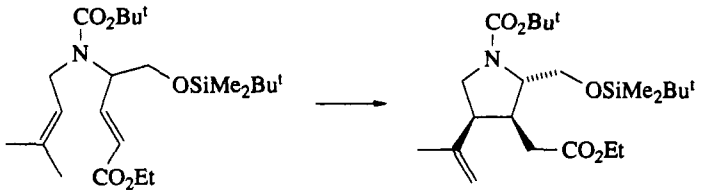


(74) (*Z*) R = (–)-8-phenylmenthyl (76) (77)
(75) (*E*)

Oppolzer and coworkers used an intramolecular ene reaction as the key step in the synthesis of α-kainic acid (**81**).[96] Thermolysis of diene (**78**) at 180 °C results in reversible isomerization to diene (**79**), which undergoes an intramolecular ene reaction to give the expected *cis*-substituted pyrrolidine (**80**) in 90% yield. Hydrolysis gives α-kainic acid (**81**) in 60% yield. This approach was extended to the synthesis of (–)-α-kainic acid.[97] Thermolysis of (**82**) for 40 h at 130 °C gives the key intermediate (**83**) in 75% yield.

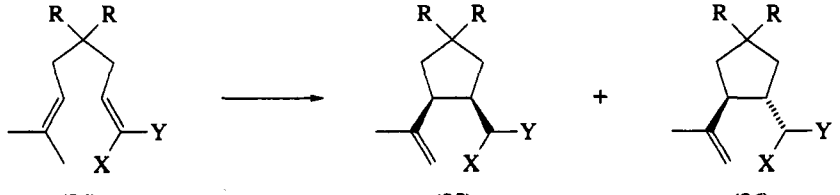


(78) $\Delta^{3,4}$ (80) (81)
(79) $\Delta^{2,3}$

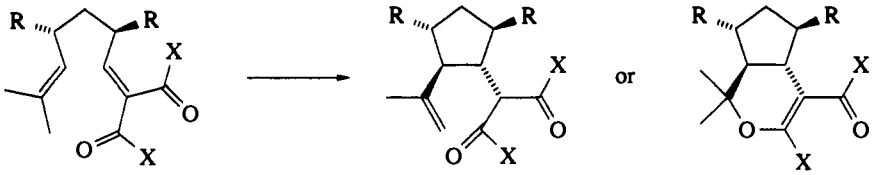


(82) (83)

Ghosh and Sarkar examined the effects of activating groups and geminal substitution on the rates and stereoselectivities of the thermal ene reactions of (**84**).[98] Cyclization of the (*E*)-isomer (**84**; X = CO_2Me; Y = H) gives a 3:1 mixture of (**85**) and (**86**), while cyclization of the (*Z*)-isomer (**84**; X = H; Y = CO_2Me) gives a 2:3 mixture of (**85**) and (**86**). Diester (**84**; X = Y = CO_2Me) gives a ~15:85 mixture of (**85**) and (**86**). Geminal substitution (R = Me) in (**84**) leads to a 3–4-fold rate enhancement over the unsubstituted case (R = H). The presence of a second ester on the dienophile (**84**; X = Y = CO_2Me) leads to a 13–17-fold rate enhancement over either the (*E*)- or (*Z*)-monoester. Tietze and coworkers found that $ZnBr_2$ catalyzed ene reactions of a series of malonates (**87**; X = OMe) at 25 °C proceed in excellent yield with high selectivity for the all-*trans* isomer (**88**).[99] Under these conditions the diketones (**87**; X = Me) give the inverse-electron Diels–Alder adduct (**89**).

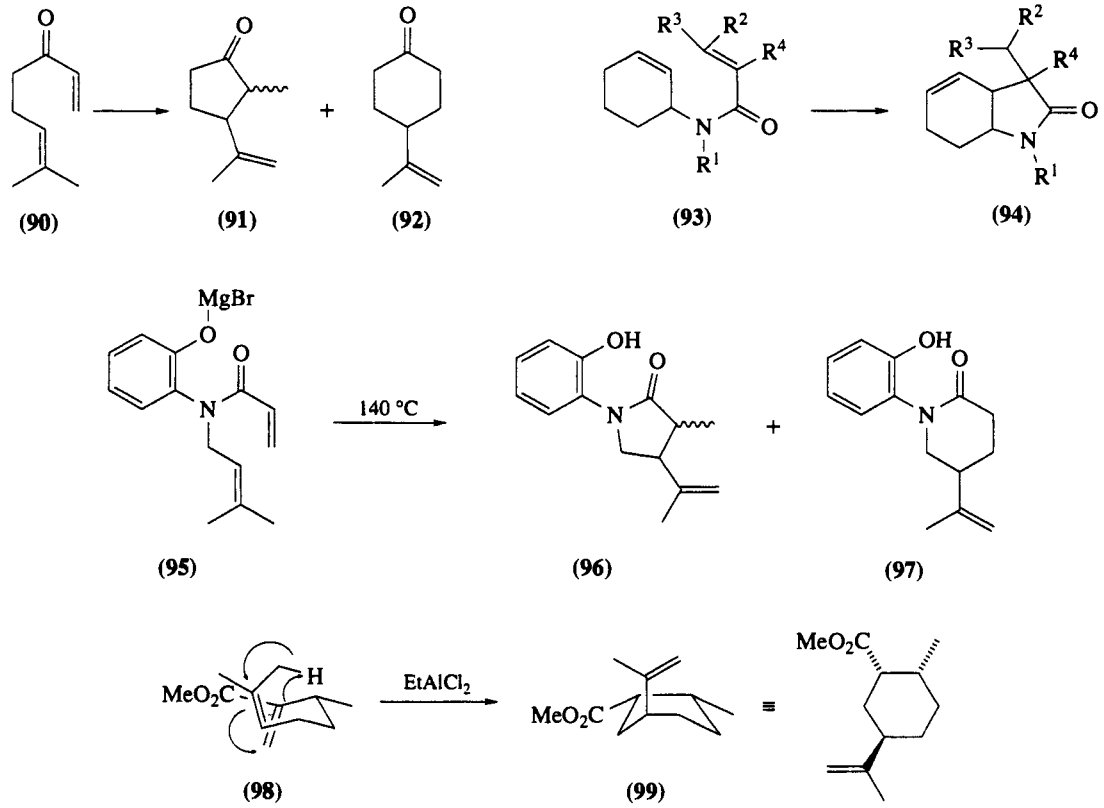


(84) (85) (86)



(87) R = H, Me (88) X = OMe (89) X = Me

Introduction of an electron-withdrawing group on the internal carbon of the enophile should favor bond formation between the terminal carbon of the enophile and the ene to give a type IV adduct (equation 7). Flash vacuum pyrolysis of (**90**) at 570 °C leads to a mixture of the type I adducts (**91**) and the type IV adduct (**92**).[100] Lewis acid catalyzed cyclization of (**90**) should favor the formation of (**92**), but a stepwise reaction leading to other products occurs.[48] Cyclohexenylacrylamides (**93**) cyclize only to the type I product (**94**) on heating above 200 °C.[101] However, the magnesium salt of hydroxyphenylacrylamides (**95**) undergoes intramolecular ene reactions at 140 °C to give mixtures of adducts (**96**) and (**97**) rich in the type IV adduct (**97**).[102] Treatment of (**98**) with 0.9 equiv. of $EtAlCl_2$ at 40 °C for 5 d gives exclusively the type IV adduct (**99**).[103]



(90) (91) (92) (93) (94)

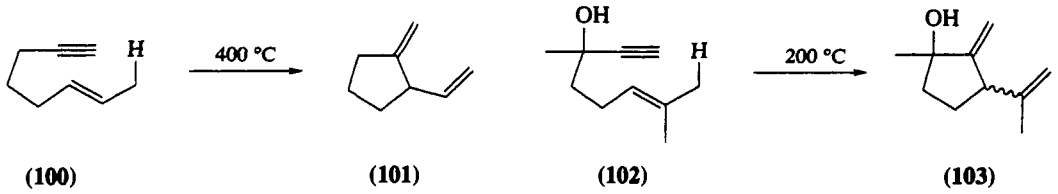
(95) (96) (97)

(98) (99)

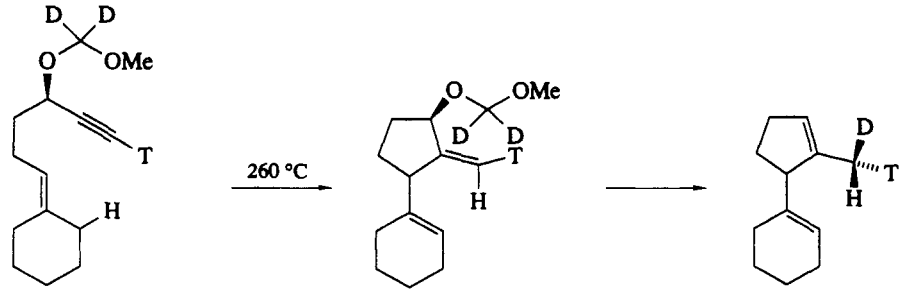
1.1.3.2 Formation of 1-Vinyl-2-alkylidinecyclopentanes from 1,6-Enynes

Alkynes are generally more reactive than alkenes as enophiles in both inter- and intra-molecular ene reactions.[1,3] 6-Octen-1-yne (**100**) cyclizes to 1-methylene-2-vinylcyclopentane (**101**) on brief heating at 400 °C.[104,105] Dehydrolinalool (**102**) undergoes an ene reaction at 200 °C to give (**103**) in quantitative yield.[106,107] This ene reaction can also be carried by heating for 15 min in a microwave oven at 400–425 °C.[108] Arigoni has used an intramolecular ene reaction followed by a retro-ene reaction for the synthesis of chiral acetic acid.[109] Thermolysis of optically active (**104**) at 260 °C for 2.5 h gives (**105**), which undergoes a retro-ene reaction to give (**106**). Kuhn–Roth degradation of (**106**) gives (*R*)-[^{2}H,^{3}H]acetic

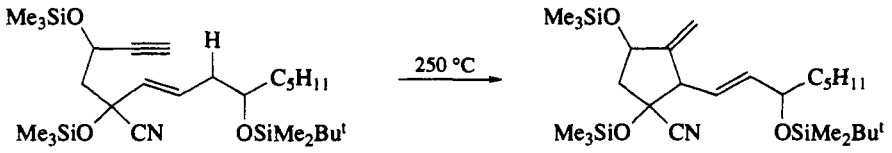
acid. Stork and Kraus carried out a prostaglandin synthesis using the intramolecular ene reaction of (**107**) at 250 °C to give (**108**) in 60% yield as the key step.[110]



(**100**) (**101**) (**102**) (**103**)

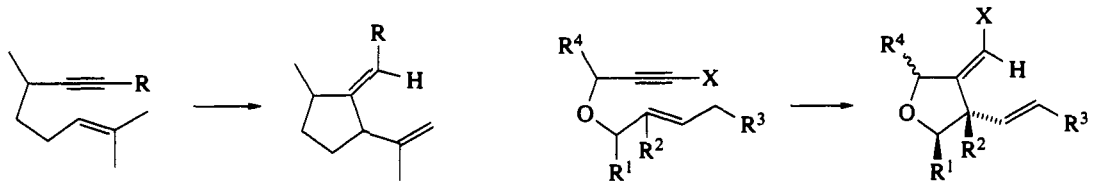


(**104**) (**105**) (**106**)



(**107**) (**108**)

Snider and Killinger have examined the intramolecular ene reaction of 1,6-enynes containing a hydrogen, methyl or methoxycarbonyl substituent on the alkyne.[111] Since the alkyne is acting as the enophile, a methyl substituent retards the reaction while a methoxycarbonyl group accelerates it. Pyrolysis of (**109**) for 62 h at 210 °C gives (**112**) in >95% yield. Pyrolysis of (**111**) for 48 h at 225 °C gives only 15% conversion to (**114**). Pyrolysis of ester (**110**) for 24 h at 135 °C gives (**113**) in >95% yield. Nakai and coworkers have examined the intramolecular ene reactions of crotyl propargyl ethers (**115**) to give (**116**).[112] As in the all carbon system, esters cyclize faster than terminal alkynes which cyclize faster than internal alkynes. High 1,2-*trans* diastereoselectivity is observed with α-alkylcrotyl systems, as shown in the formation of (**116**).

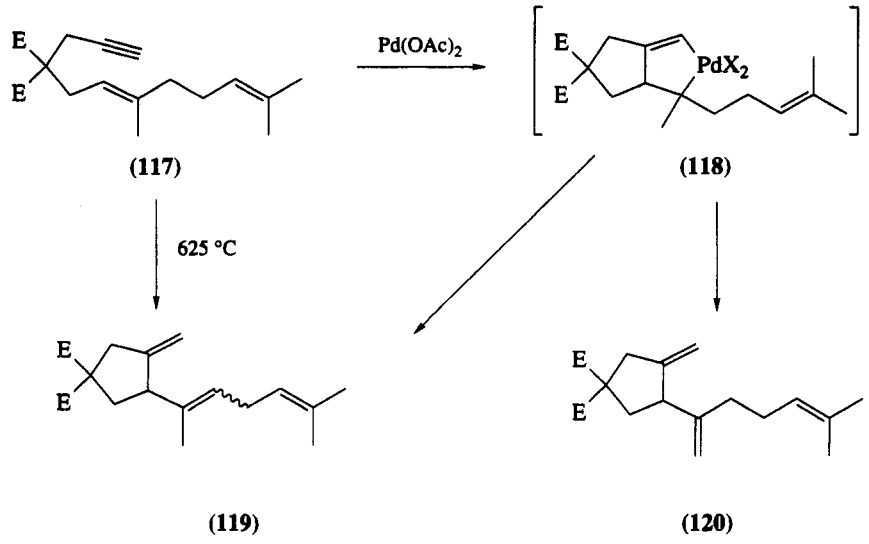


(**109**) R = H
(**110**) R = CO_2Me
(**111**) R = Me

(**112**) R = H
(**113**) R = CO_2Me
(**114**) R = Me

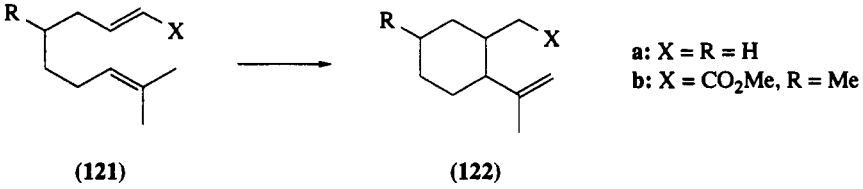
(**115**) X = H, CO_2Me, Me_3Si, Me (**116**)
R = H, alkyl or aryl

Trost has discovered that $Pd(OAc)_2$ and other Pd^{II} compounds catalyze the cyclization of terminal 1,6-enynes to give ene-type adducts.[113] Treatment of (**117**) with 5 mol % $Pd(OAc)_2$ at 60–66 °C gives metallocyclopentene (**118**), which reacts further to give a 6:94 mixture of (**119**) and (**120**) in 80% yield. Flash vacuum pyrolysis of (**117**) at 625 °C gives a 100:0 mixture of (**119**) and (**120**) in 83% yield. The palladium reaction not only occurs under much milder conditions but gives different isomer ratios. In many other cases the palladium-catalyzed cyclization gives products which are not available from a thermal ene reaction.

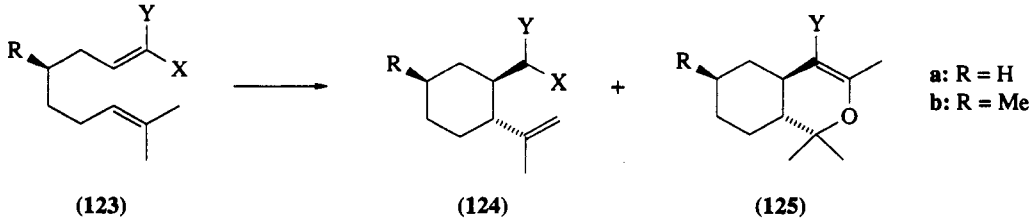


1.1.3.3 Formation of 1-Vinyl-2-alkylcyclohexanes from 1,7-Dienes

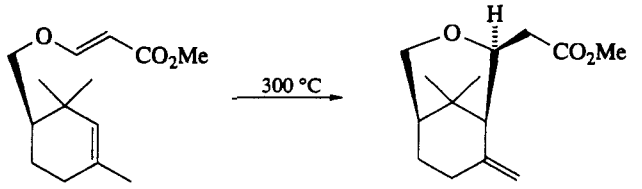
1,7-Dienes undergo intramolecular ene reactions much less readily than 1,6-dienes due to the more negative entropy of activation with the longer tether. These reactions require higher temperatures, proceed in lower yields and are not generally synthetically useful except in the case of 1,7-dienes containing two electron-withdrawing groups on the terminal carbon of the enophile. Flash vacuum pyrolysis of (**121a**) at 490 °C gives only 25% of (**122a**). Flash vacuum pyrolysis of (**121b**) with a monoactivated enophile at 400 °C gives an 82% yield of (**122b**).[114–116]



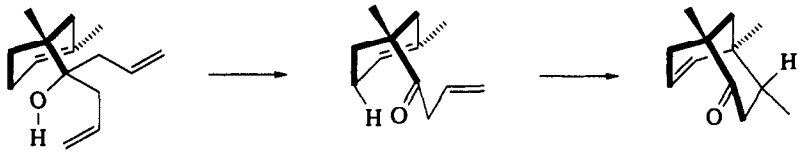
Intramolecular ene reactions of 1,7-dienes with doubly activated enophiles (**123**; X, Y = CO_2R, CN, COMe) proceed readily either thermally or with Lewis acid catalysis to give (**124**) and stereoisomers.[115,117–121] In an elegant series of studies, Tietze and coworkers have explored the stereochemistry of these cyclizations.[118–121] Dienes (**123a**; X, Y = CO_2Me, CN) undergo thermal or $ZnBr_2$ catalyzed ene reactions, providing the *trans* isomer (**124a**) selectively in up to 89% yield.[118] Dienes (**123a**) in which one or both of the activating groups is a methyl ketone behave quite differently, giving mainly or exclusively the inverse electron demand intramolecular Diels–Alder adduct (**125a**).[118] Dienes (**123b**) behave similarly, giving adducts (**124b**) and (**125b**) with high selectivity for the fully equatorial diastereomer.[119,120] Anhydrous $FeCl_3$ on basic alumina proved to be the best catalyst for the cyclization of (**124b**; X = Y = CO_2Me) giving, at –78 °C, a 98.8:1.2 mixture of (**124b**) and the other diastereomer with *trans* isopropenyl and malonate substituents in 92% yield.[119] Malonate (**124b**) was converted to enantiomerically pure veticadinol by a six-step sequence.[121] Tietze has also exploited the inverse electron demand intramolecular Diels–Alder reaction of doubly activated 1,7-dienes.[122–124] This process, rather than an intramolecular ene reaction, is the main or exclusive reaction when the activating groups in (**123**) are diketones, Meldrum's acid or dimethylbarbituric acid.



Nussbaumer and Fráter have used a vinylogous carbonate as an enophile. Pyrolysis of a solution of (**126**) in toluene at 300 °C for 9 h gives (**127**), an intermediate in a synthesis of *cis*-γ-irone, in 25% yield as the only cyclization product.[125] Acid-catalyzed cyclization of (**126**) gives only the isomer of (**127**) with an endocyclic double bond. Thomas and Lander-Schouwey found that pyrolysis of (**128**) in decalin at 300 °C results in a retro-ene reaction to give propene and (**129**) which undergoes an intramolecular ene reaction to give (**130**).[126]



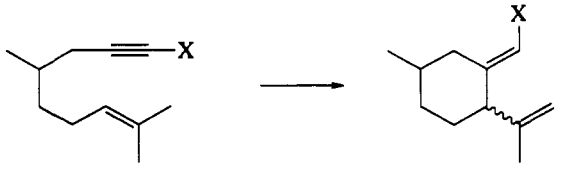
(**126**) (**127**)



(**128**) (**129**) (**130**)

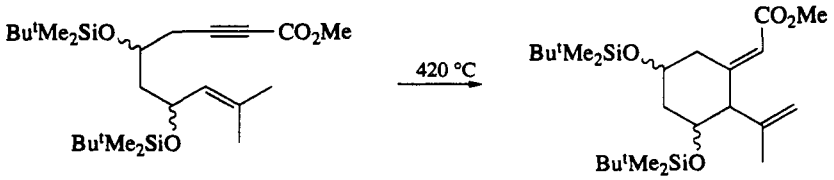
1.1.3.4 Formation of 1-Vinyl-2-alkylidinecyclohexanes from 1,7-Enynes

Only a few examples of intramolecular ene reactions of 1,7-enynes are known. Pyrolysis of terminal alkyne (**131**) in toluene for 48 h at 255 °C results in 17% conversion to ene adduct (**133**).[111] Ester (**132**) is more reactive, giving ene adduct (**134**) in 85% yield on heating for 62 h at 225 °C. Ficini and coworkers have found that similar reactions can be carried out conveniently by flash vacuum pyrolysis. Pyrolysis of (**135**) at 420 °C at 200 Torr gives 80% conversion to ene adduct (**136**), a model for the synthesis of the A ring of 1*S*,25-dihydroxycalciferol.[127] Dreiding found that flash vacuum pyrolysis of ynone (**137**) at 550 °C gives ene adduct (**138**) in 15% yield along with other products.[128]

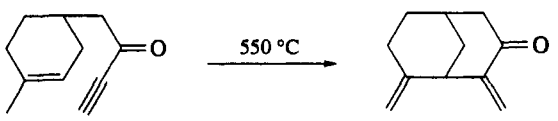


(**131**) X = H
(**132**) X = CO_2Me

(**133**) X = H
(**134**) X = CO_2Me



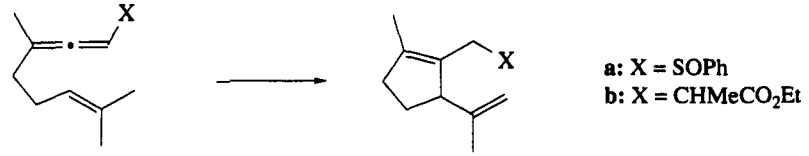
(**135**) (**136**)



(**137**) (**138**)

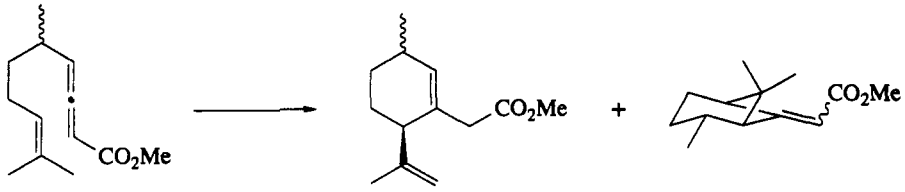
1.1.3.5 Miscellaneous Reactions

Allenes have occasionally been used as enophiles in intramolecular ene reactions.[129] Thermolysis of (**139a**) at 200 °C gives ene adduct (**140a**) in >90% yield. Similar reaction occurs at 25 °C with $BF_3{\cdot}Et_2O$ catalysis. Flash vacuum pyrolysis of allene (**139b**) at 380 °C at 200 Torr gives ene adduct (**140b**) in 80% yield. Treatment of allenic ester (**141**) with $EtAlCl_2$ for 12 d at 25 °C in CH_2Cl_2 gives ene adduct (**142**) in 49% yield, as a 2.9:1 mixture of α-methyl and β-methyl isomers, and cyclobutane (**143**) in 27% yield, as a 2:1 (*E*):(*Z*) mixture.[74] Only cyclobutanes are formed in related reactions with mono- or 1,2-di- rather than tri-substituted alkenes.



a: X = SOPh
b: X = $CHMeCO_2Et$

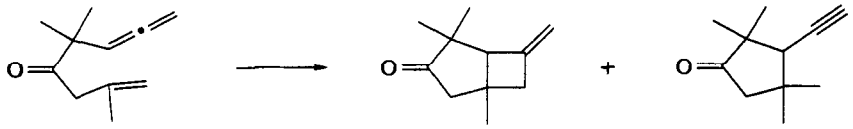
(**139**) (**140**)



(**141**) (**142**) (**143**)

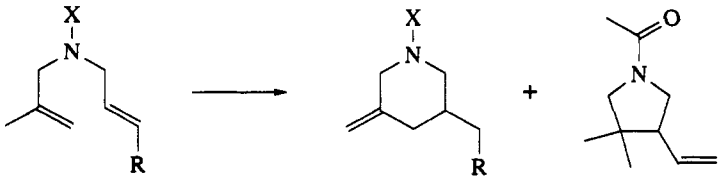
Allenes and alkynes occasionally react as ene components when other ene reactions are not possible. Pyrolysis of (**144**) for 2 h at 200 °C gives ene adduct (**145**) in 43% yield.[79] Flash vacuum pyrolysis of (**146**) at 490 °C gives a 3:1 mixture of cycloadduct (**147**) and ene adduct (**148**).[130]

(**144**) (**145**)



(**146**) (**147**) (**148**)

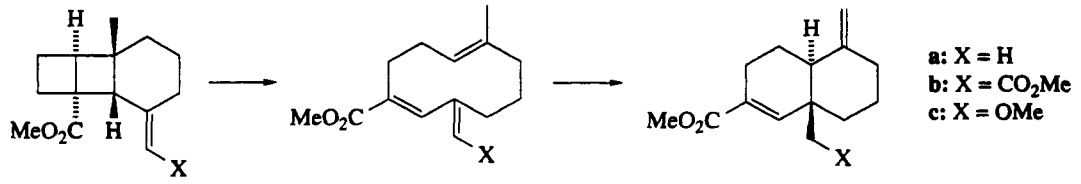
Type II reactions with carbonyl compounds as enophiles are well-known, synthetically useful reactions.[131] Type II reactions with alkenes as enophiles are very rare because competing type I reactions usually occur more readily. Thermolysis of (**149a**) at 280 °C gives ene adduct (**150a**) in 40% yield.[3] Thermolysis of (**149b**) at 230–280 °C leads to type I adduct (**151**) rather than type II adduct (**150b**).[79]



a: X = Ts, R = H
b: X = COMe, R = Me

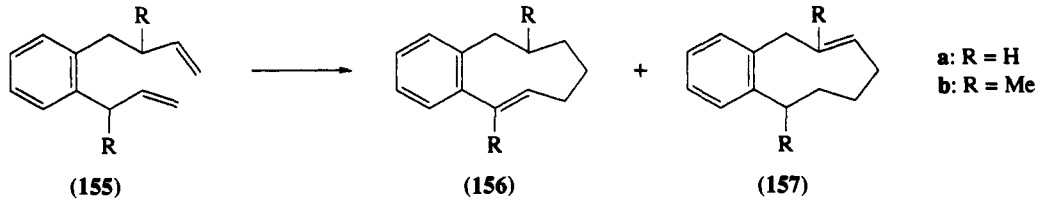
(**149**) (**150**) (**151**)

Wender and Letendre have reported a series of transannular ene reactions.[132] Pyrolysis of (**152a**) for 2 h at 210 °C gives cyclodecadiene (**153a**) as a transient intermediate which undergoes a transannular ene reaction to give (**154a**) in 95% yield. Ester (**152b**) gives a quantitative yield of (**154b**) under similar conditions. Heating ether (**152c**) to 210 °C for 1 h gives (**153c**) which is stable at that temperature. Transannular ene reaction to give (**154c**) occurs in 60% yield on heating (**153c**) at 260 °C for 5 h.

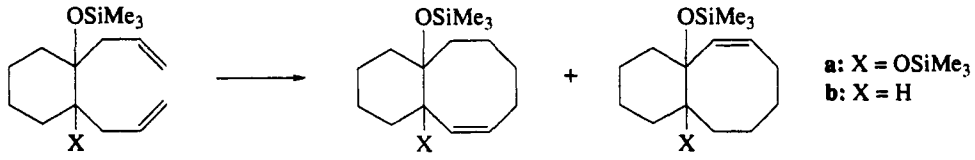


(**152**) (**153**) (**154**)

Type III intramolecular ene reactions provide a route to medium sized rings.[133–136] Lambert found that heating (**155a**) for 24 h at 350 °C gives a quantitative yield of a 1:1 mixture of (**156a**) and (**157a**). Both benzocyclononadienes result from intramolecular ene reactions, with different double bonds acting as enophiles.[133,134] Pyrolysis of (**155b**) under similar conditions gives a 4:1 mixture of (**156b**) and (**157b**). Marvell found that pyrolysis of bis-silyl ether (**158a**) for 90 h at 300 °C gives (**159a**) in 80% yield.[135] The *cis* isomer reacts three times faster than the *trans* isomer. Monosilyl ether (**158b**) gives a 9:1 mixture of (**159b**) and (**160b**).

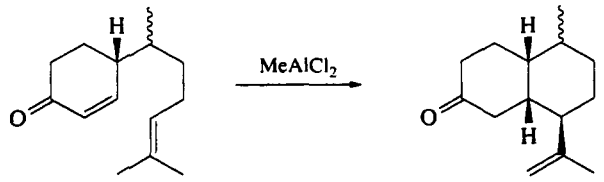


(**155**) (**156**) (**157**)



(**158**) (**159**) (**160**)

Lewis acid catalyzed intramolecular ene reactions with enones or enals sometimes occur in good yield. For instance, $MeAlCl_2$ catalyzed ene reaction of enone (**161**) at room temperature gives ene adduct (**162**) in 85% yield.[48] In many other cases, Lewis acid or proton catalyzed intramolecular additions of enones or enals to alkenes give zwitterions, which yield mixtures of products.[48,137–140]

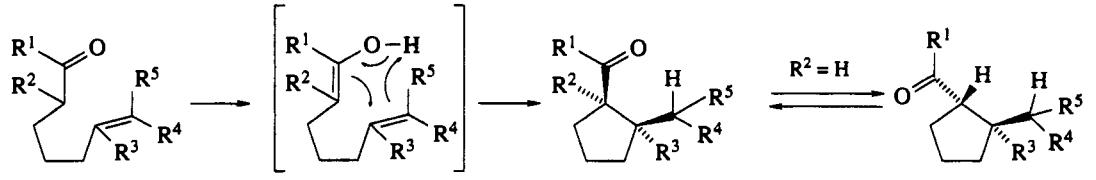


(**161**) (**162**)

1.1.4 INTRAMOLECULAR REACTIONS: ENOLS AS THE ENE COMPONENT; 'THE CONIA REACTION'

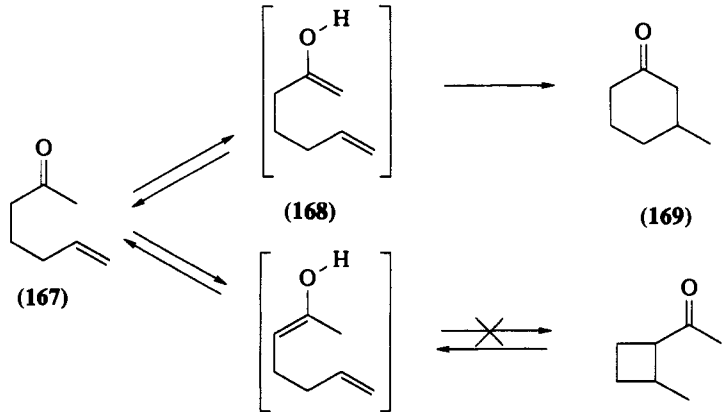
Conia and coworkers have developed an extensive series of thermal intramolecular ene reactions of unsaturated ketones which occur on extended heating (30 min to several hours) at 300–400 °C in pyrex.[141] The initial step of the reaction is reversible tautomerization of the ketone (**163**) to give enol

(**164**), which undergoes an intramolecular type I ene reaction with the enol as the ene component and the unactivated alkene as the enophile to give the *cis*-substituted adduct (**165**) selectively. If R^2 = H, equilibration with the more stable *trans*-substituted isomer (**166**) occurs rapidly under the reaction conditions. Related reactions with electron-deficient alkenes are Michael reactions rather than ene reactions.



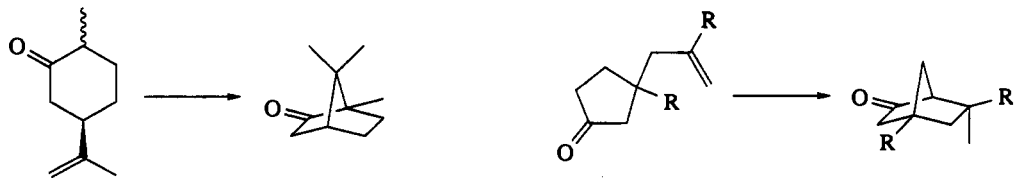
(**163**) (**164**) (**165**) (**166**)

As with other intramolecular ene reactions, this reaction is best suited to the preparation of cyclopentanes, but can also be used for the preparation of cyclohexanes. The reaction cannot be used for the formation of cyclopropanes or cyclobutanes since the unsaturated carbonyl compound is more stable than the ene adduct. δ,ε-Unsaturated ketones (**167**) do not give cyclobutanes (**171**) by enolization to give (**170**) followed by a type I reaction but instead give cyclohexanones (**169**) by enolization to give (**168**) followed by a type II reaction. Alkynes can replace alkenes as the enophile. Enols can be prepared from pyrolysis of enol esters, enol ethers and acetals and from β-keto esters and 1,3-dicarbonyl compounds. The reaction is well suited to the preparation of fused or bridged bicyclic and spirocyclic compounds. Tandem ene reactions in which two rings are formed in one pot from dienones have also been described. The examples discussed below[142–163] are restricted to those published since Conia and Le Perchec's 1975 review.[141]

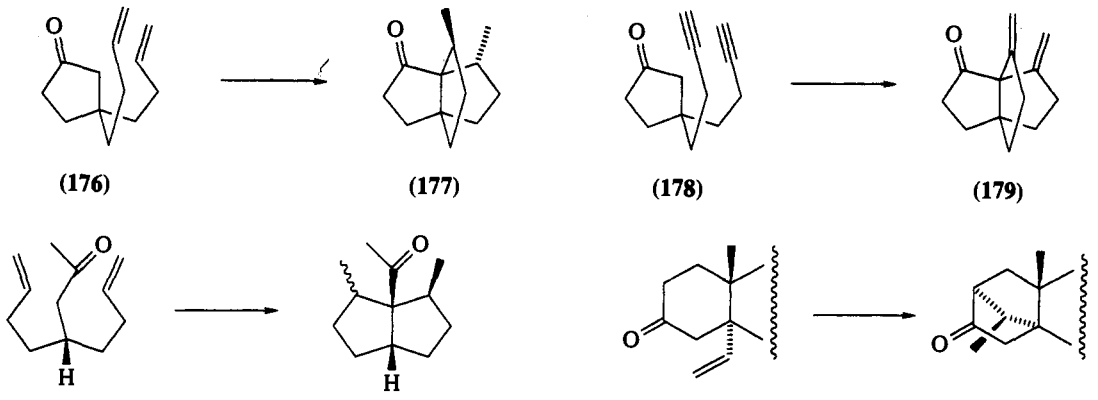


(**167**) (**168**) (**169**) (**170**) (**171**)

Conia and Lange[143] and Wolff and Agosta[144] have extended the reaction to the synthesis of bicyclo[2.2.1]heptanones and bicyclo[2.2.2]octanones. Cyclization of (+)-dihydrocarvone (**172**) at 400 °C for 20 h gives (+)-camphor (**173**) in 55% yield.[143] Pyrolysis of (**174**; R = H or Me) for 6 h at 375 °C gives *endo*-6-methylbicyclo[2.2.1]heptan-2-one (**175**; R = H, Me) in 60–70% yield.[144] Conia and coworkers have prepared [3.3.3]propellanes by tandem ene reactions. Pyrolysis of (**176**) for 2 h at 335 °C gives (**177**) in 50% yield.[147] Pyrolysis of (**178**) for 100 min at 290 °C gives (**179**) in 63% yield.[147] Pyrolysis of (**180**) for 6 h at 335 °C gives a 1:3 mixture of (**181**) and (**182**) in 40% yield.[146] Yates examined the pyrolysis of 5-vinylcholestan-3-ones.[145,148] The 5α-isomer (**183**) gives (**184**) in 41% yield.



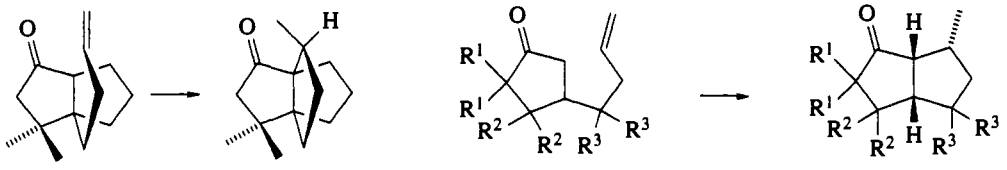
(**172**) (**173**) (**174**) (**175**)



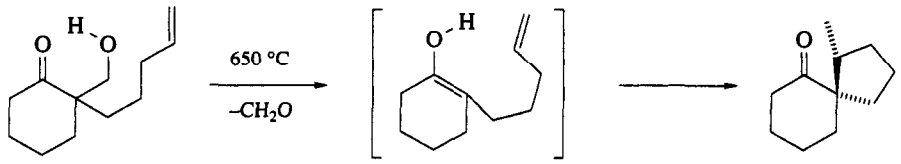
(176) (177) (178) (179)

(180) (181) α-Me (182) β-Me (183) (184)

Schostarez and Paquette used a 'Conia' ene reaction as a key step in their synthesis of modhephene.[149] Pyrolysis of (**185**) for 4 h at 360 °C gives (**186**) as a single stereoisomer in 85% yield, which was converted to epimodhephene. Cyclization of the corresponding alkyne gives an intermediate that was converted to modhephene. Paquette and coworkers examined the cyclization of (**187a–c**) as a part of a study directed toward the synthesis of proposed structures for senoxydene.[154] Enones (**187a**) and (**187c**) cyclize cleanly to give (**188a**) and (**188c**); (**187b**) does not give (**188b**). Mandville and Conia discovered that the enol intermediates could be prepared regioselectively from α-hydroxymethyl ketones.[151] Flash vacuum pyrolysis of (**189**) at 650 °C gives (**190**) which reacts further to give (**191**) in 99% yield.



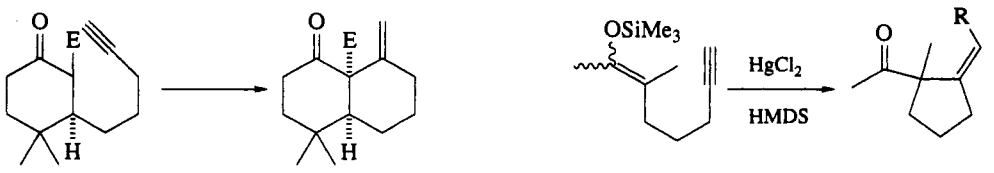
(185) (186) (187) **a**: $R^1 = R^3 = H$; $R^2 = Me$ (188)
b: $R^2 = R^3 = H$; $R^1 = Me$
c: $R^1 = R^2 = H$; $R^3 = Me$



(189) (190) (191)

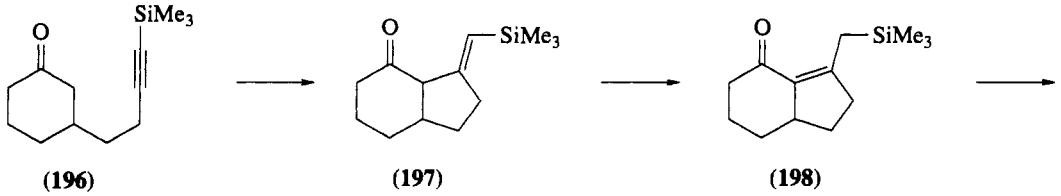
A major advance in the past decade has been the development of catalysts for the cyclization of alkynic ketones. Jackson and Ley found that (**192**) cyclizes to (**193**) in quantitative yield on heating at 280 °C, treatment with ZnI_2 in toluene at reflux or treatment with $SnCl_4$ in CH_2Cl_2 at 25 °C.[150] Conia has found that double catalysis by H^+ and Hg^{2+} lowers the temperature necessary to achieve cyclization.[152] Treatment of (**178**) with hydrochloric acid and mercury(II) chloride in 1,1,2,2-tetrachloroethane at 110 °C gives the isomer of (**179**) with one endocyclic double bond in 43% yield and the monocyclized product in 23% yield. Improved results were obtained with Hg^{2+} on a solid support.[157]

Drouin, Conia *et al.* have found that these reactions can be carried out under even milder conditions by cyclization of silyl enol ethers of alkynones.[153,155,156,158] Treatment of (**194**), as an (*E*)–(*Z*) mixture, with $HgCl_2$ in CH_2Cl_2 in the presence of hexamethyldisilazene for 30 min at 30 °C gives vinylmercurial (**195**; R = HgCl) in quantitative yield. Cleavage of the carbon–mercury bond can be carried out to give (**195**; R = H, D, CO_2Me, Br or COMe).



(192) E = CO_2Et (193) (194) (195)

Kende has examined a variant of this reaction using trimethylsilylalkynes. Pyrolysis of (**196**) neat at 300 °C for 2 h gives (**197**), which isomerizes to (**198**); the latter undergoes a 1,5-trimethylsilyl shift to give (**199**), which isomerizes to give (**200**) in 60–65% yield.[159] Kende has also developed a 'vinylogous Conia' rearrangement. Pyrolysis of (**201**) for 1.5 h at 285 °C gives (**202**) in 72% yield.[160]

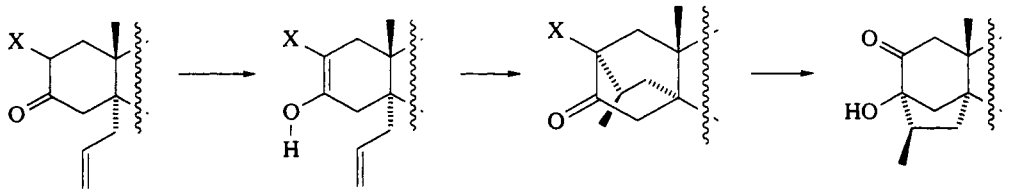


(196) (197) (198)

(199) (200)

(201) (202)

Marples and coworkers have found that ene reactions of unsaturated acyloins occur under much milder conditions than for the corresponding unsaturated ketones.[161–163] Pyrolysis of (**203a**) at 110 °C for 18 h gives (**205a**) in 33% yield and (**206**) in 6% yield. Tautomerization of (**203a**) gives ene diol (**204a**) in which either enol can act as the ene component to give ene adducts (**205a**) and the isomer of (**206**) with the opposite stereochemistry at the methyl group. Apparently only ene adduct (**205a**) is formed; acyloin (**206**) is formed by isomerization of (**205a**). Ene reaction of the corresponding ketone requires much higher temperatures. Pyrolysis of the allyl ketone (**203b**) in decalin at 330 °C gives (**205b**) in 79% yield.



(203) **a**: X = OH **b**: X = H (204) (205) (206)

1.1.5 ADDENDUM

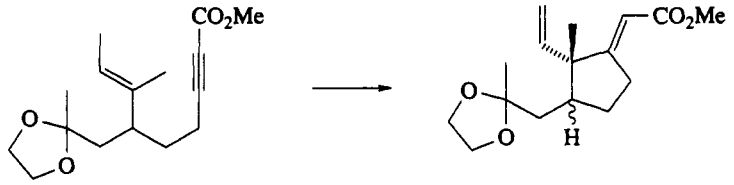
Section 1.1.2.1.2 (i) Acrylate esters. Narasaka and coworkers found that *N*-acryloyloxazolidinone undergoes a [2 + 2] cycloaddition with 1,1-bis(methylthio)ethylene in the presence of $TiCl_2(OPr^i)_2$ and (**213**) to give 74% of the cyclobutane in 88% enantiomeric excess.[164]

Section 1.1.2.1.2 (ii) α,β-Unsaturated ketones and aldehydes. Engler and coworkers found that a 1:1 mixture of $TiCl_4$ and $Ti(OPr^i)_4$ catalyzes the addition of methoxymethyl vinyl ketone to styrenes and methylenecyclohexane to give cyclobutanes.[165]

Section 1.1.3.1 Formation of 1-vinyl-2-alkylcyclopentanes from 1,6-dienes. Nakai and coworkers found that (**207**) undergoes an ene reaction on heating in toluene for 20 h at 200 °C to give 97% of (**208**).[166] The stereochemistry of the enophile does not affect the stereochemistry of the product. The isomer with an (*E*) double bond in the ene component gives mixtures of stereoisomers.

(**207**) (**208**)

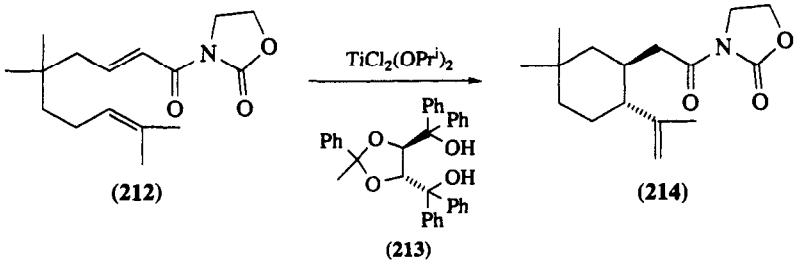
Section 1.1.3.2 Formation of 1-vinyl-2-alkylidinecyclopentanes from 1,6-enynes. Nakai and coworkers reported that pyrolysis of (**209**) in toluene for 90 h at 170 °C gives 86% of a 4:1 mixture of ene adducts (**210**) and (**211**).[167] The major isomer (**210**) was converted to a steroid C/D ring synthon.



(**209**)

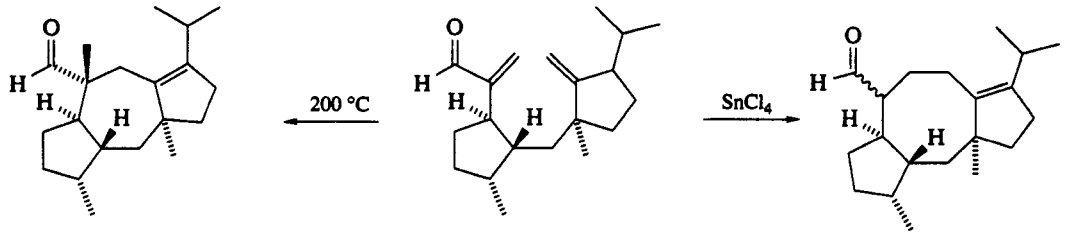
(**210**) α-H
(**211**) β-H

Section 1.1.3.3 Formation of 1-vinyl-2-alkylcyclohexanes from 1,7-dienes. Narasaka demonstrated that the chiral titanium alkoxide prepared from $TiCl_2(OPr^i)_2$ and (**213**) catalyzes the asymmetric intramolecular ene reaction of oxazolidinone (**212**) in Freon 113 at 0 °C to give 63% of ene adduct (**214**) in >98% enantiomeric excess and 25% of the hetero Diels–Alder adduct.[168]



(**212**) (**213**) (**214**)

Section 1.1.3.5 Miscellaneous reactions. Takeshita and coworkers reported the remarkable use of intramolecular ene reactions to form cycloheptanes and cyclooctanes.[169] Pyrolysis of (**216**) in toluene at 200 °C gives 97% of the cycloheptane (**215**). Reaction of (**216**) with $SnCl_4$ in THF gives 85% of cyclooctane (**217**), which is an intermediate in the synthesis of cycloaraneosene.



(215) (216) (217)

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1.2
Metallo-ene Reactions

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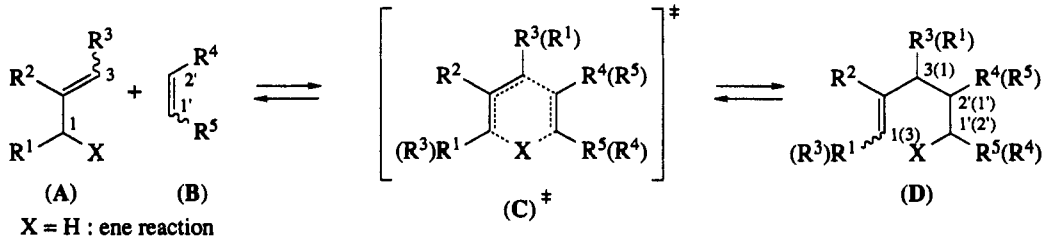
1.2.1 INTRODUCTION

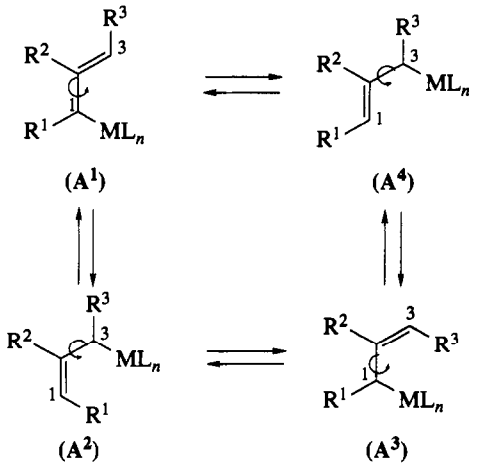
The ene reaction, discovered 45 years ago by Alder,[1] usually involves the thermal reaction of an alkene containing an allylic hydrogen (ene) with an electron-deficient unsaturated compound (enophile) to form 1:1 adducts *via* a cyclic six-electron transition state (*e.g.* **A** + **B** → **C**‡→ **D**; X = H; Scheme 1).



Scheme 1

Starting with a few reports in the early 1960s, additions of allylmetal compounds to alkenes and alkynes became increasingly acknowledged. These reactions resemble the classical ene process (Scheme 1), but involve a transfer of a metal instead of a hydrogen. This analogy prompted Oppolzer to classify transformations like (**A**) + (**B**) → (**D**), with X = metal, as metallo-ene reactions. However, allylmetal

compounds (**A**) have specific properties mainly determined by the metal. This may profoundly influence their reactivity towards enophiles (**B**) and their compatibility with functional groups, as well as the final functionalization of the metallo-ene products (**D**). Furthermore, allylmetal species undergo relatively fast 1,3-metal migrations, $(A^1) \leftrightarrow (A^2) \leftrightarrow (A^3) \leftrightarrow (A^4)$ and $(A^1) \leftrightarrow (A^4)$, also resulting in (*E*)/(*Z*) equilibration (Scheme 2).



Scheme 2

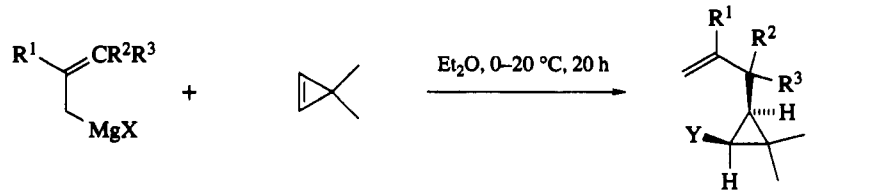
This 1,3-metal shift usually precedes the metallo-ene reaction and thus obscures rationalizations and predictions of the regio- and stereo-chemistry. As to the regiochemistry of metallo-ene reactions involving nonsymmetrical ene (**A**) and enophile units (**B**), the question arises: which enophile (C-1′ or C-2′) or ene terminals (C-1 or C-3) will be joined by the new carbon–carbon bond? Regarding the stereochemistry, it is worth noting that inversion of metalated sp^3 centers C—M can occur either below (M = Mg, Zn, Al, Li) or above (M = Pd, Pt, Ni) the reaction temperature. Hence the suprafacial mode of allylmetal additions permits a C—Pd → C—C chirality transfer and, regardless of the metal, controls the (*E*)/(*Z*) configuration of the vinylmetal moiety which results from an alkyne enophile. Employing alkenic enophile components (**B**) often leads to the generation of stereogenic centers in (**D**) which are linked by the new carbon–carbon bond. These are difficult to control since they depend on the (rapidly equilibrating) (*E*)/(*Z*) configuration of the allylmetal component (**A**) as well as on its orientation towards the enophile unit in the transition state. Several of these problems may be efficiently overcome by employing intramolecular versions which, consequently, are far more attractive and useful in organic synthesis. Given the lack of any comprehensive information, intermolecular metallo-ene reactions will be reviewed in the first part of this chapter.

1.2.2 INTERMOLECULAR METALLO-ENE REACTIONS

1.2.2.1 Magnesium-ene Reactions

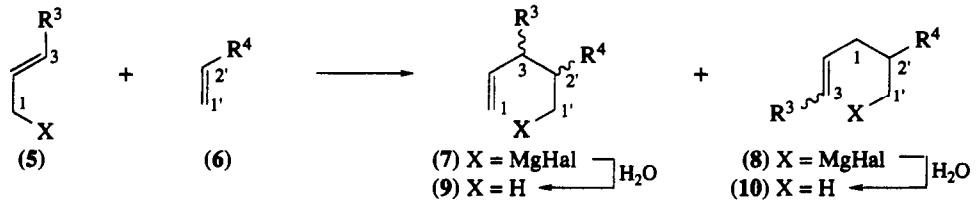
Starting in 1970, the addition of allylic Grignard reagents (**A**; X = MgCl) to alkenes or alkynes has been systematically studied.[2] Kinetic measurements showed negative activation entropies of $\Delta S^{\ddagger} = -18$ to -24 cal K^{-1} mol^{-1} (-75 to -100 J K^{-1} mol^{-1}).[2b] Further evidence for a concerted suprafacial reaction *via* transition state ($C^{\ddagger}$; X = MgL_n) (Scheme 1) was provided by the addition of 2-alkenylmagnesium halides (**1**) to 3,3-dimethylcyclopropene (**2**) at 0–20 °C; subsequent carboxylation with CO_2 yielded *cis*-2-allylcyclopropanecarboxylic acids (**3**) (Scheme 3).[2c] Given that the configuration of a cyclopropyl–magnesium bond is stable and is carboxylated (CO_2) with retention,[3] it thus follows that the allyl unit and the metal are transferred to the same face of cyclopropene (**2**) to furnish intermediates (**3**).

In contrast, bimolecular additions of allylmagnesium halides (**5**) to nonstrained alkenes (**6**) (Scheme 4; Table 1) are notoriously inefficient due to low reaction rates and the formation of regio- and stereoisomer mixtures, as well as uncontrolled consecutive reactions of the metallated addition products (**7**) and (**8**).[2] Only trimethylsilylethylene showed a useful reactivity towards allylic Grignard reagents[2f]



Scheme 3

(1,2-dialkyl-alkenes do not react at all). Therefore it is not surprising that the bimolecular magnesium-ene reaction has received little attention as a strategic tool in organic synthesis.



Scheme 4

Table 1 Additions of Allylmagnesium Halides to 1-Substituted Alkenes Followed by Protonolysis

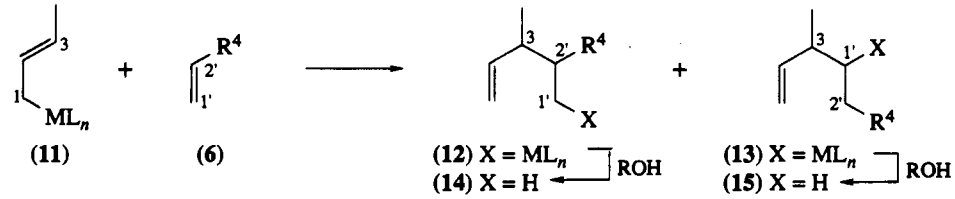
Entry	R^3	R^4	*Hal*	*Reaction temp. (°C) (time, h)*	*Yield*[a] **(9) + (10)** *(%)*	*Ratio* **(9):(10)**
1	H	C_6H_{13}	Cl	100 (48)	2.5 (2)	100:0
2	Me	C_6H_{13}	Cl	100 (48)	32 (11)[b]	91:9[b]
3	H	$CH{=}CH_2$	Br	45 (96)	25 (25)[c]	~100:0[c]
4	H	Ph	Br	100 (3)	51 (25)	28:72
5	H	Ph	Br	100 (6)	39 (39)	19:81
6	H	$SiMe_3$	Cl	90 (48)	47 (45)	96:4
7	Me	$SiMe_3$	Cl	90 (48)	77 (77)	~100:0

[a]Yield based on allylmagnesium halide (in parenthesis based on alkene). [b](9) isolated as a stereoisomer mixture. [c]2:1 mixture of 1,6- and 1,5-heptadienes.

1.2.2.2 Zinc- and Aluminum-ene Reactions

Preformed dicrotylzinc (**11**; ML_n = Zn—CH=CHMe) underwent metallo-ene reactions with terminal alkenes under significantly milder conditions (20–50 °C) to give, after protonolysis, the alkenes (**14**) and (**15**) in 42–100% yield (Scheme 5; Table 2, entries 1–4). However, the regioselectivity was low on additions to 1,3-butadiene and styrene (entries 3, 4).[4]

Allylaluminum reagents, prepared *in situ* from triscrotylborane and triethylaluminum, showed a comparatively higher reactivity (–10 to 20 °C) and regioselectivity on additions to 1-butene, 1-hexene and styrene yielding, after methanolysis, alkenes (**14**) (entries 5–7, 50–55%).[5] Both zinc- and aluminum-ene reactions suffer from a lack of diastereochemical control.



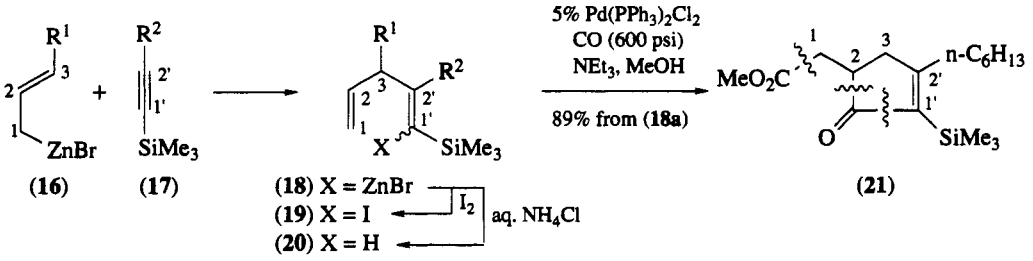
Scheme 5

Table 2 Metallo-ene Reactions of Dicrotylzinc and *In Situ* Prepared Allylaluminum Reagents with Alkenes Followed by Protonolysis

Entry	*R*	*M*	*Reaction temp. (°C) (time, h)*	*Yield* (14) + (15) *(%)*	*Ratio* (14):(15)	*Diastereomer ratio of* (14)
1	H	Zn	20 (20)	~100	99.9:0.1	—
2	C_6H_{13}	Zn	50 (20)	85	~100:0	35:65
3	Ph	Zn	20 (66)	42	33:67	75:25
4	$CH{=}CH_2$	Zn	20 (43)	81[a]	42:58	52:48
5	Et	Al	−10	50	~100:0	75:25
6	Bu	Al	0 (0.5)	55	~100:0	67:33
7	Ph	Al	20	53	91:9	63:37

[a]Reaction mixture contains 3-methyl-1,5-heptadiene (10.2%).

Intermolecular additions of allylzinc halides (**16**) to silylated alkynes (**17**) are apparently facilitated by the silyl group (Scheme 6; Table 3). This substituent also governs the regiochemistry as it directs the metal transfer to the silylated carbon, yielding the non-isolated 1,1-dimetalloalkene products (**18**). Selective replacement of the zinc atom by iodination or protonolysis gave dienylsilanes (**19**) or (**20**).[6] These products may be useful in synthesis, as illustrated by the Pd-catalyzed carbon monoxide insertion sequence (**19a**) → (**21**).[6c] It is also worth mentioning that crotylzinc chloride (**16b**) formed the new C—C bond at the more substituted terminal C-3, in keeping with a six-centered transition state (**C**)‡ (the presence of Cp_2ZrCl_2 led to exclusive C—C bond formation at C-1 which was attributed to a four-centered insertion mechanism[6a]). As to the (*E*)/(*Z*) configuration of the *gem*-dimetallated alkenic bond in (**18**), the products (**19**) and (**20**) indicate an initial *cis* addition process (entries 1–5); in contrast, the less-reactive branched enophiles (**17f–h**) require prolonged heating, which seems to result in a *cis*/*trans* isomerization of the intermediates (**18**) to furnish products corresponding to a net *trans* addition topicity (entries 6–8). The even more congested alkyne (**17i**) is completely unreactive (entry 9).



Scheme 6

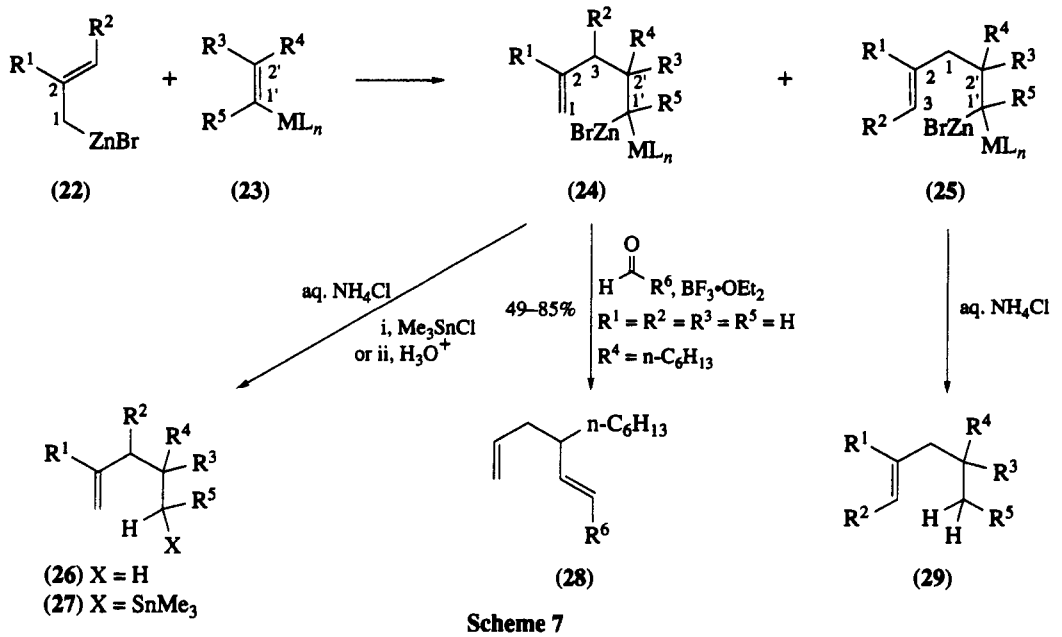
Table 3 Zinc-ene Reactions of 1-Trimethylsilylacetylenes

Entry	R^1	R^2	*Reaction temp. (°C)*	*Product*	*Yield*[a] *(%)*	*Stereoisomer ratio*[c]
1 **a**	H	$(CH_2)_5Me$	60	(**19a**)	83	85:15
2 **b**	Me	$(CH_2)_5Me$	—[b]	(**20b**)	68	90:10
3 **c**	H	$(CH_2)_3Me$	67	(**20c**)	70 (85)	85:15
4 **d**	H	$(CH_2)_3Cl$	67	(**20d**)	63 (80)	81:19
5 **e**	H	Ph	r.t.	(**20e**)	(78)	>95:<5
6 **f**	H	$CH(OBn)(CH_2)_3Me$	67	(**20f**)	(74)	<5:>95
7 **g**	H	$CH(OSiMe_3)(CH_2)_3Me$	67	(**20g**)	(52)	<5:>95
8 **h**	H	$C(Me){=}CH_2$	67	(**20h**)	(57)	<5:>95
9 **i**	H	Bu^t	67	(**20i**)	0	—

[a]Yields in parenthesis determined by GC. [b]Not reported. [c]$R^2/SiMe_3$ *cis*:*trans*.

A related approach to 1,1-dimetallated compounds relies on the allylation of 1-alkenyl-magnesium, -lithium, and -aluminum derivatives (**23**) with allylzinc bromides (**22**), which proceeds readily at 35 °C (Scheme 7; Table 4).[7] The resulting *gem*-dimetallic intermediates can be trapped by protonation (**24** → **26**, **25** → **29**), stannylation (**24** → **27**) or, more interestingly, with aldehydes in the presence of $BF_3{\cdot}OEt_2$ (*e.g.* **24a** → **28**). The dimetallated species (**24**) were also trapped with alkylidene malonates, I_2/H_3O^+,

MeSSMe/H_3O^+ or MeSSMe/allyl bromides.[7c] Regarding the regioselectivity of the addition process, it appears that the nature of the C-3 substituent R^2 in the allylzinc bromides (**22**) may direct the enophile attack either to C-3 (R^2 = Me, OEt, entries 4, 5, 11) or to C-1 (R^2 = $SiMe_3$, entry 10).[7b]



Scheme 7

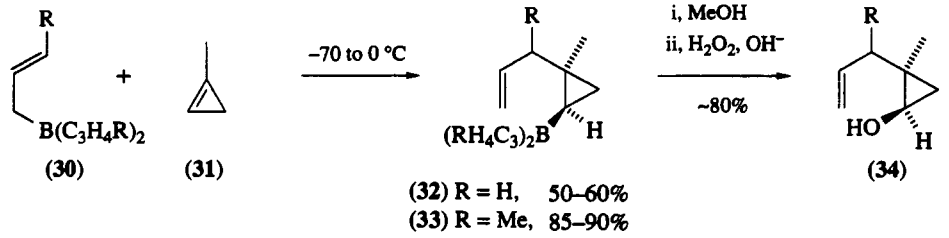
Table 4 Additions of Allylzinc Bromides to 1-Alkenyl-magnesium, -lithium and -aluminum Derivatives

Entry	R^1	R^2	R^3	R^4	R^5	ML_n	*Ratio* (**24**):(**25**)	*Final Product*	*Yield (%)*	*(E):(Z) ratio*
1 **a**	H	H	H	C_6H_{13}	H	MgBr	—	(**26**) = (**29**)	93	—
2 **a**	H	H	H	C_6H_{13}	H	MgBr	—	(**28**; R^6 = C_5H_{11})	75	94:6
3 **b**	Me	H	H	C_6H_{13}	H	MgBr	—	(**26**) = (**29**)	92	—
4 **c**	H	Me	H	C_6H_{13}	H	MgBr	100:0	(**26**)[a]	82	—
5 **d**	H	Me	H	H	$SiEt_3$	MgBr	100:0	(**26**)	83	—
6 **e**	H	H	Me	H	H	MgBr	—	(**26**) = (**29**)	58	—
7 **f**	H	H	Me	Me	H	MgBr	—	(**27**)	69	—
8 **g**	H	H	H	C_6H_{13}	H	Li[b]	—	(**26**) = (**29**)	90	—
9 **h**	H	H	C_6H_{13}	H	H	$AlEt_2$	—	(**26**) = (**29**)	71	—
10 **i**	H	$SiMe_3$	H	C_6H_{13}	H	MgBr	0:100	(**29**)	96	91:9
11 **j**	H	OEt	H	C_6H_{13}	H	MgBr	100:0	(**26**)[a]	65	—

[a]Diastereoisomer ratios of products (*E*:*Z* ratios of **23**): (**26c**), 70:30 (9:1); (**26j**), 86:14 (12:88). [b]Reaction conditions: 5 °C, 15 h.

1.2.2.3 Boron-ene Reactions

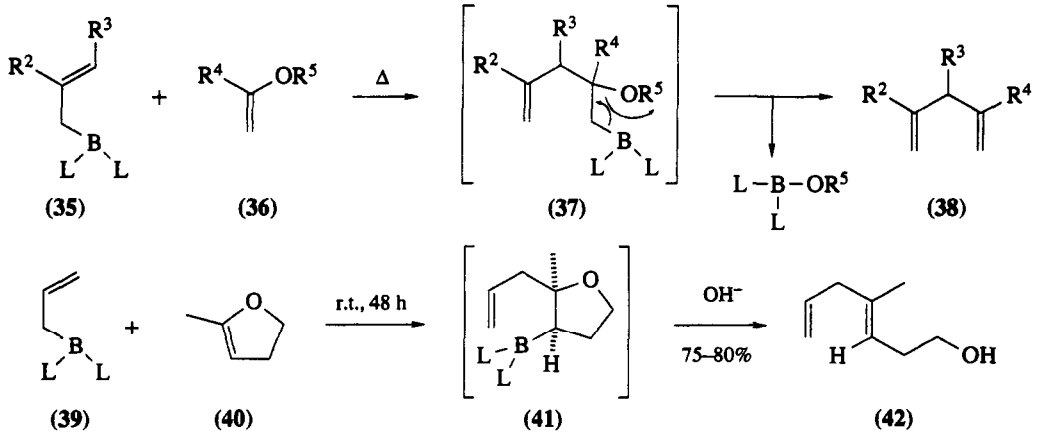
Triallylboranes (**30**) add to 1-methylcyclopropene (**31**) with participation of up to two allyl groups at low temperature in a *cis* fashion. The resulting isolable cyclopropylboranes (**32**) and (**33**) afforded *cis*-allylcyclopropanols (**34**) on methanolysis/oxidation (Scheme 8).[8]



(**32**) R = H, 50–60%
(**33**) R = Me, 85–90%

Scheme 8

Analogous boron-ene addition to enol ethers (**36**) requires 110–140 °C. Under these harsh conditions the initially formed 2-alkoxyboranes (**37**) undergo a spontaneous β-elimination to furnish 1,4-dienes (**38**) in good yields (Scheme 9; Table 5).[9] Application of this *cis*-metallo-allylation/*syn*-elimination sequence to cyclic enol ethers provides a stereocontrolled access to 1,4-dienols containing a trisubstituted alkenic bond, as illustrated by the transformation (**39**) + (**40**) → (**42**) (Scheme 9).

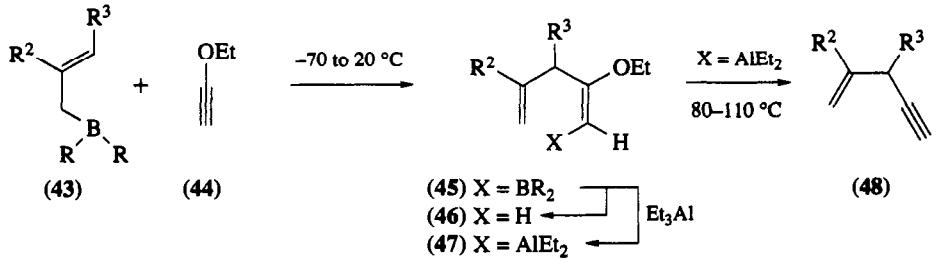


Scheme 9

Table 5 Boron-ene Reactions of Enol Ethers: Preparation of 1,4-Dienes (**38**)

Entry	R^2	R^3	R^4	R^5	*Reaction temp.* (°C)	*Yield* (%)
1 **a**	H	H	H	Bu	110–140	80
2 **b**	H	Me	H	Bu	120–135	50
3 **c**	Me	H	H	Bu	120–140	80–90
4 **d**	H	H	Me	Et	135	75–85

Enophile activation by an alkoxy substituent was also observed with the particularly smooth and *cis* stereospecific additions of dialkylallylboranes (**43**) to ethoxyacetylene (**44**).[10] The resulting dienylboranes (**45**) are interesting polyfunctional building blocks and provide 2-ethoxy-1,4-dienes (**46**) or 1,4-enynes (**48**) (75–81%) by protonolysis or alumination/elimination (Scheme 10; Table 6).



Scheme 10

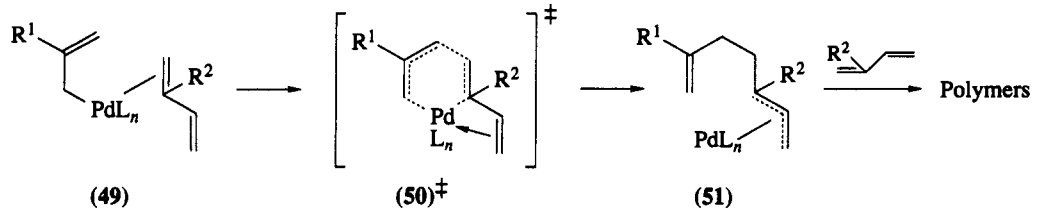
Table 6 Boron-ene Reactions of Ethoxyacetylene: Preparation of 2-Ethoxy-1,4-dienes and 1,4-Enynes

Entry	R^2	R^3	*Reaction* (**43**) + (**44**) → (**45**) *temp.* (°C)	*Yield of* (**46**)[a] (%)	*Yield of* (**48**)[a] (%)
1 **a**	H	H	–70 to 0	80–96	75
2 **b**	Me	H	–70 to 20	75–90	80
3 **c**	H	Me	0 to 20	90–95	81

[a]Yield based on allylborane.

1.2.2.4 Palladium- and Nickel-ene Reactions

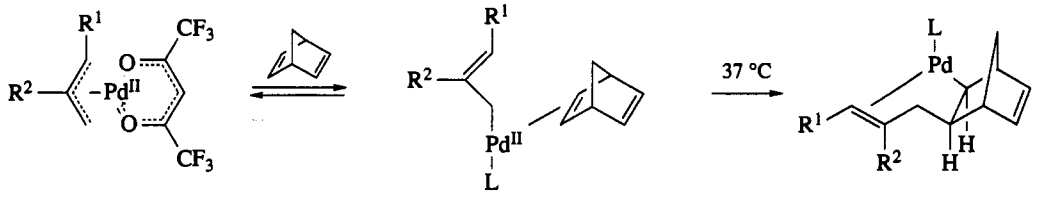
Metallo-ene reactions involving the transfer of palladium and nickel have been described since the early 1960s, mostly in connection with their crucial role in the Pd- and Ni-catalyzed polymerization of butadiene.[11] Hence, insertions of 1,3-dienes into allylpalladium compounds were extensively studied.[12] Thus preformed allylic complexes (**49**) underwent the metallo-ene reactions (**49**) → (**51**) at 20 °C (20 h) or 35 °C (<5 min) or 70 °C (1 h); the reaction rate depended on the substituents R^1 and R^2 as well as on the ligand L and decreased in the order R^1 = Cl > H > Me; R^2 = H > Me; L = F_6acac > acac > Cl. Further diene insertion into the resulting allylpalladium product (**51**) (polymerization) was generally slower than the initial step (**49**) → (**51**) and again relies on the nature of the ligand L (Scheme 11).[12b]



(**49**) (**50**)‡ (**51**)

Scheme 11

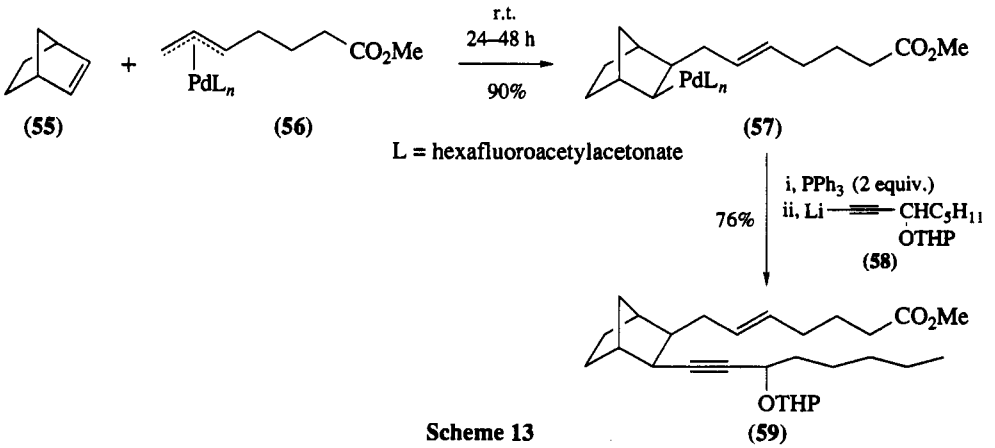
Additional regio- and stereo-chemical information was obtained from palladium-ene reactions of strained alkenes. An instructive example is the reaction of stoichiometric amounts of the allylpalladium species (**52**) which undergo rapid, reversible formation of the σ-allylpalladium–norbornadiene complexes (**53**) to give at 37 °C the *cis* insertion products (**54**) (Scheme 12). Carbon–carbon bond formation (at the least substituted allyl terminal) and palladium transfer from the same (*exo*) face of norbornadiene were ascribed[13] to a σ-allypalladium alkene insertion.



(**52**) (**53**) L = hexafluoroacetylacetonate (**54**)

Scheme 12

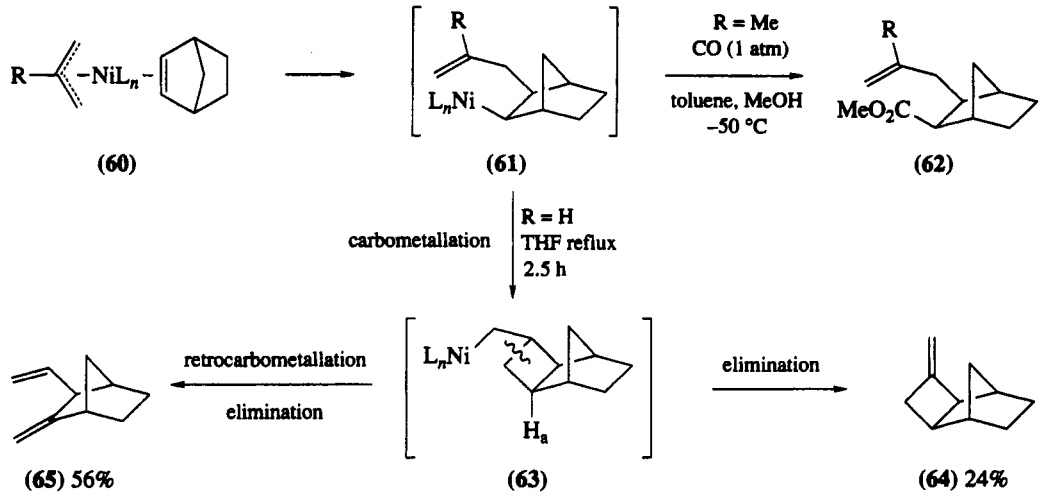
An analogous regio- and stereo-selectivity characterizes the palladium-ene reaction (**55**) + (**56**) → (**57**) which, *via* a coupling of the isolated σ-Pd product (**57**) with the lithium acetylide (**58**), afforded the prostaglandin endoperoxide analogue (**59**) (Scheme 13).[14]



(**55**) (**56**) (**57**)

Scheme 13 (**59**)

Allylnickel species undergo analogous additions to strained alkenes, as exemplified by the *cis* stereospecific metallo-allylation/methoxycarbonylation of norbornene, (**60**) → (**61**) → (**62**), employing a stoichiometric amount of 2-methallylnickel chloride (Scheme 14).[15] The nickel-catalyzed allylation (**60**) → (**61**) was accomplished on heating allyl acetate, norbornene and $Ni\{P(OPr^i)_3\}_4$ (2 mol %) in THF. The isolated products (**64**) and (**65**) (80% overall) result apparently from (**61**) *via* carbometallation, retrocarbometallation and β-elimination processes.[16]

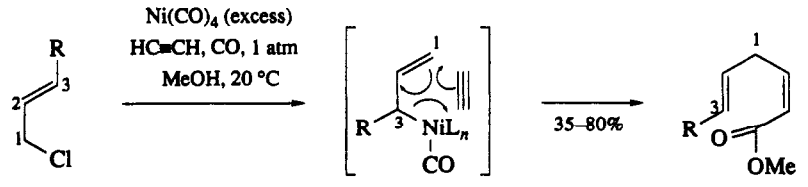


(**60**) (**61**) (**62**)

(**65**) 56% (**63**) (**64**) 24%

Scheme 14

Tetracarbonylnickel is an inexpensive (although toxic) source of Ni^0 and its use for the *in situ* generation of allylnickel intermediates dates back at least 25 years. In fact, the nickel allylation/methoxycarbonylation of alkynes with allyl chloride and an excess of $Ni(CO)_4$ in methanol has been reviewed (Scheme 15).[17] Accordingly, dienoates (**68**) (35–80%) were obtained in a regio- and stereo-selective manner corresponding to a metallo-ene *cis* addition of an allylnickel compound at the less-substituted terminal C-1 of (**67**), followed by a CO insertion into the resulting vinylnickel species. The dienyl esters (**68**) were accompanied by variable amounts of cyclopentenones, indicating the possibility of consecutive CO insertion processes.

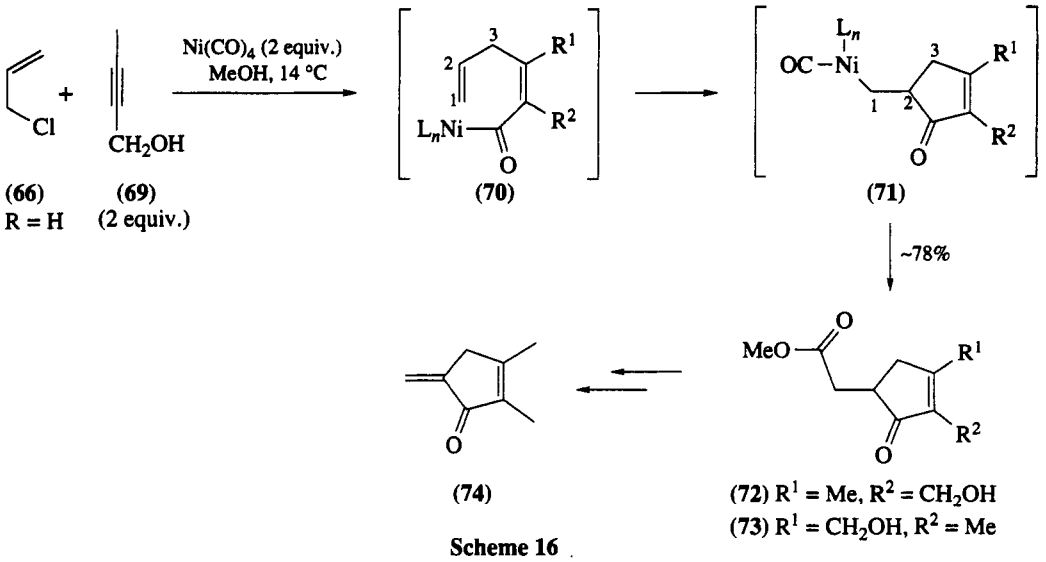


(**66**) (**67**) (**68**)

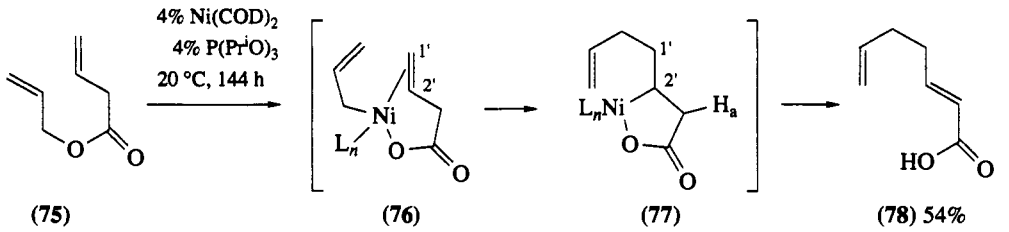
Scheme 15

A recent synthesis of methylenomycin-B (**74**), based on these observations, features an allylation/carbonylation (**69**) → (**70**) followed by a C-1—C-2 bond/nickel acyl insertion (**70**) → (**71**) and a final methoxycarbonylation (**71**) → (**72**). Thus 2-butyn-1-ol (1,2-dialkylacetylenes are inert) afforded in one synthetic operation a 1:4 mixture (78%) of regioisomeric cyclopentenones (**72**) and (**73**) which was converted to the antibiotic (**74**) (Scheme 16).[18]

An interesting example of anchimeric assistance is the catalytic isomerization of allyl 3-butenoate (**75**) to (*E*)-2,6-heptadienoic acid (**78**), which proceeded at 20 °C with 4 mol % of an equimolar mixture of $Ni(COD)_2/P(OPr^i)_3$. It seems that the appropriately placed carboxylate substituent serves as a ligand for Ni^{II}, facilitating the transformation (**76**) → (**77**); a subsequent β-elimination of H_a leads to (**78**) with concomitant regeneration of the Ni^0 catalyst (Scheme 17).[19]



Scheme 16



Scheme 17

1.2.3 INTRAMOLECULAR METALLO-ENE REACTIONS

1.2.3.1 General

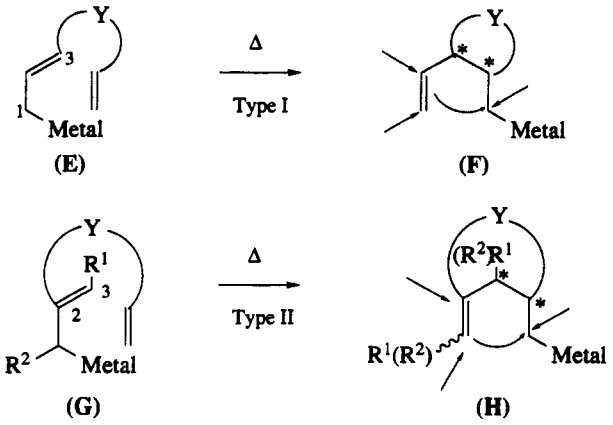
Intermolecular metallo-ene reactions have received until now virtually no attention as a method in target-oriented organic synthesis despite the extensive work and interesting prospects. Problems of regio- and stereo-selectivity and overall efficiency seem to limit their applicability to specifically activated enophiles.

In contrast, intramolecular versions of the metallo-ene process may be regio- and stereo-selective as well as entropically favored and are thus more efficient, similar to intramolecular ene reactions (Volume 5, Chapter 1.1)[20] and [4 + 2] cycloadditions (Volume 5, Chapter 4.4).[21] This holds for two different modes of cyclization in which the enophile is linked by a suitable bridge, either to the terminal carbon atom C-3 (type I) or to the central carbon atom C-2 (type II) of the metallo-ene unit (Scheme 18). The propensity of the cyclized alkylmetal intermediates (**F**) and (**H**) for further functionalizations and cyclizations, involving the metallated and two alkenic sites, offers a considerable potential in organic synthesis.

1.2.3.2 Intramolecular Magnesium-, Zinc- and Lithium-ene Reactions

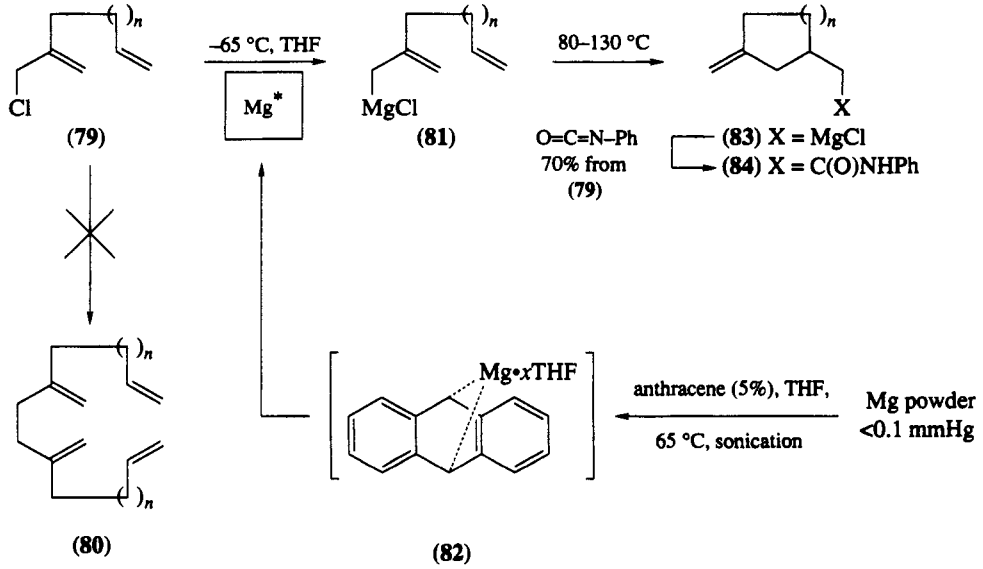
Essential for the practicality of (inter- and) intra-molecular magnesium-ene processes was a convenient preparation of the 2-alkenylmagnesium precursors (**E**) and (**G**) (Scheme 18, with metal = Mg). In particular, the conventional treatment of allylic halides with Mg turnings in Et_2O frequently led to coupling products, *e.g.* (**79**) → (**80**) (Scheme 19).

Magnesium, activated by evaporation[22a] or, much more conveniently, by sonication with anthracene (5%),[22b] usually accomplished the metallation of 2-alkenyl chlorides, *e.g.* (**79**) → (**81**), at –65 °C in THF



Type I : enophilic chain linked to terminal carbon of ene unit (C-3)
Type II : enophilic chain linked to central carbon of ene unit (C-2)

Scheme 18



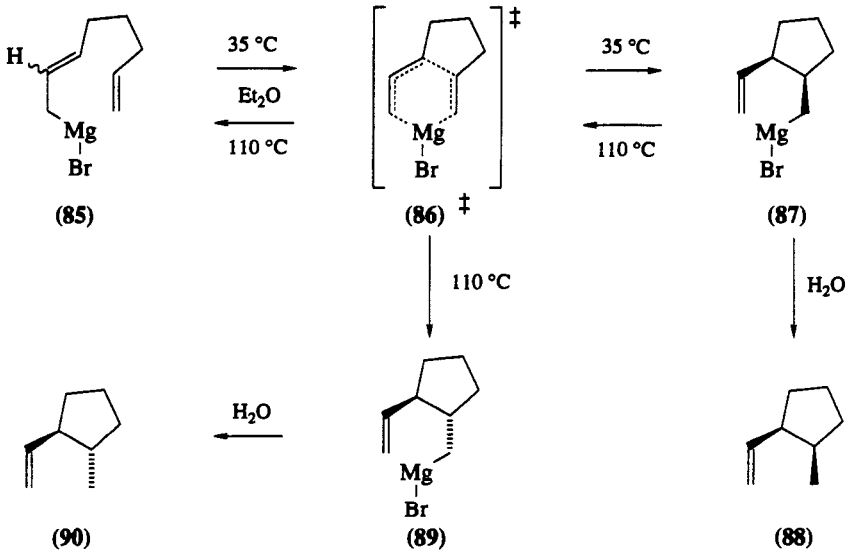
Scheme 19

without significant coupling.[22c] The resulting clean, alkali metal and alkali halide free solutions of Grignard reagents (**81**) are compatible with the thermal cyclization/trapping sequence (**81**) → (**83**) → (**84**).[22c]

1.2.3.2.1 Type I cyclizations

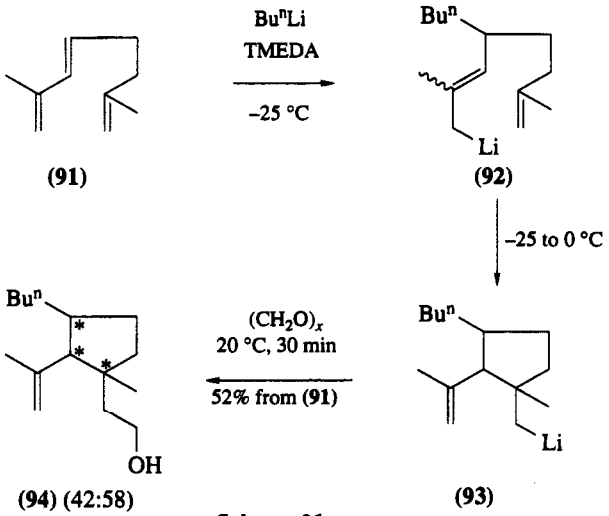
(i) Initial Studies

The first encouraging example of an intramolecular type I magnesium-ene reaction dates back to 1972. As described by Felkin *et al.*, [23a] 2,7-octadienylmagnesium bromide (**85**) cyclized in boiling Et_2O to give, after aqueous work-up, selectively *cis*-2-methylvinylcyclopentane (**88**) in 67% yield (Scheme 20). Heating the solution of the transient Grignard product (**87**) to 110 °C (sealed tube, 24 h) furnished, after hydrolysis, mainly the thermodynamically more stable *trans*-cyclopentane (**90**) (**90:88** > 11:1), indicating the reversibility of the cyclization (**85**) ↔ (**87**) at a higher temperature.[23b] It is worth noting that (**85**) could be obtained *in situ* from 1,3-butadiene, Pr^nMgBr and $(PPh_3)_2NiCl_2$ (2 mol %) and that (**87**) and (**89**) were also trapped by D_2O or acetone. The conversion (**85**) → (**87**) was also reported in a patent.[23c]



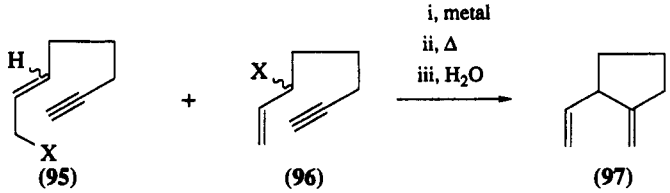
Scheme 20

Two years later, the transformation of the isoprene dimer (**91**) to (**94**) (mixture of stereoisomers) was observed and interpreted as a conjugate addition of Bu^nLi to diene (**91**) followed by a (surprisingly smooth) intramolecular lithium-ene addition (**92**) → (**93**) (Scheme 21).[24]



Scheme 21

A comparative study demonstrated the moderate efficiency of a metallation/cyclization/hydrolysis reaction sequence of enynyl bromides, (**95**) + (**96**) → (**97**), which obviously implies intramolecular zinc- and magnesium-ene additions to a terminal alkyne unit (Scheme 22; Table 7).[25]



Scheme 22

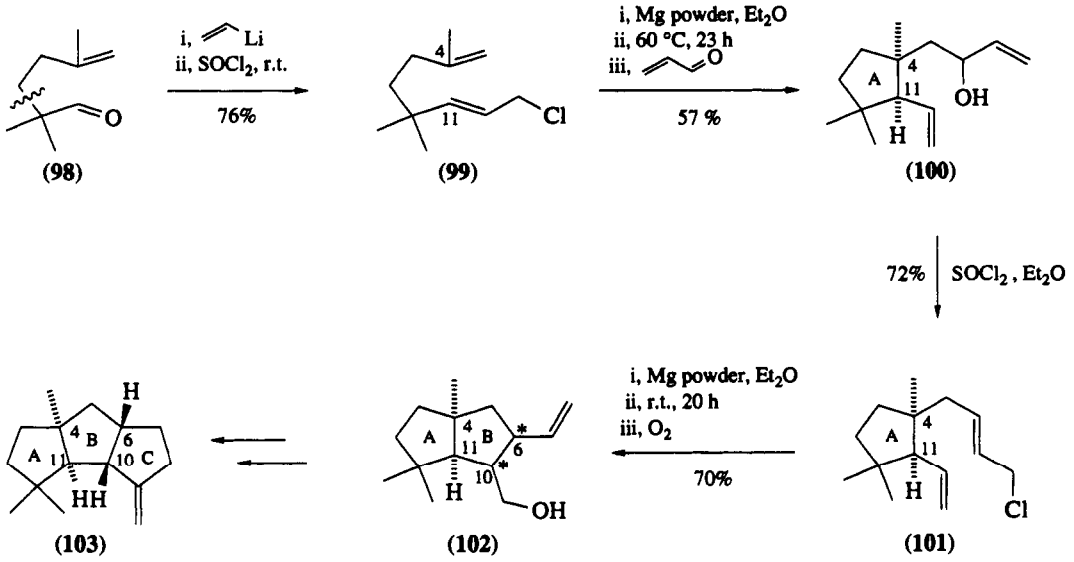
Table 7 Intramolecular Zinc- and Magnesium-ene Reactions of Alkynes

Leaving Group X	*Metal*	*Solvent*	*Temp.* (°C) *(time,* h)	*Yield* (97) *(%)*
Br	Zn	THF	20 (2)	43
Br	Mg	Et_2O	reflux (2)	15

(ii) Applications to Syntheses of Natural Products

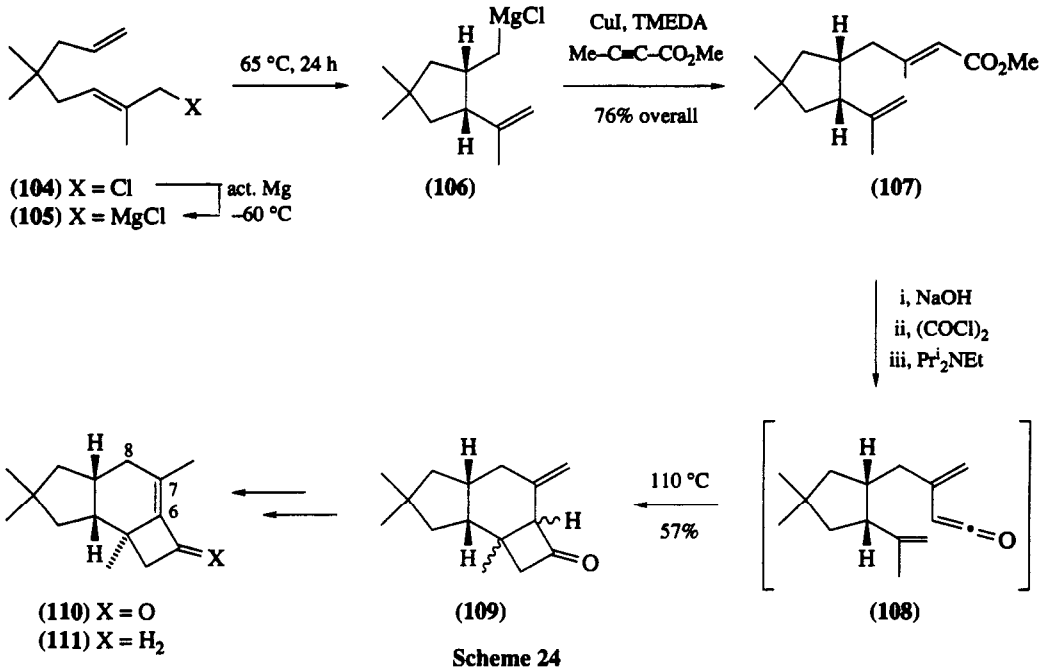
After these more or less isolated reports it was the challenge of natural product synthesis that spurred the most relevant exploration and extensions of the intramolecular magnesium-ene reaction. Its strategic role in synthesis is also illustrated by the following examples.

The synthesis of $\Delta^{9(12)}$-capnellene (**103**), published in 1982,[26] addressed the issue of rendering this process iterative to assemble progressively polycyclopentanoid systems (Scheme 23). Thus in the first key step (**99**) → (**100**) the congested bond between C-4 and C-11 was formed with high stereochemical control, whilst trapping of the cyclized Grignard intermediate with acrolein set the stage for the second magnesium-ene cyclization which occurs at room temperature. Scavenging the bicyclic magnesium-ene product with oxygen furnished alcohol (**102**) as a 3:2 mixture of stereoisomers. This kinetically derived lack of diastereoselection was of minor importance since the remaining closure of ring c was accomplished by an intramolecular aldolization with thermodynamic control over the configuration at C-6 and/or at C-10. Hence the mixture (**102**) was channelled efficiently into the pure *cis-anti-cis*-triquinane (**103**).



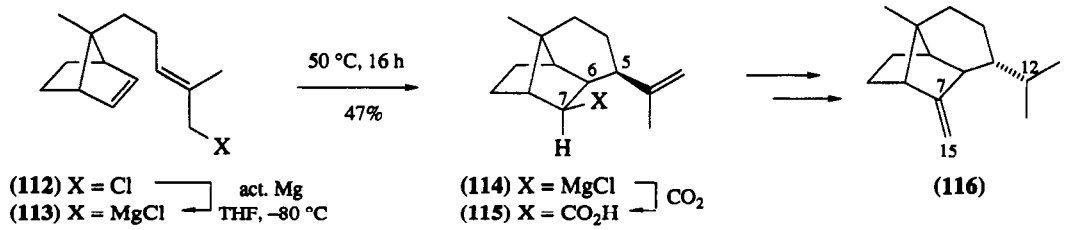
Scheme 23

Highly diastereocontrolled formation of a *cis*-1,2-disubstituted five-membered ring was again observed in the key step (**105**) → (**106**) of the synthesis of (±)-6-protoilludene (**111**) (Scheme 24).[27] Copper-promoted trapping of the cyclized organomagnesium species (**106**) by 1,4-addition to methyl 2-butynoate furnished the conjugated ester (**107**) in one synthetic operation from (**104**) (76%). The thus generated 1,2-*cis*-disposed functionalities in (**107**) were ideally suited to form the remaining six- and four-membered rings simultaneously by an intramolecular vinylketene/alkene cycloaddition (**108**) → (**109**) (*cf.* Volume 5, Chapter 2.1). The carbonyl group in (**109**) (chromatographically purified) furthermore directed the alkene bond into the 6/7-position (instead of the otherwise favored 7/8-position). Although the [2 + 2] addition (**108**) → (**109**) did not show the desired high stereoselectivity, this approach to the protoilludene skeleton (**109**) in only 2–3 synthetic operations from the readily available acyclic diene (**104**) exemplifies the general potential of magnesium-ene cyclizations when coupled with cycloaddition processes.



Scheme 24

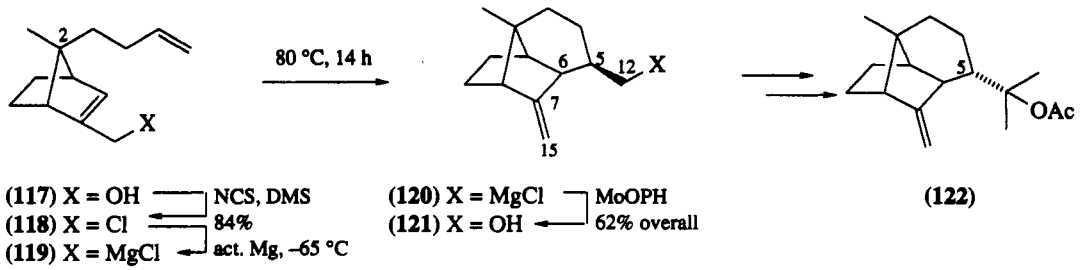
Another approach to an unusual sesquiterpene, sinularene (**116**),[28] involves the diastereocontrolled formation of a six-membered ring by a magnesium-ene process (Scheme 25). Successive treatment of allylic chloride (**112**) with activated magnesium, heating to 50 °C and CO_2 trapping led to the formation of the bond between C-5 and C-6 as well as that between C-7 and C-15, giving the crystalline carboxylic acid (**115**) (47% overall) in a single operation. In this case, however, the kinetically controlled *cis* relation of magnesium donor and acceptor sites in (**114**) required an epimerization at C-5 at a later stage of the synthesis of the target molecule (**116**).



Scheme 25

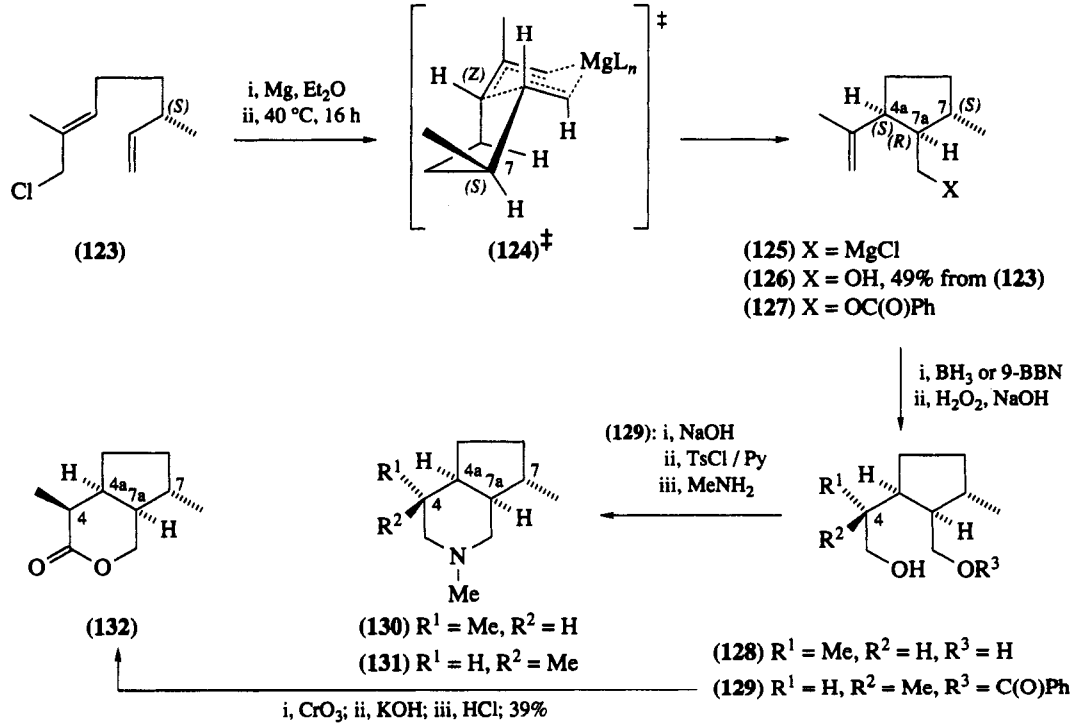
A related synthesis of 12-acetoxysinularene (**122**)[29] differs in that the magnesium-ene unit is part of the norbornene skeleton which carries the enophilic chain at C-2 (Scheme 26). Hence, by reversing the relative position of the reaction partners the bond between C-5 and C-6 was closed in the key step (**119**) → (**120**) with simultaneous formation of both the C-7/C-15 methylene group and the C-12 Mg functionality. Accordingly, one synthetic operation provided alcohol (**121**) in 62% yield from allyl chloride (**118**) (again the initial *cis* relation of C-12/C-7 was altered thereafter by an epimerization at C-5).

The stereodirecting bias of a preexisting stereogenic center on the intramolecular magnesium-ene reaction is illustrated by the enantioselective syntheses of (+)-α-skytanthine (**130**) and (+)-δ-skytanthine (**131**), as well as of (+)-iridomyrmecine (**132**) (Scheme 27).[30] Allylic chloride (**123**), easily available in 94% enantiomeric purity, was metallated with commercial Mg powder. Heating of the resulting solution under reflux followed by oxidative trapping of (**125**) with MoOPH at –78 °C yielded an 88.4:5.9:3.0:1.4 stereoisomer mixture of cyclized alcohols (58%). The major isomer (**126**), isolated by flash chromatography (49% from (**123**), has the desired (4*aS*,7*aR*) configuration. This result is consistent with a favored transition state (**124**)‡ (with the C-7 methyl group oriented toward the convex face) assuming that 2,3-substituted 2-alkenylmagnesium halides react in their (*Z*)-form (*cf.* Section 1.2.3.2.2 (i)). Stereoconvergent control over the remaining center C-4 was achieved by hydroboration (BH_3)/oxidation of the free



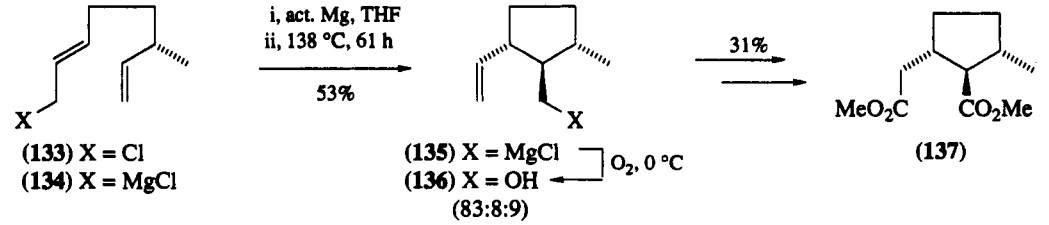
Scheme 26

alcohol (**126**) to give diol (**128**), which was cyclized to give (+)-α-skytanthine (**130**); alternatively, hydroboration (BBN)/oxidation of the benzoate (**127**) furnished predominantly the C-4 epimer (**129**) which was transformed either to (+)-δ-skytanthine (**131**) or to (+)-iridomyrmecine (**132**).



Scheme 27

Whereas all foregoing applications rely on a kinetically determined stereoselectivity of magnesium-ene cyclizations, it is apparently thermodynamic control which governs the cyclization (**134**) → (**135**) at 138 °C over 61 h to give, after oxidative quenching with O_2, an 83:8:9 mixture of stereoisomers. The major 'all-*trans*' alcohol (**136**) was converted to the dimethyl ester of *trans,trans*-boschnialic acid (**137**) (Scheme 28).[31]

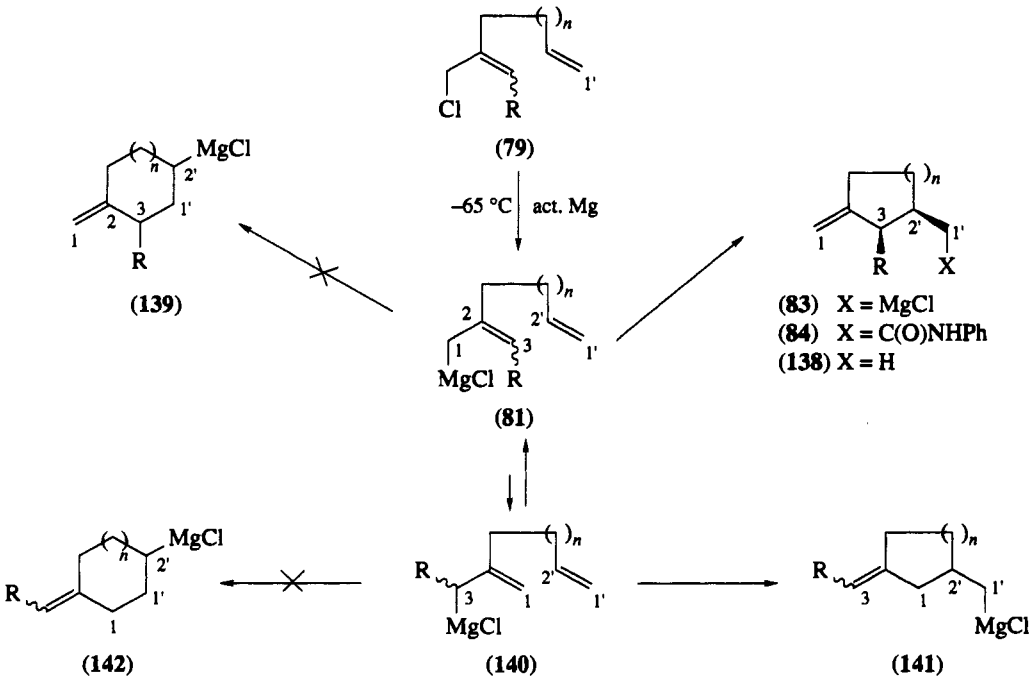


Scheme 28

1.2.3.2.2 Type II cyclizations

(i) Type II Magnesium-ene Cyclizations

This version, in which the enophilic chain is attached to the central atom C-2 of the metallo-ene moiety, was not described until 1982. A systematic investigation dealing with the efficiency, regio- and stereo-selectivity of this reaction (Scheme 29; Table 8)[32] involved heating (2-alkenyl)allylmagnesium chlorides (**81**) followed by quenching of the cyclized Grignard reagents with phenyl isocyanate (entries 1–5) or water (entry 6). It is worth noting that a six-membered ring (entries 2, 5, 6) was formed more readily than a five-membered (entry 1) or a seven-membered ring (entry 4), reflecting the counterplay of entropic and angle strain factors.



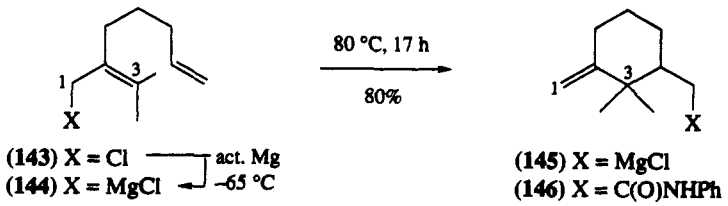
Scheme 29

Table 8 Intramolecular Type II Magnesium-ene Reactions (**79**) → [(**81**) → (**83**)] → (**84**) or (**138**)

Entry	*Bridge length n*	*R*	*Temp.* (°C) *(time,* h)	*Product*	*Yield (%)*
1 **a**	1	H	130 (23)	(**84**)	71
2 **b**	2	H	80 (17)	(**84**)	72
3 **c**	3	H	80 (17)	(**84**)	71
4 **d**	3	Me	90 (60)	(**84**)	40[a]
5 **e**	2	Me	80 (17)	(**84**)	86
6 **f**	2	n-C_6H_{13}	80 (17)	(**138**)	81

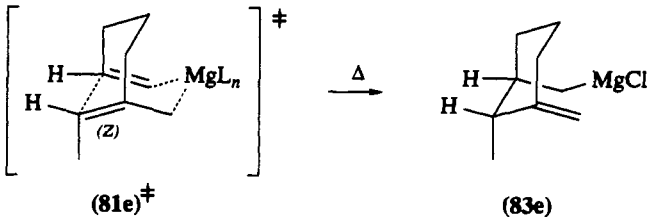
[a]20% of noncyclized dienylanilide isolated.

This study also revealed an astonishing regioselectivity insofar as only products (**84**) or (**138**) (but no isomers derived from **139** or **142**) were observed regardless of the distance between the reactive units. Accordingly, the magnesium was transferred to the distal site C-1′ of the enophile and the new C—C bond was formed at the proximal C-2′ site. As to type II cyclizations of nonsymmetrically substituted magnesium-ene species (entries 4–6), a rapid 1,3-metal migration (**81**) ⇌ (**140**) (*cf.* Scheme 2)[33] leaves two possibilities: C—C bond formation with either the more or less substituted ene terminal C-3 (**81** → **83**) or C-1 (**140** → **141**), of which only the former regiochemistry was observed. Also the 3,3-dimethyl-substituted magnesium-ene component of (**144**) underwent C—C bond formation only to C-3, generating a quaternary center to give (**146**; 80%) (Scheme 30).



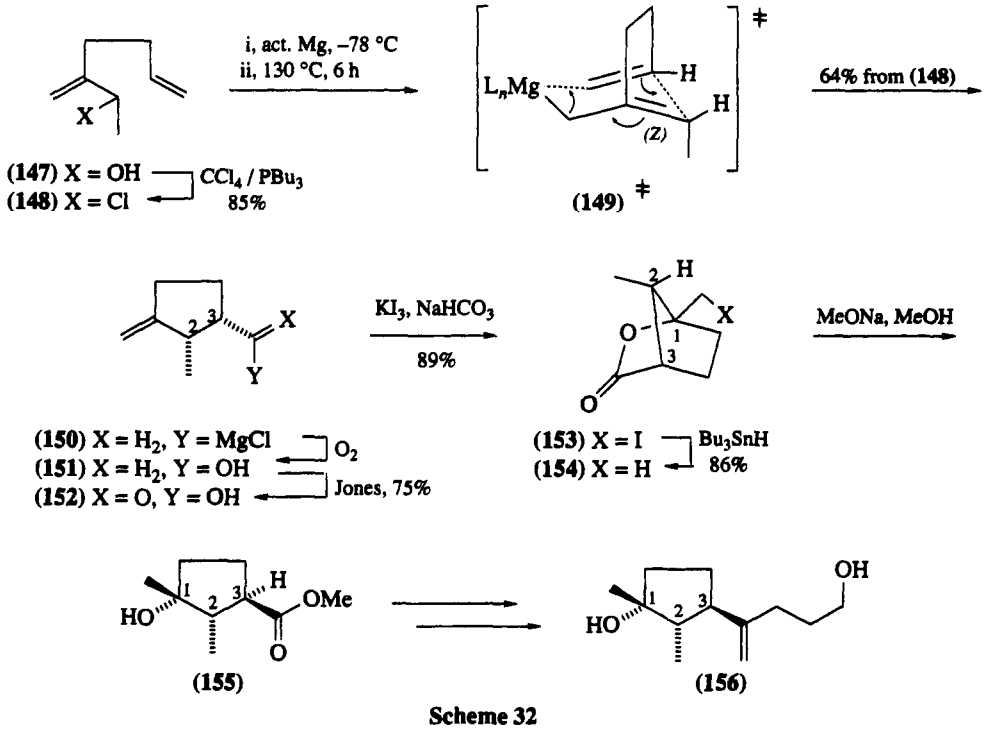
Scheme 30

Focusing on the stereochemistry, it is interesting to note that only *cis* isomers (**84**) and (**138**) were observed; this indicates highly selective alkene 'insertion' into a (*Z*)-ene unit (**81**) (Scheme 31) which is in a rapid equilibrium with (*E*)-(**81**) (*via* the 1,3-Mg shift, **81** ⇌ **140**).



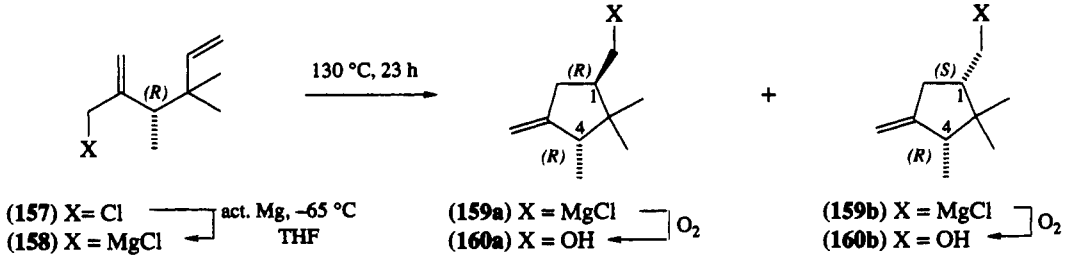
Scheme 31

This type of stereocontrol is featured in a synthesis of the fungitoxin (±)-chokol-A (**156**) (Scheme 32).[34] Alcohol (**147**) (easily prepared from 1-hexen-5-one in two steps) efficiently gave the allyl chloride (**148**) (CCl_4/PBu_3). The metallation/cyclization/oxidation step (**148**) → (**149**)‡→ (**150**) → (**151**) (described in detail) furnished *cis*-cyclopentylmethanol (**151**) (64% from **148** together with 2% of its *trans* epimer and 6% of a positional isomer derived from **141**) which was oxidized to *cis*-carboxylic acid (**152**). Iodolactonization/reduction (**152**) → (**153**) → (**154**) secured the desired *cis* disposition of the *t*-hydroxy (C-1) and *s*-methyl (C-2) groups. Basic methanolysis of lactone (**154**), accompanied by C-3 epimerization, furnished (**155**) with a *trans*-related C-3 methoxycarbonyl substituent which was transformed into the pentenol side chain of (**156**).



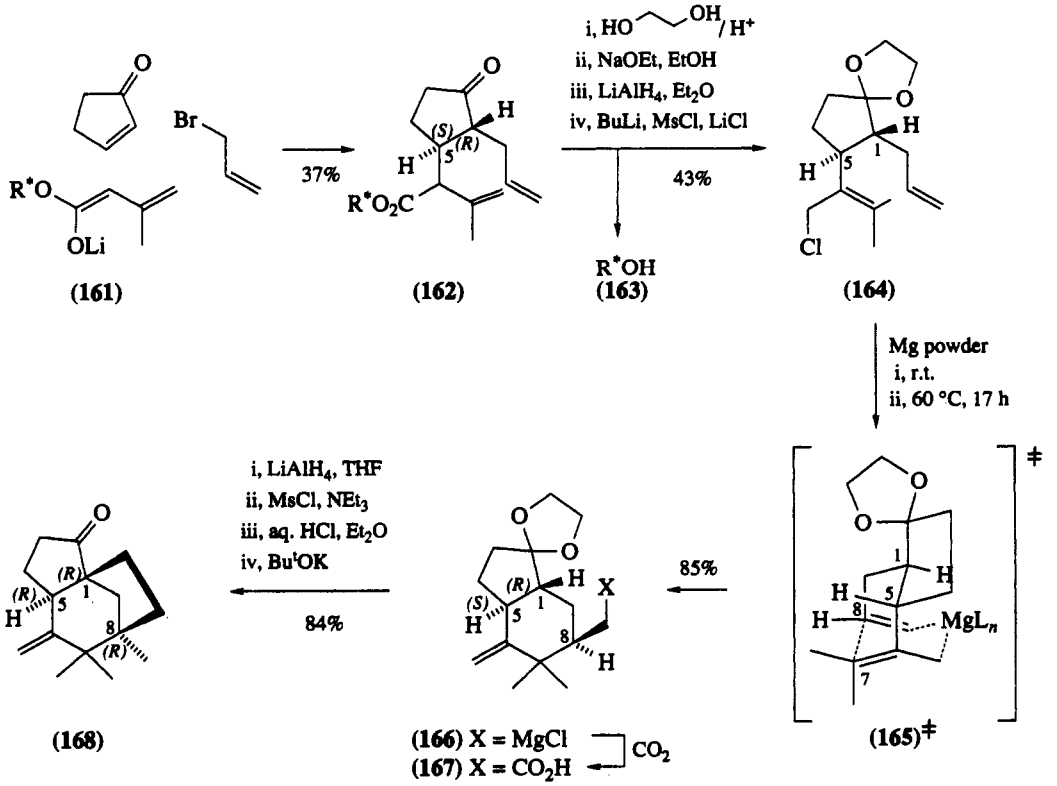
Scheme 32

By contrast, no diastereoselectivity was found in the type II magnesium-ene cyclization/oxidation (**158**) → (**159**) → (**160**), which afforded the carrion beetle defense compound β-necrodol (**160a**) together with its C-1 epimer (**160b**) (61%, 1:1 mixture) (Scheme 33).[35] This is not surprising since the corresponding transition states suffer similar steric crowding due to the *gem*-dimethyl substitution. Nevertheless, (*R*)-(**157**), obtained in enantiomerically pure form *via* a methylcopper addition/Mannich reaction of a chiral *N*-crotonoylsultam, provided, after separation from (**160b**), optically pure β-necrodol (**160a**), thus enabling an assignment of the absolute configuration of the natural product.



Scheme 33

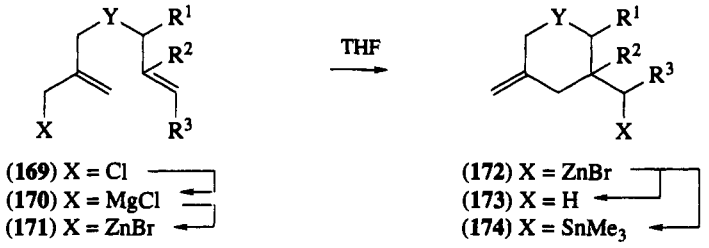
A culmination of the type II magnesium-ene cyclization methodology is its ideal application to the regio-, diastereo- and enantio-selective synthesis of the otherwise elusive, odoriferous norsesquiterpene (+)-khusimone (**168**) (Scheme 34).[36] Conjugate addition of a chiral dienolate (**161**) to cyclopentenone, coupled with enolate trapping by allyl bromide, chromatography and crystallization, directly gave enantiomerically pure (**162**) (37% from cyclopentenone), which was readily converted into allylic chloride (**164**). Slow addition of (**164**) to Mg powder in THF, heating the solution at 60 °C for 17 h and quenching with CO_2 gave, after crystallization, bicyclic carboxylic acid (**167**) (85% from **164**). No regio- or stereo-isomer of (**167**) was found in the mother liquor. This particularly strong bias of the preexisting centers C-5 and C-1 in (**164**) on the generation of stereogenic center C-8 conforms with the sterically least congested transition state (**165**)‡. Hence the magnesium-ene step provided the thermodynamically unstable, encumbered 7,7-dimethyl-6-methylene moiety with perfect control over the chirality at C-8.



Scheme 34

(ii) Type II Zinc-ene Cyclizations

The thermal type II cyclizations of alkenic allylzinc bromides (**171**) show interesting possibilities; the latter were prepared *in situ* from chlorides (**169**) *via* transmetalation of the Grignard intermediates (**170**) with $ZnBr_2$ (1.5 equiv). Quenching of the cyclized alkylzinc species (**172**) with H_2O (→ **173**) or $ClSnMe_3$ (→ **174**) provided oxygen and nitrogen heterocycles (Scheme 35; Table 9).[37] Analogous attempts to cyclize the allylmagnesium chlorides (**170**) failed except for the transformation (**170g**) → (**174g**) (76%). However, the less nucleophilic zinc derivatives (**171**) cyclized readily at 80 °C even with a terminally methyl-substituted alkenyl (although at 130 °C, entry 3) but not with a cyclohexenyl enophile unit (entry 6).



Scheme 35

Table 9 Intramolecular Type II Zinc-ene Reactions Followed by Trapping (**171**) → (**172**) → (**173**) or (**174**) in THF

Entry	*Y*	*R^1*	*R^3*	*R^2*	*Temp.* (°C) *(time,* h)	*Product*	*Yield*[a] *(%)*
1 **a**	O	H	H	H	80 (23)	(**174**)	57
2 **b**	O	H	H	Me	80 (45)	(**173**)	80
3 **c**	O	H	Me	H	130 (22)	(**173**)	50
4 **d**	O	Ph	H	H	80 (48)	(**173**)	76[b]
5 **e**	OCH_2	H	H	H	80 (24)	(**174**)	62
6 **f**	O	—$(CH_2)_3$—		H	130 (24)	(**173**)	0
7 **g**	NMe	H	H	H	80 (24)	(**174**)	64

[a] Based on (**169**). [b] 2:1 *trans/cis* mixture.

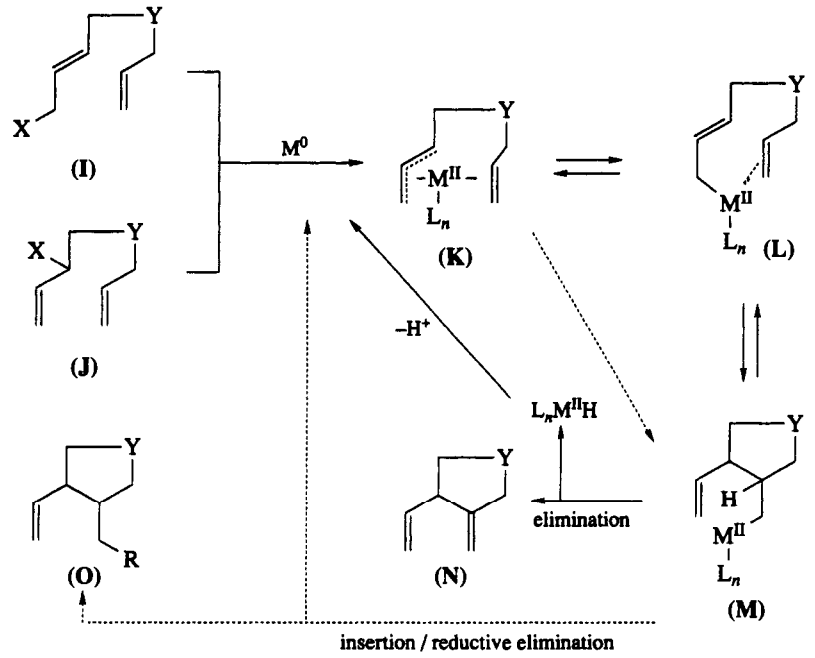
1.2.3.3 Intramolecular Palladium- and Nickel-ene Reactions

1.2.3.3.1 Catalytic type I palladium-ene cyclizations

Whereas stoichiometric additions of allylpalladium species to norbornene and 1,3-dienes are known (*cf.* Section 1.2.2.4), simple alkenes (*e.g.* styrene, cyclohexene, 1,4-cyclohexadiene and 1,5-cyclooctadiene) did not undergo this reaction.[13] However, it can be assumed that the intramolecular ene process (**L**) → (**M**) (Scheme 36) is entropically favored and that a subsequent irreversible β-elimination (**M**) → (**N**) withdraws the ene product (**M**) from the equilibrium (**L**) ⇌ (**M**). Further options are insertion/reductive elimination processes (**M**) → (**O**). The thereby regenerated Pd^0 species should continue the catalytic cycle by oxidative addition to allyl derivatives (**I**) or (**J**) (*e.g.* X = OR), thus providing *in situ* the alkenic allylpalladium intermediates (**K**).

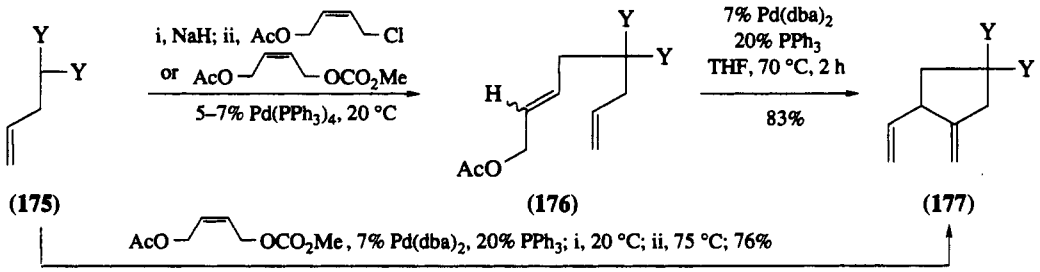
The first example of this concept was published in 1987.[38] Acetoxydienes (**176**) were readily obtained, predominantly as their (*E*) isomers, *via* $Pd(PPh_3)_4$ catalyzed alkylation[39] of disulfones (**175a**; Y = SO_2Ar) or malonates (**175b**; Y = CO_2Me) with 4-acetoxy-2-butenyl methyl carbonate. Heating diene (**176a**; Y = Ts) with $Pd(dba)_2$ (0.07 equiv)/PPh_3 (0.2 equiv) in THF at 70 °C for 2 h gave the expected cyclized 1,4-diene (**177a**; Y = Ts) in 82% yield. Even more conveniently, product (**177a**; Y = Ts) was obtained (76% yield) in one operation from (**175a**) *via* Pd^0 catalyzed alkylation/cyclization (Scheme 37; Table 10, entry 2).[38]

Solvent effects significantly influence this novel ene process, as illustrated by the cyclization of malonate (**176b**) → (**177b**; Y = CO_2Me). Whereas no reaction took place in toluene, dichloromethane or DMF, the rate and yield increased on proceeding from THF (20%) to methanol (65%) to acetic acid (77%; entries 3–5). Interestingly, the presence of the phosphine turned out to be indispensable for the transformation (**176b**) → (**177b**).[38]



X = OAc, OH, OTHP; Y = $C(SO_2Ar)_2$, $C(CO_2Me)_2$, CH_2, NR, O

Scheme 36



Scheme 37

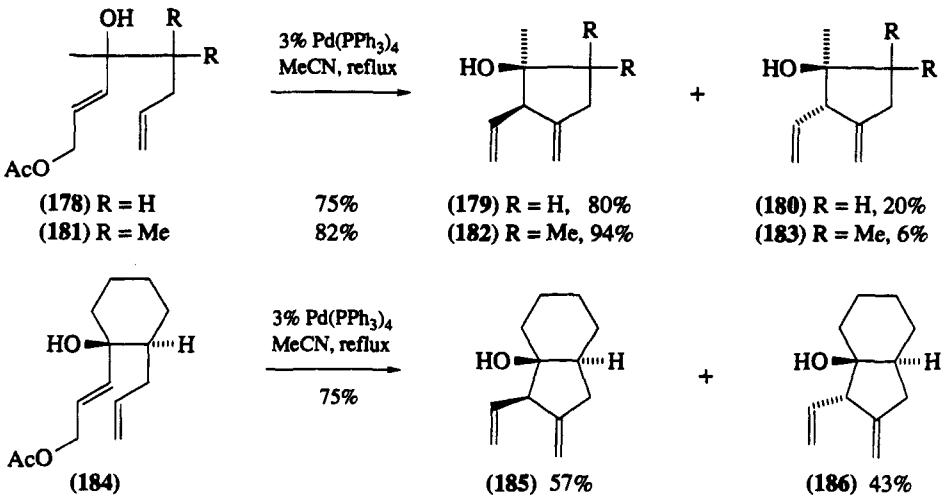
Table 10 $Pd(dba)_2/PPh_3$ Catalyzed Cyclizations (**176**) → (**177**)

Entry	*Y*	*Solvent*	*Reaction temp. (°C) (time, h)*	*Yield of* (**177**) *(%)*
1 **a**	$SO_2C_6H_4Me$-*p*	THF	70 (2)	82
2 **a**	$SO_2C_6H_4Me$-*p*	THF	'1-pot'[a]	76
3 **b**	CO_2Me	THF	80 (40)	20
4 **b**	CO_2Me	MeOH	80 (8)	65
5 **b**	CO_2Me	AcOH	80 (1.5)	77

[a] '1-pot' from (**175a**).

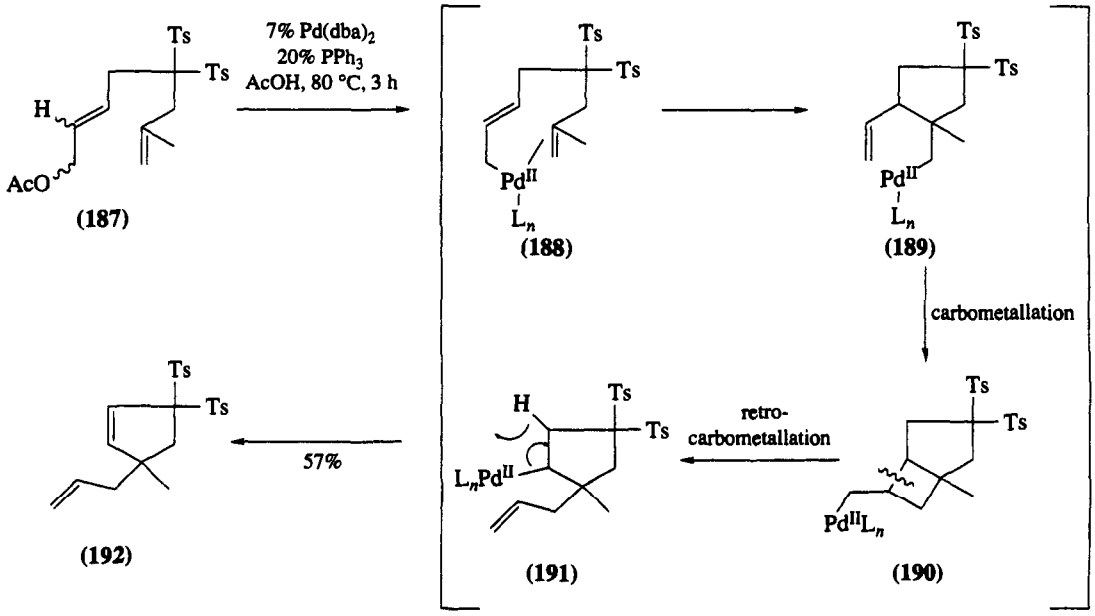
The significance of the medium for this type of reaction accounts also for unsuccessful attempts to achieve Pd^0 catalyzed cyclizations of various 2,7-octadienyl acetates in aprotic solvents. Nevertheless, Pd^0 catalyzed cyclization of 4-alkyl-4-hydroxy-2,7-octadienyl acetates such as (**178**), (**181**) and (**184**) were readily accomplished in boiling acetonitrile.[40] Some of these (presumably hydroxy assisted) ring closures led preferentially to products with *cis*-related hydroxy and vinyl groups, *e.g.* (**179**) and (**182**) (Scheme 38).

Intramolecular insertion of a 1,1-dialkylalkene into an allylpalladium unit (**188**) → (**189**) proceeded under the usual conditions, as illustrated by the cyclization (**187**) → (**192**) (Scheme 39).[41] It appears that the cyclized alkylpalladium intermediate (**189**), unable to undergo β-elimination, carbometallates the ad-



Scheme 38

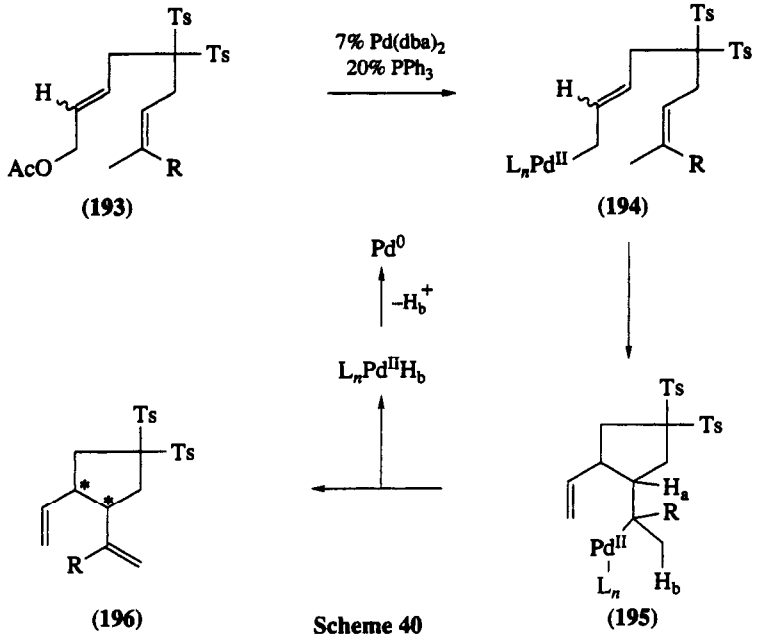
jacent vinyl group to give the transient cyclobutane (**190**) which undergoes retro-carbometallation/β-elimination, (**190**) → (**191**) → (**192**).



Scheme 39

In striking contrast to 8-alkyl-substituted 2,7-dienylmagnesium halides that did not cyclize (*cf.* Section 1.2.3.2), the allylpalladium unit of (**194**) inserted readily into a terminally mono- and even di-methyl-substituted alkenic bond, (**194**) → (**195**) (Scheme 40; Table 11).[38] The efficient Pd^0 catalyzed cyclizations (AcOH, 75 °C, 1, 5 h) of acetoxydienes (**193a**) and (**193b**) gave, in each case, a single 1,5-diene product (**196a**; 91%) and (**196b**; 71%), respectively. It follows that the cyclic alkylpalladium intermediate (**195**) eliminates the exocyclic H_b preferentially over H_a, in agreement with the conformational constraints of a *syn* β-elimination process. Again acetic acid proved to be a better solvent than THF (*cf.* entries 1, 2 and 3, 4).

A study of the stereochemistry of the cyclization (**197**) → (**198**) + (**200**) showed a kinetically controlled 2:1 preference for the formation of the *trans*-divinylcyclopentane (**200**) (independent of the ene *E*/*Z* configuration, *cf.* Scheme 48) which increased to 9:1 when more catalyst and a longer reaction time were employed (Scheme 41, Table 12).[41] This useful predominance of the thermodynamically more stable



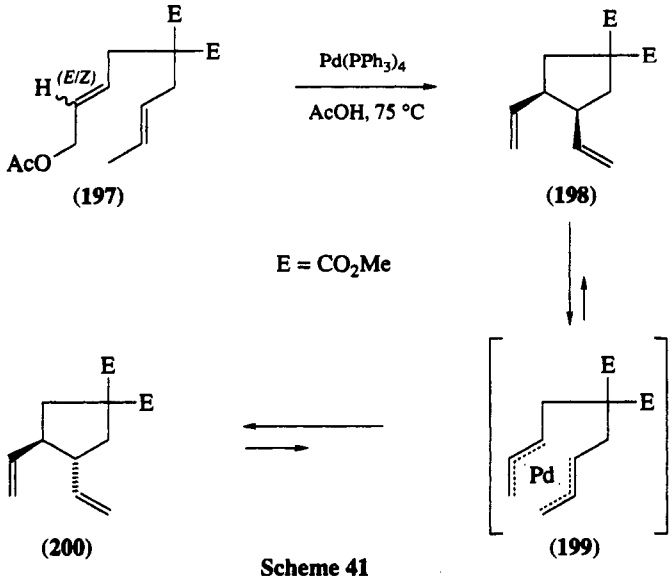
Scheme 40

Table 11 $Pd(dba)_2/PPh_3$ Catalyzed Cyclizations (**193**) → (**196**)

Entry	*R*	*Solvent*	*Reaction temp. (°C) (time, h)*	*Yield of (196) (%)*
1 **a**	H	THF	75 (15)	80
2 **a**	H	AcOH	75 (1.5)	91
3 **b**	Me	THF	85 (40)	40
4 **b**	Me	AcOH	75 (1.5)	71

trans product (**200**) (entry 4) presumably involves a palladium-catalyzed 'Cope-type' equilibration (**198**) ⇌ (**199**) ⇌ (**200**).

As expected, $Pd(PPh_3)_4$ also proved to be a suitable catalyst for intramolecular palladium-ene reactions (Scheme 42). Conversion (**201**) → (**202**) illustrates the feasibility of this method for six-membered ring formation.[38] Acetoxydiene (**203**), containing a cyclic enophile unit, furnished stereoselectively the bicy-



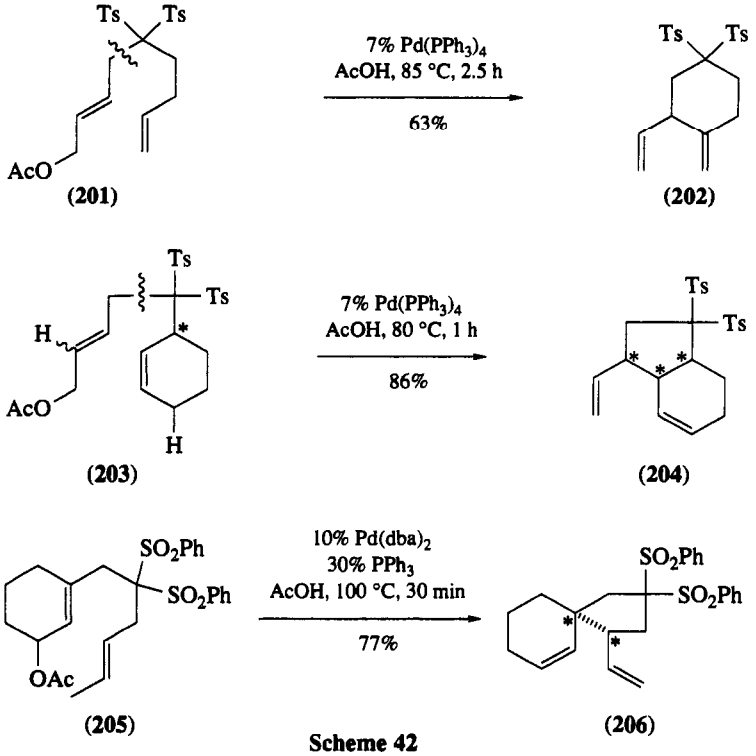
Scheme 41

Table 12 Stereochemistry of $Pd(PPh_3)_4$ Catalyzed Cyclizations[a] (**197**) → (**198**) + (**200**)

Entry	*Educt* (**197**) *(E):(Z)*	*Equiv. $Pd(PPh_3)_4$*	*Reaction time* (h)	*Yield of* (**198**) + (**200**) (%)	*Ratio* (**198**):(**200**)
1	0:100	0.05	5	70	36:64
2	60:40	0.05	5	67	36:64
3	60:40	0.07	2	26 (80)[b]	32:68
4	60:40	0.10	24	52	10:90

[a]75 °C, AcOH. [b]Yield in parenthesis based on recovered (**197**).

clic product (**204**) in 86% yield. The palladium-ene unit may be also part of a ring, as shown by the stereoselective formation of a spiro system, (**205**) → (**206**).[38c,42]



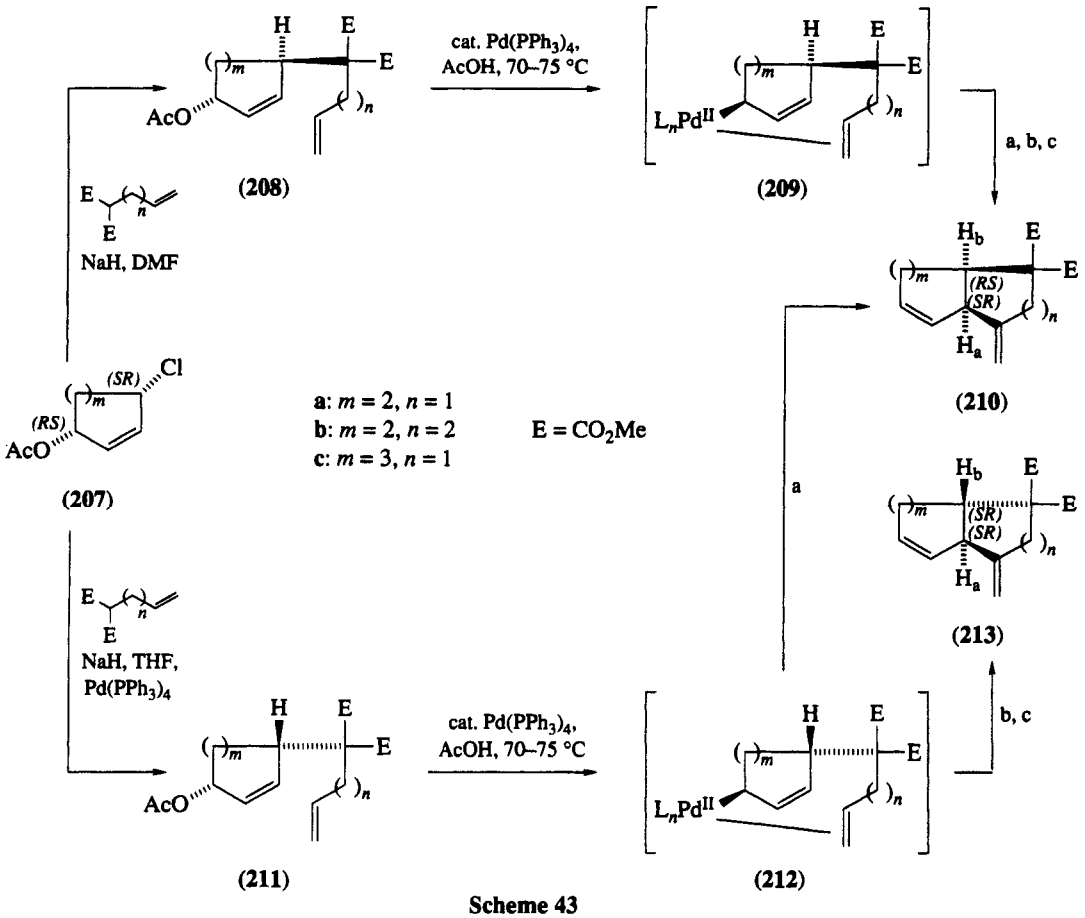
(**201**) (**202**) (**203**) (**204**) (**205**) (**206**)

Scheme 42

Stereochemically even more striking are the cyclizations depicted in Scheme 43 and Table 13. Comparison of entries 1 and 2 shows that the *trans* or *cis* alkenic cyclohexenyl acetates (**208a**) or (**211a**) gave the same *cis*-annulated hexahydroindene (**210a**).[38] However, the conversion (**211a**) → (**210a**) is significantly slower and presumably implies a relatively slow *trans/cis* isomerization (**212a**) → (**209a**). It appears that in initially formed (**212a**) the coordination of the Pd atom with the *trans*-disposed enophile is highly unfavorable, which prevents its conversion to (**213a**). However, a longer bridge or a larger preexisting ring should permit allylpalladium alkene coordination even in the *trans* intermediates (**212**). Indeed, the *trans*-acetoxydiene (**208b**) furnished exclusively the *cis*-fused octahydronaphthalene (**210b**), whereas the *cis*-acetoxydiene (**211b**) gave, with 95% stereospecificity, the *trans*-annulated product (**213b**) (entries 3, 4).[42,43] This interesting C—O → C—Pd → C—C chirality transfer also provides selective routes to *cis*- or *trans*-fused hexahydroazulenes (**210c**) or (**213c**) (entries 5, 6).[41,43] These findings confirm that the alkene inserts predominantly into the σ-(or π-)allylpalladium unit *cis* relative to the Pd atom (*i.e.* in a suprafacial manner).

Scheme 44 exemplifies the analogous enantiospecific preparation of a hexahydropentalene (**217**) from a readily available, optically pure hydroxyacetate (**214**).[43]

The *gem*-disulfone and malonate functionalities described above facilitate the preparation of the 'palladium-ene' precursors (**I**) (Scheme 36) and can be readily removed or modified, but they are not essential for the cyclization process. Thus 3-acetoxy-1,7-octadienes (**J**) (*e.g.* **218**) containing simple carbon bridges are very easily accessible and undergo smooth Pd-catalyzed cyclizations (Scheme 45).[41,44] Only



Scheme 43

Table 13 Stereocontrolled Syntheses of [4.3.0], [4.4.0] and [5.3.0] Ring Systems by Pd-catalyzed Cyclizations of Acetoxydienes (**208**) and (**211**)

Entry[a]	*Starting material*	*m*	*n*	*Reaction time* (h)	*Yield (%)* (**210**) + (**213**)	*Ratio* (**210**):(**213**)
1 **a**	(**208**)	2	1	1.1	84	≥98:≤2
2 **a**	(**211**)	2	1	4	55	≥98:≤2
3 **b**	(**208**)	2	2	3	60	>99:<1
4 **b**	(**211**)	2	2	3	69	5:95
5 **c**	(**208**)	3	1	4	73	99:1
6 **c**	(**211**)	3	1	1.8	80–92	2:98

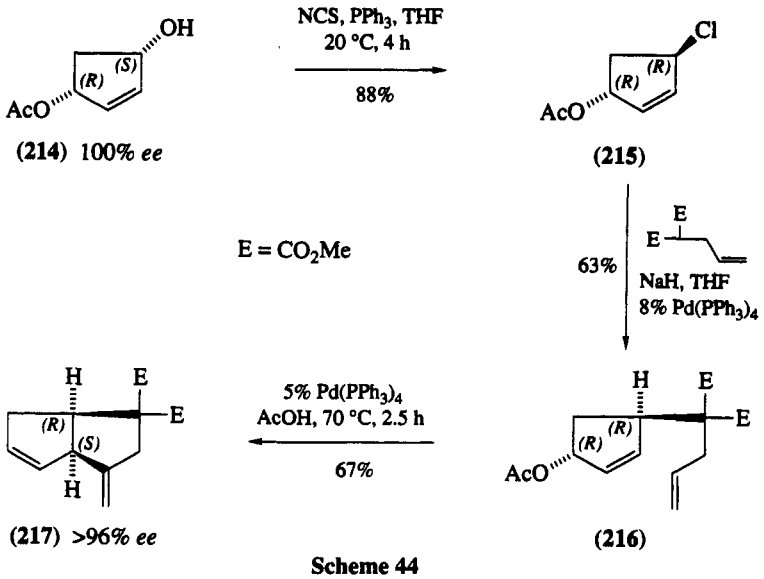
[a]Entries 1–4: 7 mol % $Pd(PPh_3)_4$, 75 °C; entry 5: 10 mol % $Pd(PPh_3)_4$, 70 °C; entry 6: 5 mol % $Pd(PPh_3)_4$, 70 °C.

products (**220**) containing an (*E*)-alkenic bond were found, indicating the ene-type reaction of (*E*)-allylpalladium intermediates.

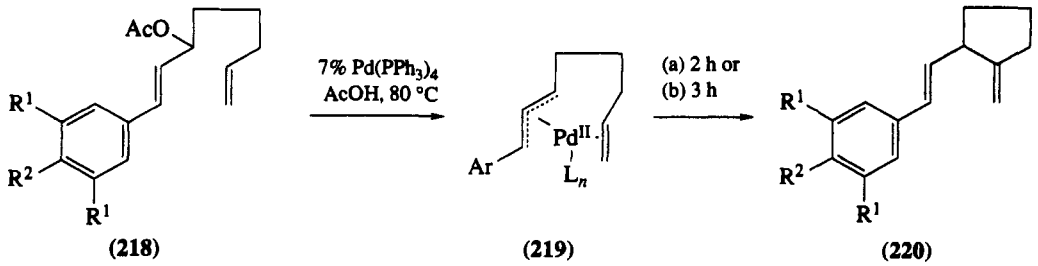
Catalytic palladium-ene cyclizations may also open new perspectives in alkaloid synthesis, considering the smooth formation of pyrrolidines and piperidines.[42,45] Scheme 46 and Table 14 illustrate the cyclizations of 'palladium-ene' precursors (**I**) (**221**; *entries 1–4*) and (**J**) (**223**; *entries 5, 6*) containing a nitrogen atom as part of the bridge. The leaving group in (**223**) can even be a simple hydroxy group (entry 6).[45a]

Stereospecific formation of a *cis*-fused octahydroquinoline (**226**; 85%) is depicted in Scheme 47, which also shows the conversion of diallyl ether (**227**) into a 1:1 *cis/trans* mixture of tetrahydrofurans (**228**; 75%).[45a] It is worth noting that analogous nickel(0)-catalyzed cyclization of the corresponding acetate gave exclusively the *trans* isomer of (**228**).[45b]

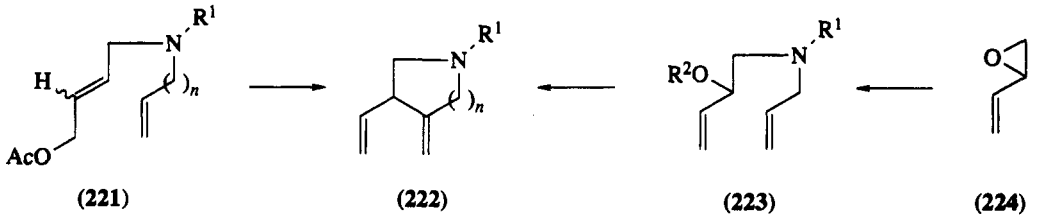
Pd^0 catalyzed cyclizations of (*E,Z*)-, (*Z,Z*)-, (*E,E*)- and (*Z,E*)-*N*-trifluoroacetamides (**229**) and (**232**) again represent the insertion of terminally methyl-substituted alkenic bonds into (*E*)-allylpalladium components followed by β-elimination of a methyl-hydrogen atom (Scheme 48; Table 15).[45a]



Scheme 44



Scheme 45



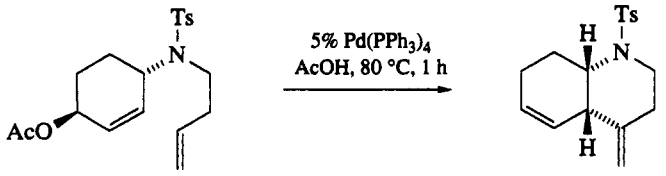
Scheme 46

Table 14 Pyrrolidines and Piperidines by Pd^0 Catalyzed[a] Cyclizations (221) → (222) and (223) → (222)

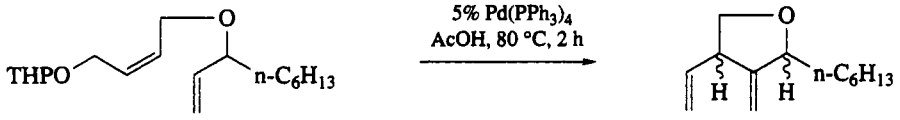
Entry	*Starting material*	R^1	*n*	R^2	*Reaction time* (h)	*Yield* (%)
1 **a**	(221)	CH_2Ph	1	—	3	72
2 **b**	(221)	CO_2CH_2Ph	1	—	1	69
3 **c**	(221)	$SO_2C_6H_4Me$-*p*	1	—	0.5	72
4[b] **d**	(221)	$SO_2C_6H_4Me$-*p*	2	—	4	77
5 **e**	(223)	C(O)Ph	1	C(O)Ph	0.5	81
6[b] **f**	(223)	$SO_2C_6H_4Me$-*p*	1	H	3.5	78

[a]AcOH, 80 °C, $Pd(PPh_3)_4$ (5 mol %). [b]7 mol % of $Pd(PPh_3)_4$ used.

Entries 2 and 5 in Table 15 exemplify the use of a polymer-supported palladium(0)–phosphine catalyst which may offer practical advantages for carrying out palladium-catalyzed ene-type cyclizations.[46] As to the stereochemistry, dienes (**229**) containing a (*Z*)-enophile gave, under kinetic control, predominantly

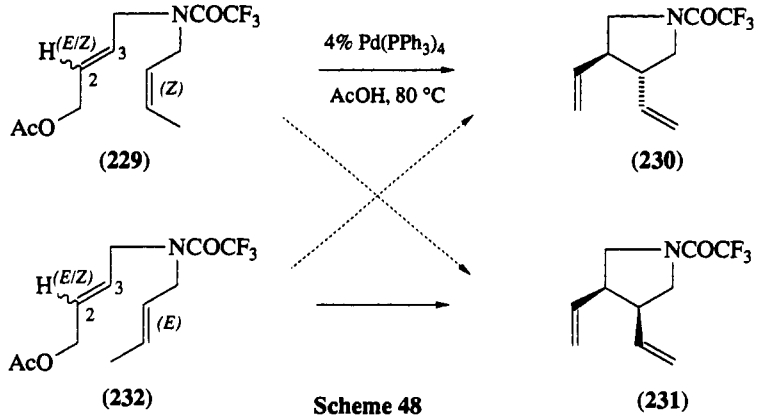


(225) (226) 85%



(227) (228) 75% (1:1)

Scheme 47



(229) (230)

(232) (231)

Scheme 48

Table 15 Pd^0 Catalyzed Cyclizations (**229**) → (**230**) + (**231**) and (**232**) → (**230**) + (**231**)

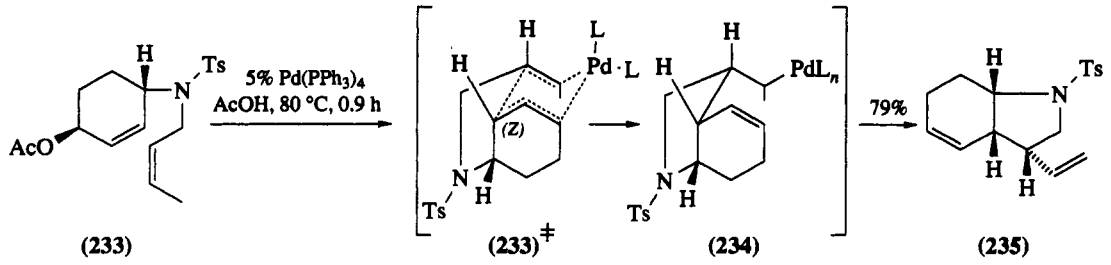
Entry	*Starting material*	*E/Z C(2)—C(3)*	*Reaction time* (h)	*Yield (%)* (**230**) + (**231**)	*Ratio* (**230**):(**231**)
1	(**229**)	*E*	0.6	76	88:12
2[a]	(**229**)	*E*	20	75	88:12
3	(**229**)	*Z*	1.9	59	91:9
4	(**232**)	*E*	2	67	28:72
5[a]	(**232**)	*E*	52	62	30:70
6	(**232**)	*Z*	2.5	51	30:70

[a] 10 mol % of (polymer-C_6H_4-PPh_2)$_4$Pd (Fluka).

the *trans*-divinylpyrrolidine (**230**) (~8:1, *entries 1–3*) whereas dienes (**232**) containing an (*E*)-enophile afforded, less selectively (2.5:1), the *cis* product (**231**) (*entries 4–6*). This stereochemical outcome was independent of the (*E*/*Z*) configuration of the allyl acetates (**229**) and (**232**), in agreement with a (*Z*)- → (*E*)-allylpalladium isomerization prior to the insertion (indeed, isomerizations (*Z*)-(**229**) → (*E*)-(**229**) and (*Z*)-(**232**) → (*E*)-(**232**) were observed under the cyclization conditions).

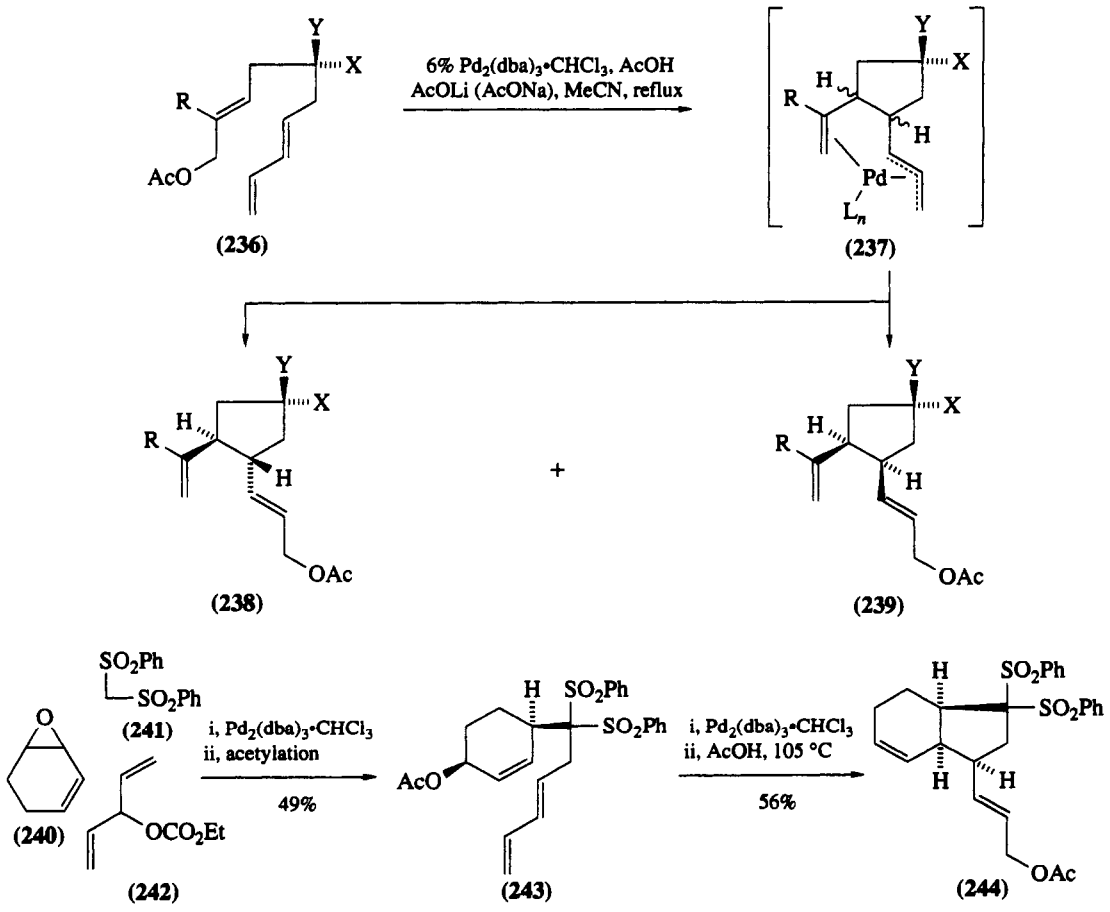
By contrast, if the (*Z*) configuration of the allylpalladium unit (*e.g.* in **233**‡) is enforced by incorporation into a ring, only cis-substituted insertion products were expected, as confirmed by the annulation (**233**) → (**235**) (Scheme 49).[45a]

A recent report described analogous palladium(0)-catalyzed cyclizations of allyl acetates containing a conjugated dienyl-enophile component.[47] Thus heating trienes (**236**) with acetic acid and lithium or sodium acetate in acetonitrile under reflux furnished mixtures of *trans* and *cis* cyclization products (**238**) and (**239**). It appears that the cyclized allylpalladium species (**237**) is trapped by acetate (*via* reversal of the oxidative addition (**I**) → (**K**), Scheme 36) which results in an overall isomerization (**236**) → (**238**) + (**239**). As previously observed (*cf.* Scheme 37), the presence of triphenylphosphine was required for the corresponding transformation of the malonate (**236e**). Cyclizations of the monodesulfonated substrates



Scheme 49

(**236c**) and (**236d**) provided exclusively the all-*cis* products (**239c**) and (**239d**), respectively (Scheme 50, Table 16).



Scheme 50

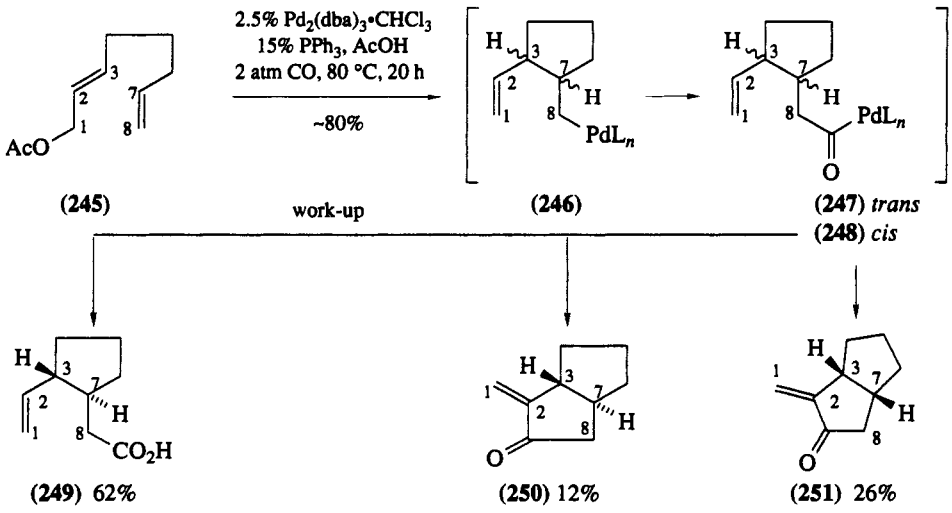
Table 16 Pd^0 Catalyzed Cyclizations *via* Isomerizations of α-Dienyl-ω-allyl Acetates

Entry	*R*	*Y*	*X*	*PPh_3* (mol %)	*Yield* (**238**) +(**239**)	*Ratio* (**238**):(**239**)
a	H	SO_2Ph	SO_2Ph	—	60–70	70:30
b	Me	SO_2Ph	SO_2Ph	—	62	58:42
c	H	SO_2Ph	H	—	68	0:100
d	Me	SO_2Ph	H	—	62	0:100
e	H	CO_2Et	CO_2Et	24	75	—[a]

[a]Ratio not reported.

Direct palladium(0)-catalyzed bisalkylation of disulfone (**241**) by (**240**) and (**242**) and acetylation furnished the cyclohexenyl precursor (**243**) with a *cis*-related acetoxy group and dienyl chain. This configuration is, however, unfavorable for the cyclization step (*cf.* Scheme 43), which explains the high reaction temperature (AcOH, 105 °C). The all-*cis* configuration of (**244**) parallels that one of (**235**) (*cf.* Scheme 49).

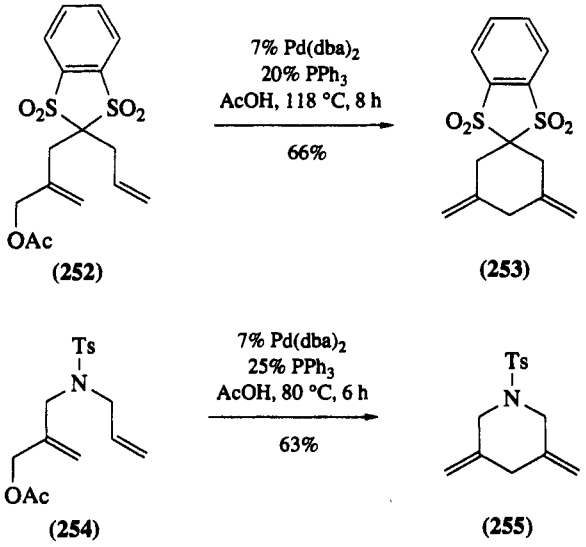
Trapping of the cyclized σ-alkylpalladium species by carbon monoxide (2 atm) is exemplified by Scheme 51.[48] Again the use of acetic acid as a solvent was essential for the cyclization of the butadiene telomer (**245**) giving initially σ-Pd species (**246**). Subsequent C—Pd/CO insertion (**246**) → (**247**) + (**248**) was followed more readily an alkene/acylpalladium insertion–β-elimination sequence (**248** → **251**) when the two adjacent moieties were *cis* disposed, whereas the *trans* intermediate (**247**) mainly provided the *trans*-vinylcyclopentane acetic acid (**249**) (50% from **245**). Ligand variations have so far failed to increase the diastereoselectivity of these cyclizations.



Scheme 51

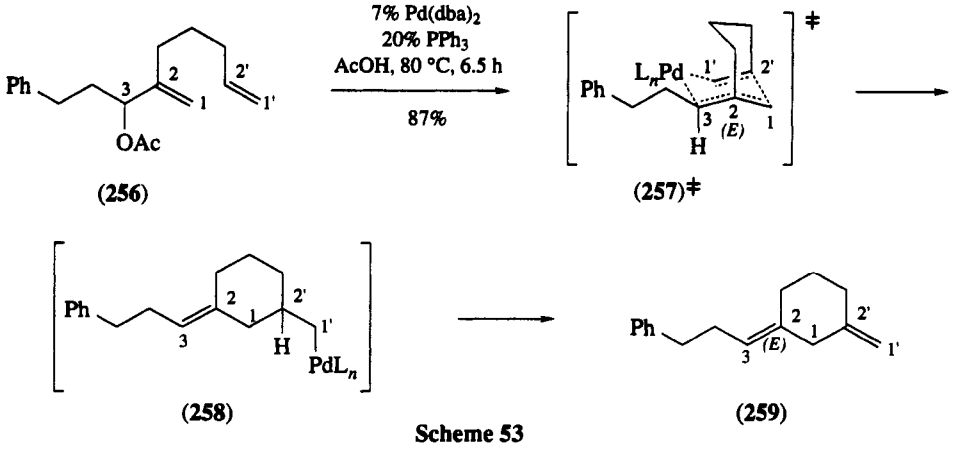
1.2.3.3.2 Catalytic type II palladium-ene cyclizations

Scheme 52 illustrates the feasibility of carrying out catalytic type II palladium-ene cyclizations; for example, the transformation (**252**) → (**253**) (118 °C, 8 h, 66% yield).[42,49] Cyclization of (**254**) proceeded under milder conditions (80 °C, 6 h) to give piperidine (**255**; 63%).[49]



Scheme 52

Dienyl acetate (**256**) (readily prepared from 1-hepten-6-one and lacking the disulfone moiety) was also easily transformed to (*E*)-1,4-diene (**259**; 87%) (Scheme 53).[42,49] This regiochemistry parallels that of stoichiometric additions of allylpalladium complexes to norbornadiene,[13] but was subject to uncertainty in view of the relatively fast 1,3-Pd migration within the allyl component.[39] Therefore the conversion (**256**) → (**259**) demonstrates a new stereocontrolled access to exocyclic trisubstituted alkenes which implies C—C bond formation at the less-substituted allylpalladium terminal and thus shows a regio- and stereo-chemistry both opposite to the type II magnesium-ene process (*cf.* Section 1.2.3.2.2; **81** → **83**).



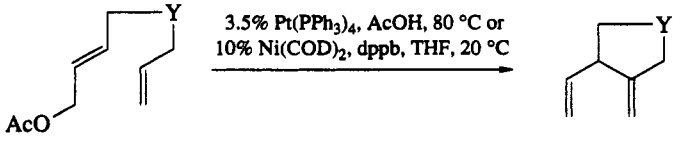
(**256**) (**257**)‡ (**258**) (**259**)

Scheme 53

1.2.3.3.3 Catalytic platinum- and nickel-ene cyclizations

The above concept of catalytic metallo-ene cyclizations (Scheme 36) may also be extended to platinum and nickel, as one would expect in view of previous work on intermolecular nickel-ene reactions (*cf.* Section 1.2.2.4).

Recently, a platinum-catalyzed cyclization/elimination was accomplished on heating dienyl acetate (**260a**) with 3.5 mol % of $Pt(PPh_3)_4$ in acetic acid at 80 °C, which furnished the expected cyclopentane (**261a**) in 84% yield (Scheme 54; Table 17, *entry 1*).[42,50a]



(**260**) (**261**)

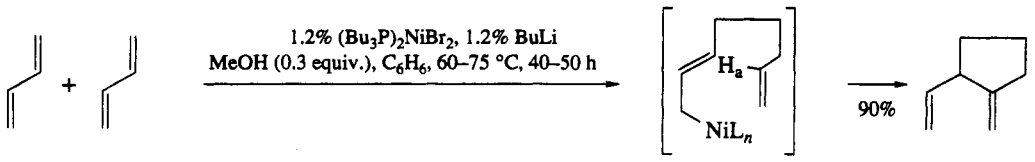
Scheme 54

Table 17 $Pt(PPh_3)_4$ (Pt^0) or $Ni(COD)_2$/dppb (1:1) (Ni^0) Catalyzed Cyclizations (**260**) → (**261**)

Entry	*Bridge Y*	*Catalyst* (mol %)	*Solvent*	*Reaction temp.* (°C) (*time*, h)	*Yield* (%)
1 **a**	$C(SO_2Ph)_2$	Pt^0 (3.5)	AcOH	80 (5)	85
2 **a**	$C(SO_2Ph)_2$	Ni^0 (10)	THF	20 (3)	83
3 **b**	$NSO_2C_6H_4Me$-*p*	Ni^0 (10)	THF	20 (12)	76
4 **c**	N—CPh_3	Ni^0 (10)	THF	20 (0.7)	92

The first indication, reported in 1971, for a nickel-catalyzed intramolecular allylation of an alkenic bond was the dimerization of butadiene to 2-methylvinylcyclopentane (**263**).[51] This efficient transformation (90%) proceeded with 1.2 mol % of a Ni^0 catalyst (prepared *in situ* from $(Bu_3P)_2NiBr_2$ and BuLi) in the presence of methanol and presumably involves a nickel-ene reaction of (**262**) followed by a β-elimination of H_a (Scheme 55).

The feasibility of Ni^0 complexes as catalysts for intramolecular metallo-ene reactions was, despite the encouraging precedents, not straightforward and depended strongly on their ligands. Systematic studies showed that a 1:1 mixture of $Ni(COD)_2$/1,4-bis(diphenylphosphino)butane catalyzes (10 mol %) the

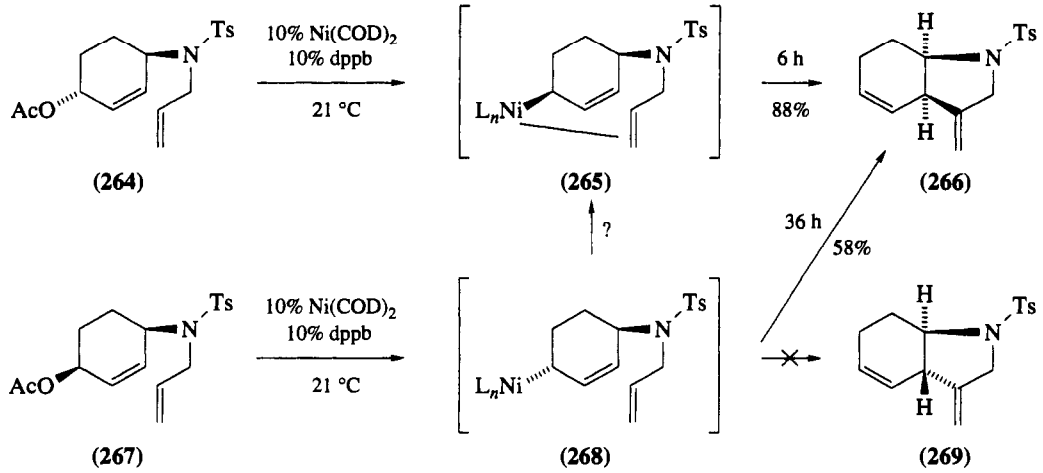


(262) (263)

Scheme 55

allylation/elimination (**260**) → (**261**) at 20 °C in THF with a synthetically useful efficiency (76–92%) (Scheme 54; Table 17, entries 2–4).[50a]

The catalyst Ni(COD)dppb, formed *in situ*, also induced smooth conversion of monocyclic *trans*-acetoxydiene (**264**) to the *cis*-fused 3-methylenehexahydroindole (**266**; 88%), which is also formed much more slowly (12 h, 58%) from the *cis* precursor (**267**) (Scheme 56).[50a] This indicates a preferred *cis*-allylnickel/alkene insertion (**265**) → (**266**) analogous to the closely related palladium-catalyzed annulations (**209a**) or (**212a**) → (**210a**).



(264) (265) (266)

(267) (268) (269)

Scheme 56

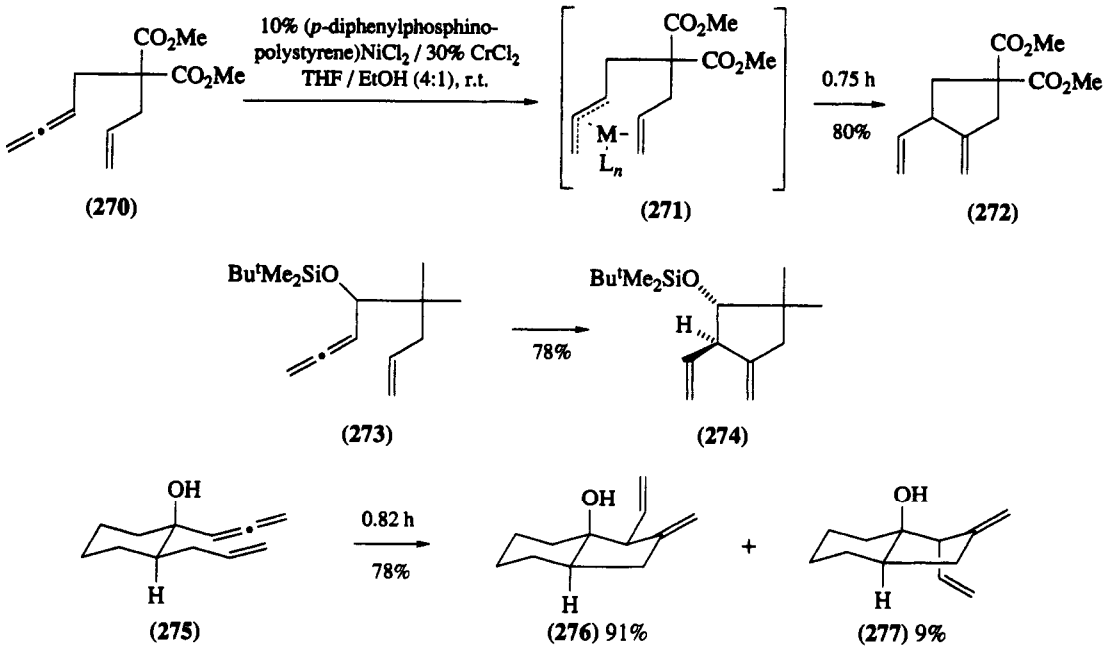
The nickel/chromium-catalyzed cyclizations of 1,2,7-trienes (**270**) to (**272**) were postulated to proceed *via* a metal hydride addition to the allene unit of (**270**), generating an allylmetal intermediate (**271**) which undergoes a metallo-ene/β-elimination sequence.[52] It is worth noting that these cyclizations can be stereocontrolled by the presence of resident stereogenic centers, as demonstrated by the transformations (**273**) → (**274**) and (**275**) → (**276**) (Scheme 57).

Coupling of an intramolecular nickel-ene process with a methoxycarbonylation shows a striking preference for products with *cis*-related metal donor (C-1) and acceptor (C-8) sites.[50] Thus tricarbonyl(triphenylphosphine)nickel (25 mol %),[53] a stable, easy-to-handle solid [compared with the highly volatile and toxic $Ni(CO)_4$], readily catalyzed the conversion of dienyl iodide (**278**) (THF/MeOH 4:1, 1 atm CO, r.t.) into monocyclic *cis*-substituted pyrrolidine (**280**; 29%) and the bicyclic cyclopentanone (**281**; 47%, 4:1 isomer mixture) (Scheme 58).[50a]

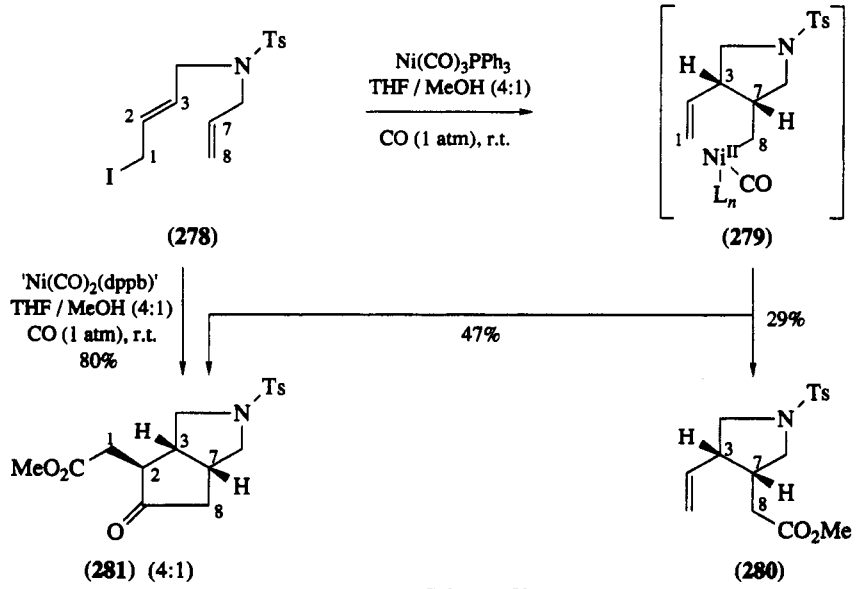
It follows that a *cis* stereoselective nickel-ene process yields (**279**) and that (**279**) forms a *C*-acylnickel intermediate which inserts into either methanol (→ **280**) or the internal alkenic bond affording, after final methoxycarbonylation, keto ester (**281**). It is interesting to note that the bidentate ligand dppb favored the latter process and that no β-elimination of (**279**) was observed. Thus a catalyst, prepared *in situ* from $Ni(COD)_2$/dppb (1:1) under CO, effected complete bicyclization of (**278**) to give only (**281**; 80%, 10:1 epimer mixture).[50b]

Direct β-elimination cannot interfere with allylnickel/alkyne insertion–carbonylation sequences. In extension of previous work (*cf.* Scheme 16) the bicyclization of (*E*)- and (*Z*)-(**282**) to (**283**; 50%), promoted by 200 mol % of $Ni(CO)_4$ at 40 °C, has been reported (Scheme 59).[54]

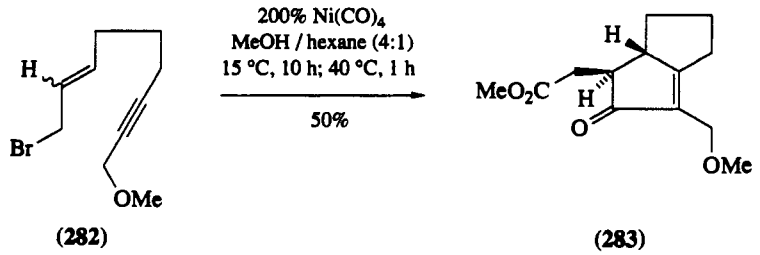
Using 25 mol % of the more practical $Ni(CO)_3PPh_3$ catalyst under CO (1 atm, THF/MeOH 4:1, r.t.), exclusive monocyclization of iodoenyne (**284a**) → (**286a**) was accomplished (Scheme 60; Table 18, entry 1).[50] This unusual stereocontrolled approach to an exocyclic trisubstituted alkenic bond is consistent with a suprafacial allylnickel/alkyne insertion, (**284**; X = NiL_n) → (**285**). Malonate (**284b**; X = I) yielded, under similar reaction conditions, monocyclized ester (**286b**; 41%) and bicyclo[3.3.0]octenone



Scheme 57

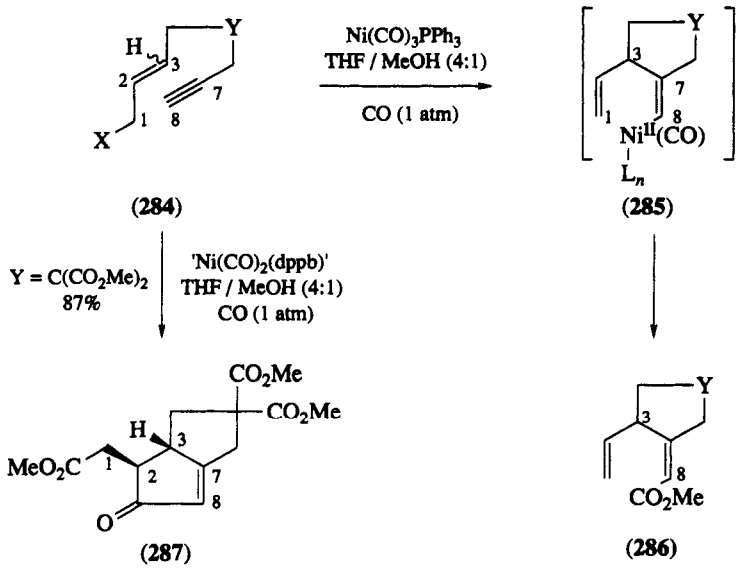


Scheme 58



Scheme 59

(**287**; 36%) in a stereospecific manner (*entry 2*). Exclusive bicyclization (**284b**) → (**287**; 87%) was observed in the presence of the bidentate ligand dppb (entry 3).[50b]



Scheme 60

Table 18 Nickel(0)-catalyzed Intramolecular Allylation/Carbonylation of Iodoenynes (**284**)

Entry	*Bridge Y*	*Catalyst* (mol %)	*Reaction temp.* (°C) (*time*, h)	*Monocyclic product* (*yield*, %)	*Bicyclic product* (*yield*, %)
1 **a**	$NSO_2C_6H_4Me$-*p*	$Ni(CO)_3PPh_3$ (25)	r.t. (20)	(**286**) (69)	—
2 **b**	$C(CO_2Me)_2$	$Ni(CO)_3PPh_3$ (25)	r.t. (20)	(**286**) (41)	(**287**) (36)
3 **b**	$C(CO_2Me)_2$	$Ni(CO)_2$dppb (25)[a]	r.t. (15)	—	(**287**) (87)

[a]Addition of dppb to $Ni(COD)_2$ (1:1) under CO (1 atm), THF/MeOH (4:1).

1.2.4 SUMMARY

Intermolecular metallo-ene reactions show interesting prospects when applied to strained or strongly polarized enophiles. Intramolecular versions, however, have proved to be far more powerful in the hands of synthesis-oriented chemists. Based on the criteria of (established and/or potential) utility in organic synthesis the following summary is focused on intramolecular magnesium-, palladium- and nickel-ene reactions.

Stoichiometric, intramolecular magnesium-ene reactions involving terminal or strained alkene enophile units have served extensively as a cornerstone in efficient syntheses of natural products. One of the reasons is the propensity of the cyclized Grignard intermediates to be trapped by a vast array of electrophiles. On the other hand, the use of Mg is incompatible with several functionalities such as certain heteroatoms in the acyclic precursor (zinc-ene cyclizations seem to surmount some of these limitations).

However, palladium and nickel catalyzed versions promise, at the moment, an even wider range of possibilities. The need to maintain the catalytic cycle by continuous regeneration of the zerovalent metal catalyst limits, nevertheless, the functionalizability of the metallated center in the cyclized intermediate. For the same reason, the readily accessible starting materials may contain various functional groups which are compatible with the reaction conditions and which may be of value for the syntheses of complex heterocycles such as alkaloids. Carbon monoxide insertion reactions of the cyclized σ-metal intermediates were shown to afford monocyclic methyl carboxylates and/or annulated cyclopentanones (cyclopentenones) with concomitant stereocontrolled formation of up to four carbon–carbon bonds.

The following further trends can be seen from the available evidence.

Ring size. The ease of cyclization decreases in the following order relative to the size of the developing ring: type I, 5 > 6 >> 7; type II, 6 > 5 ~ 7 >> 8.

Regioselectivity. Carbon–carbon bonds are preferentially formed between the proximal sites of ene and enophile in the type I process and between the more (Mg-ene reaction) or less substituted (Pd-ene reaction) ene terminal and the proximal enophile site in the type II version.

Stereoselectivity. All described metallo-ene reactions proceed apparently in a suprafacial manner. Other stereochemical features depend strongly on the metal as summarized below.

Type I magnesium-ene cyclizations usually furnish under kinetic control predominantly five- and six-membered rings carrying *cis*-disposed magnesium-donor and -acceptor units even when a quaternary center is generated. 2,3-Dialkyl-substituted allylmagnesium moieties react preferentially in their (*Z*)-form, inducing a *cis* relation of the C-3 alkyl substituent and the magnesium-acceptor site in type II cyclization products. However, the stereoselectivity of type I and type II magnesium cyclizations can be greatly diminished by severe steric hindrance, *e.g.* by critically placed *gem*-dimethyl groups (*cf.* **101** → **102**; **158** → **160**).

Related palladium-catalyzed ring closures permit simple and selective either *cis* or *trans* annulation processes *via* an almost 100% stereospecific C—O → C—Pd → C—C transfer. The diastereoselectivity of the palladium-ene cyclizations depends on the (*E*)/(*Z*) configuration of the enophile units and becomes exclusively *cis* when the (*Z*)-ene geometry is secured by incorporation into a ring. However, even acyclic allylnickel intermediates add to internally bound alkene units to form five-membered rings with *cis*-disposed nickel-donor and -acceptor sites.

As to our own work, mentioned in this chapter, it is a privilege to acknowledge the crucial contributions of my coworkers whose names are cited in the appropriate references. We thank the Swiss National Science Foundation, Sandoz AG, Basel, and Givaudan SA, Vernier, for generous support of this work. We are grateful to Professors E. Negishi and J. Tsuji for kindly communicating their results prior to publication.

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2.1
Thermal Cyclobutane Ring Formation

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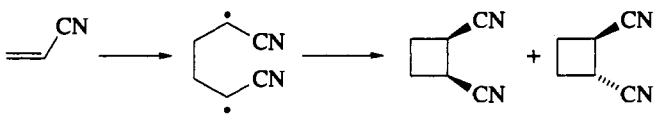
2.1.1 INTRODUCTION

This chapter reviews thermal [2 + 2] cycloadditions of alkenes to form cyclobutanes, extending the coverage provided by earlier summaries of the literature.[1–8] It does not deal with [2 + 2] cycloadditions that are achieved photochemically, or that utilize allenes, arynes or ketenes, or that are deliberately catalyzed,[9–14] or that result in heterocyclic four-membered rings, even though these other varieties of [2 + 2] cycloaddition reactions are important and of substantial interest.

Thermal [2 + 2] cycloadditions of alkenes are both well known and often overlooked or underutilized in synthetic practice. Yet a maturing mechanistic understanding of these reactions, and the growing importance of cyclobutane structures and of cyclobutanes as synthetic intermediates,[15] may soon lead to more widespread applications of this synthetic method.

2.1.2 DIMERIZATIONS OF ALKENES *VIA* 1,4-DIRADICALS

Dimerizations of monosubstituted ethylenes were among the earliest recognized examples of thermal [2 + 2] cycloadditions; the fact that acrylonitrile (**1**) gives 1,2-dicyanocyclobutanes (**3**, **4**) led to postulation of reaction by way of a tetramethylene diradical intermediate (**2**).[16]



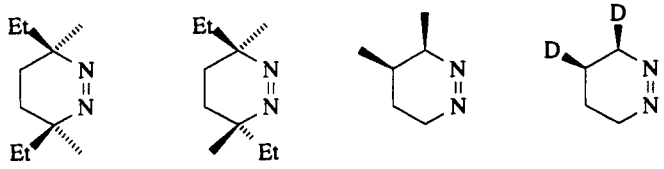
(1) (2) (3) (4)

Styrene,[17–19] butadiene[20] and divinylacetylene[21] similarly give [2 + 2] cycloadducts of head-to-head regiochemistry as mixtures of *cis* and *trans* 1,2-disubstituted cyclobutanes. The tetramethylene diradical

hypothesis accounts for the regiochemistry: these [2 + 2] cycloadditions take place through an initial carbon–carbon bond-forming step to give the most stable 1,4-disubstituted 1,4-diradical. This view was extended to explain why the reaction lacked generality (why some alkenes did not dimerize efficiently when heated) and to interpret relative rates of dimerization. The dimerization of ethylene itself, for example, is kinetically well behaved[22] but quite difficult to realize, for the diradical intermediate involved has a much higher heat of formation[23] than tetramethylene diradical systems having good radical-stabilizing groups at C-1 and C-4, and the reaction is associated with a very unfavorable change in entropy. Relative rates of cycloadditions may be correlated qualitatively with the relative potency of substituents as radical-stabilizing groups: styrene dimerizes at 240 °C faster than acrylonitrile, for phenyl is a better radical-stabilizing group than cyano.[24]

The diradical mechanism for such reactions was substantially bolstered through the theoretical insights of the Woodward–Hoffmann theory and through a number of telling stereochemical studies. Orbital symmetry considerations led Woodward and Hoffmann[25] to a recognition that the [2 + 2] cycloaddition of two ethylenes would not be a favored process: the [$\pi 2_s + \pi 2_s$] option is not thermally allowed, and the [$\pi 2_s + \pi 2_a$] alternative is ordinarily geometrically inaccessible. This analysis reinforced the view that such reactions must proceed by way of tetramethylene diradicals, or possibly zwitterionic intermediates. The theoretically based generalizations and the experimental facts are mutually reinforcing, thus providing firm guidance as to when [2 + 2] cycloadditions are likely to occur at rates and with sufficient selectivity to be synthetically useful. Structural features destabilizing an alkene and stabilizing a 1,4-diradical (or 1,4-zwitterionic) intermediate should facilitate such reactions, and regiochemistry may then be predicted with considerable confidence. More quantitative techniques for predicting or rationalizing regiochemistry based on this simple idea have been developed;[26] alternative approaches based on perturbational molecular orbital theory are also quite successful.[27]

Cyclobutanes may be converted to alkenes thermally, the reverse of the [2 + 2] cycloaddition reaction. These retroaddition or cycloreversion reactions have important synthetic applications[28] and offer further insights into the chemical behavior of the 1,4-diradical intermediates involved:[29] they may proceed to product alkenes or collapse to starting material with loss of stereochemistry.[30,31] Both observations are readily accommodated by the diradical mechanism. Generation of 1,4-tetramethylene diradicals in other ways, such as from cyclic diazo precursors, results in formation of both alkenes and cyclobutanes, with stereochemical details consistent with kinetically competitive bond rotations before the diradical gives cyclobutanes or alkenes. From the tetraalkyl-substituted systems (**5**) and (**6**), cyclobutane products are formed with very high retention stereospecificity,[32] while the diradicals generated from the azo precursors (**7**) and (**8**) lead to alkene and cyclobutane products with some loss of stereochemical definition.[33–35]

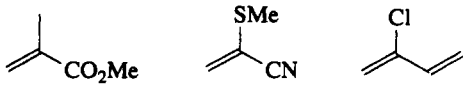


(**5**) (**6**) (**7**) (**8**)

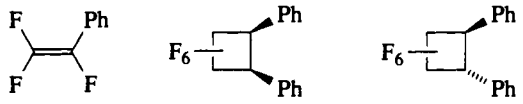
Diradical intermediates may occur in other types of cycloadditions and cycloreversions. Kinetic data for the thermal transformation of *cis,cis*-1,5-cyclooctadiene to butadiene and 4-vinylcyclohexene are consistent with a diradical intermediate;[36] the same intermediate may be involved in the reaction of butadiene leading to [2 + 2] adducts and to the Diels–Alder product 4-vinylcyclohexene.[37,38] That a Diels–Alder product may arise from a stepwise path is not as unimaginable today as may have been the case just a few years ago.[39–42] In more elaborate contexts as well, regiochemistry may be successfully rationalized through estimations of the relative stabilities of diradical intermediates.[43]

When 1,1-disubstituted ethylenes are dimerized, the same regiochemistry is observed. Alkenes (**9**),[44,45] (**10**)[46–49] and (**11**)[50] all dimerize with head-to-head regiochemistry and give *cis/trans* mixtures of 1,1,2,2-tetrasubstututed cyclobutanes. In more highly substituted systems the same pattern is followed: the trifluorostyrene (**12**) gives the head-to-head dimers (**13**) and (**14**),[51] and the cyanodihydropyridine (**15**) gives the tricyclic structure (**16**).[52]

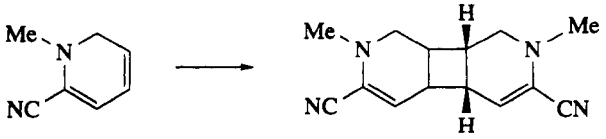
One may see [2 + 2] cycloadditions of alkenes even when radical-stabilizing groups are lacking if the alkene is of relative high energy: cyclopropenes,[53] methylenecyclopropenes, bridgehead alkenes[54] and *trans*-cycloalkenes exemplify the point.



(9) (10) (11)



(12) (13) (14)

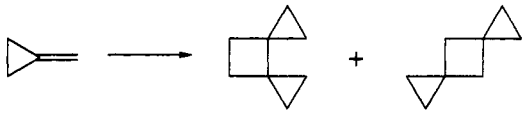


(15) (16)

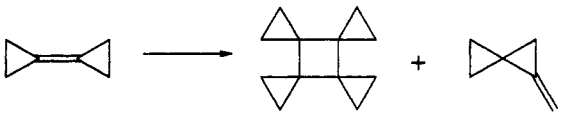
3,3-Dicyclopropylcyclopropene[55] and 3,3-dimethoxycyclopropene[56,57] both dimerize readily (**17** → **18**). Cyclopropenes having a hydrogen at C-3 often give dimers generated through ene reactions, rather than from [2 + 2] cycloadditions.

(**17**) R = cyclopropyl or methoxy (**18**)

Methylenecyclopropene (**19**) dimerizes to give (**20**) and (**21**) in a 92:8 ratio.[58–61] Bicyclopropylidene (**22**) is converted in 35% yield to dimer (**23**);[62] a competitive methylenecyclopropane rearrangement forming (**24**) is the major side reaction.



(**19**) (**20**) (**21**)

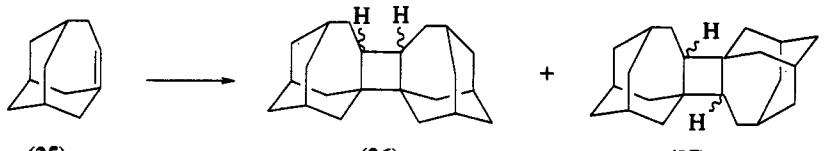


(**22**) (**23**) (**24**)

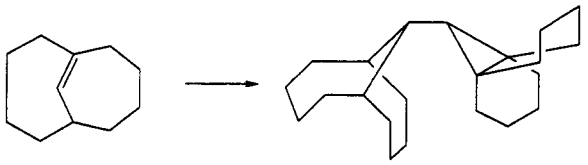
7-Methylenenorbornadiene and tetracyanoethylene give a [2 + 2] adduct, even though the methylene double bond is not directly conjugated with the other two double bonds;[63] the formal [2 + 2] cycloadditions of pentalenes are probably best viewed as allowed [2 + 8] reactions.[64]

Bridgehead alkenes such as adamantene[65–70] and 3-homoadamantene (**25**)[71] dimerize to give mixtures of head-to-head and head-to-tail [2 + 2] cycloadducts. 3-Homoadamantene reacts to form five dimers, four of which have been assigned as structures (**26**) and (**27**). The diradical intermediates corresponding to the regiochemical alternatives are apparently of comparable energy, and the intermediates show competitive rotations about carbon–carbon single bonds and cyclobutane bond-forming reactions. 1-Norbornene[72] and bicyclo[2.2.2]oct-1-ene[73] react similarly.

Bicyclo[4.4.1]undec-1(11)-ene (**28**), however, exhibits different behavior, for it dimerizes in 95% yield to form structure (**29**).[74] Whether this process involves hydrogen atom transfer from a tetramethylene diradical, or an unusual pericyclic reaction reminiscent of an ene reaction, remains unclear.

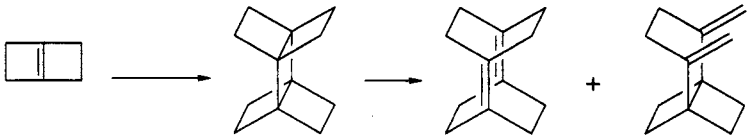


(25) (26) (27)



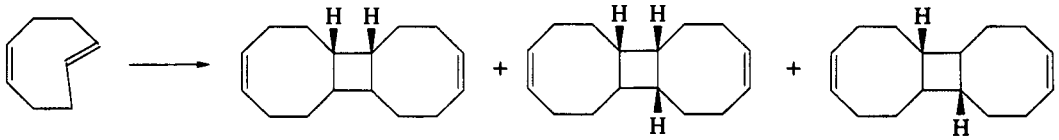
(28) (29)

Bicyclo[2.2.0]hex-1(4)-ene (**30**) dimerizes cleanly at 0 °C in very dilute solution; the products eventually isolated plausibly stem from a [2 + 2] cycloaddition to form (**31**), followed by [2 + 2] retroadditions in two different ways to give (**32**) and (**33**).[75,76]



(30) (31) (32) (33)

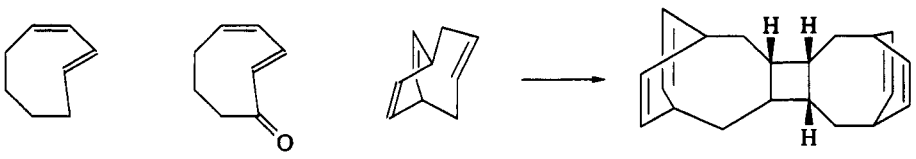
The [2 + 2] dimerizations of *cis,trans*-1,5-cyclooctadiene (**34**), uncovered by Ziegler and coworkers in 1954,[77] have been studied more recently by other groups; Leitich[78] showed that three stereoisomers are formed, and assigned them as (**35**), (**36**) and (**37**).



(34) (35) (36) (37)

When (*R*)-(−)-(**34**) is dimerized, only the second and third isomers are formed (26%, 74%), both in dextrorotatory form, suggesting that the first isomer obtained with racemic starting material stems from a pair of enantiomers. Even though the monoinversion product (the $[\pi 2_s + \pi 2_a]$ product) is not the major product with either racemic or optically active *cis,trans*-diene, the fact that it is formed at all has been read as an indication that Woodward–Hoffmann theory has some predictive validity even for reactions which are not concerted.[78] The normal diradical formulation rationalizes this outcome differently.

Largely similar behavior is evident in the dimerizations of *cis,trans*-1,3-cyclooctadiene (**38**),[79] *trans,cis*-2,4-cyclooctadienone (**39**)[80] and bicyclo[4.2.2]deca-3-*trans*,7,9-triene (**40**).[81]

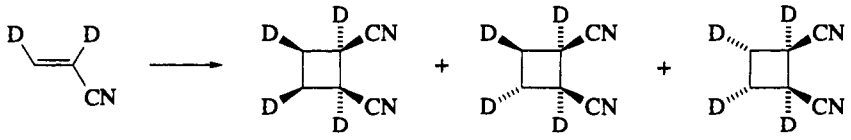


(38) (39) (40) (41)

The dimers from the bridged *trans*-cyclooctene (**40**) include the $[\pi 2_s + \pi 2_a]$ product (**41**), a result which in 1969 was seen as a beautiful example of a $[\pi 2_s + \pi 2_a]$ cycloaddition,[25] a characterization amplified in the secondary literature.[82] The same nomenclature is legitimately and conveniently used here for

two different purposes, once to designate the stereochemistry of a product and again to describe a reaction mechanism; but the product here, as elsewhere, does not inevitably signal the mechanism. The Woodward–Hoffmann theory fails to account for the other two dimers, one of which is the major isomer at 40 °C. Perhaps all three could be rationalized in a uniform and unexceptional fashion through a diradical formulation, and special treatment for the $[\pi 2_s + \pi 2_a]$ product could be unnecessary.

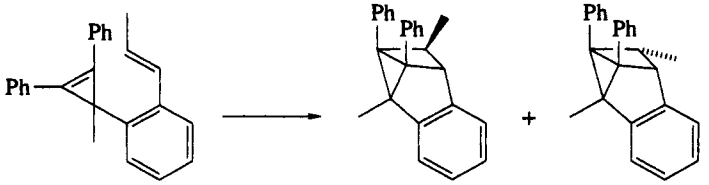
Stereochemical studies add great support to the proposition that [2 + 2] cycloadditions involve tetramethylene diradical intermediates, for these additions take place with partial or complete loss of *cis/trans* stereochemical relationships present in alkene reactants. The dimerization of acrylonitrile, for example, studied with *cis*-1,2-dideuteriocyanoethylene (**42**), gives six distinct [2 + 2] adducts:[83] the distribution of deuterium labels in the *cis*-1,2-dicyanocyclobutane products are given in structures (**43**), (**44**) and (**45**); an analogous set of three *trans* stereoisomers is formed. Recovered starting material shows partial loss of stereochemical integrity.



(42) (43) (44) (45)

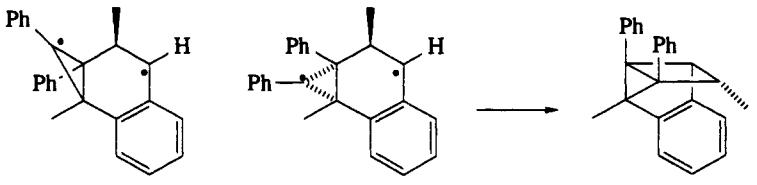
2.1.3 INTRAMOLECULAR AND MIXED [2 + 2] CYCLOADDITIONS

Several fascinating intramolecular [2 + 2] cycloadditions of cyclopropenes have been explored by Padwa and coworkers;[84–92] a typical example is 1,2-diphenyl-3-methyl-3-*o*-vinylphenylcyclopropene, which gives a [2 + 2] intramolecular product in 100% yield. The analogous *o-trans*-propenyl system (**46**) reacts to yield isomers (**47**; 82%) and (**48**; 18%).



(46) (47) (48)

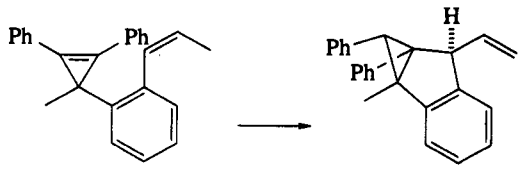
If this reaction is initiated through formation of a cyclopropylbenzylic/benzylic diradical, then product regiochemistry is set when the first bond is made to generate (**49**) or (**50**). The former leads to the major product while the latter gives the *endo* isomer (**48**), following a conformational isomerization involving substantial rotations about several carbon–carbon bonds. The substituted tetramethylene diradical (**50**) may then have a substantial lifetime, and formation of diastereoisomeric diradicals may lead to diastereoisomeric products; such product mixtures need not derive from partitioning of a single, common intermediate, though in many cases they undoubtedly do.



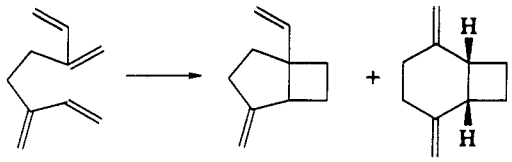
(49) (50) (48)

The *cis*-propenyl analog (**51**) gives exclusively an ene reaction product, (**52**).

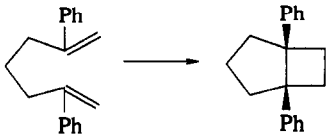
Intramolecular [2 + 2] cycloaddition of acyclic substrates take place when some activating substituent is present; for hydrocarbons, conjugating vinyl or phenyl groups are sufficient. Tetraene (**53**) gives products (**54**) and (**55**),[93] and the diphenylheptadiene (**56**) is converted thermally to the bicyclo[3.2.0] system (**57**).[94]



(51) (52)

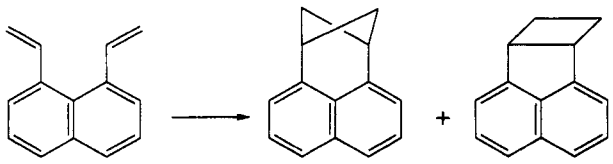


(53) (54) (55)

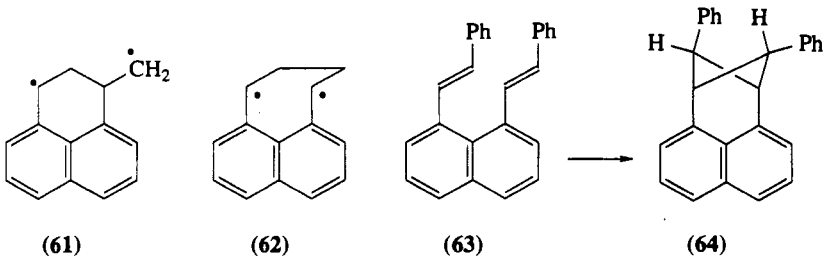


(56) (57)

The regiochemistry of intramolecular [2 + 2] cycloadditions depends on the relative stabilities of alternative 1,4-diradical intermediates, which may depend both on C-1/C-4 substituents in the tetramethylene and on geometrical constraints. 1,8-Divinylnaphthalene (**58**) isomerizes at 150 °C to cyclobutane products (**59**) and (**60**) in a 75:25 ratio, implying that diradicals (**61**) and (**62**) have similar heats of formation.[95,96] The dibenzylic diradical intermediate (**62**), presumably, is restricted geometrically so that both radical centers may not simultaneously be in full conjugation with the π-system of the naphthylene moiety. The analog (**63**) gives just one isomeric product (**64**), formally corresponding to a $[_{\pi}2_s + _{p}2_a]$ cycloaddition. The diradical involved has ample time to achieve this stereochemical result.



(58) (59) (60)

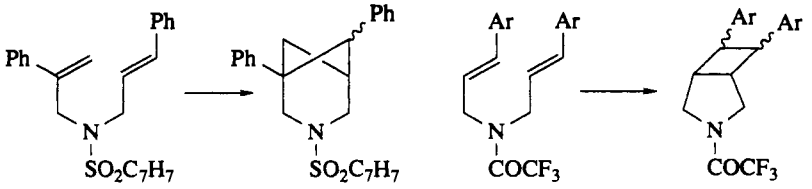


(61) (62) (63) (64)

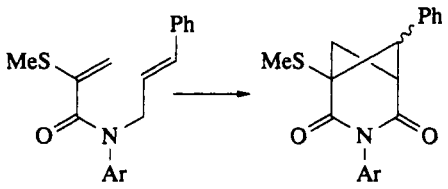
The styrene derivatives studied by Oppolzer are less constrained, and the regiochemistry is governed by the placement of substituents (**65** → **66**; **67** → **68**).[97]

A variation on these themes allowed Alder and Bellus to realize a thermal head-to-tail [2 + 2] addition of two acrylic units (**69** → **70**).[98]

Annulated polyenes like (**71**) and (**72**) isomerize at 180–200 °C to give [2 + 2] intramolecular cycloadducts, with yields and stereochemical details dependent upon the structure and stereochemistry of the

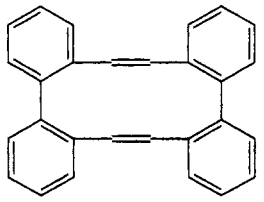


(65) (66) (67) Ar = *p*-ClC_6H_4 (68)

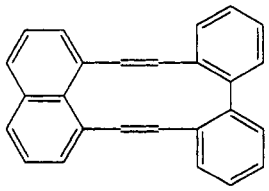


(69) Ar = 3,5-$Cl_2C_6H_3$ (70)

starting material.[99–102] At higher temperatures one obtains products derived from a cycloaddition–cycloreversion sequence, such as phenanthrene (from **71** and **72**) and acenaphthalene (from **72**).



(71)

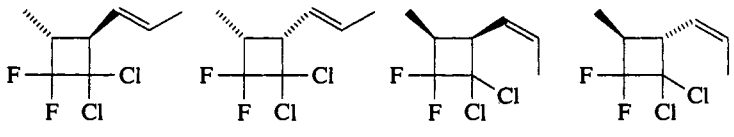


(72)

Pairs of similar alkenes may give useful yields of cycloadducts when one may be employed in large excess: the isomers of 2-butene will add to ethylene at 360–430 °C, giving 1,2-dimethylcyclobutanes showing some but not complete loss of stereochemistry.[103,104]

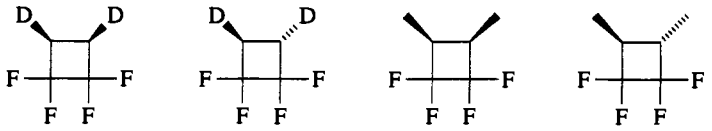
Pairs of alkenes with complementary donor–acceptor properties often give good yields of [2 + 2] cycloadducts. The relatively electron-deficient fluoro- and fluorochloro-alkenes, such as tetrafluoroethylene and 1,1,2,2-difluorodichloroethylene, are excellent participants in thermal [2 + 2] cycloadditions, providing efficient access to many novel and valuable compounds.[3] Mechanistic investigations with these alkenes sustained the credibility of the diradical intermediate mechanism, and attributed heightened reactivity both to destabilization of the ethylene reactant and stabilization of the intermediate by substituents.

In a series of classic papers, Bartlett and coworkers determined regiochemistry and reaction stereochemistry for additions of 1,1-dichloro-2,2-difluoroethylene with conjugated dienes.[5,6] These cycloadditions invariably proceed with the first new bond made between one end of the diene and the difluoro-substituted carbon of the halogenated alkene.[105] For the isomers of 2,4-hexadiene, all cycloaddition products were formed with this regiochemistry, one consistent with formation of the more stable allyl dichloro-substituted diradical intermediate; from each isomeric 2,4-hexadiene the adducts observed were consistent with competitive rates of rotation about carbon–carbon single bonds and formation of the cyclobutane adduct through bond making.[106] The *trans,trans* isomer gave rise to cyclobutanes (**73**) and (**74**), while the *cis,cis* diene gave only isomers (**75**) and (**76**). *cis,trans*-2,4-Hexadiene gave a mixture of all four adducts (**73**)–(**76**).



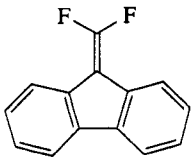
(73) (74) (75) (76)

Loss of stereochemical relationships present in starting alkenes in product cyclobutanes was demonstrated as well for additions involving ethylene or the 2-butenes with tetrafluoroethylene (TFE). The *cis* and *trans* isomers of 1,2-dideuterioethylene and TFE gave a mixture of both (**77**) and (**78**) in comparable proportions.[107] The isomers of 2-butene give (**80**) and (**81**) (42:58 from *cis*-2-butene, 28:72 from *trans*-2-butene).[108]



(77) (78) (79) (80)

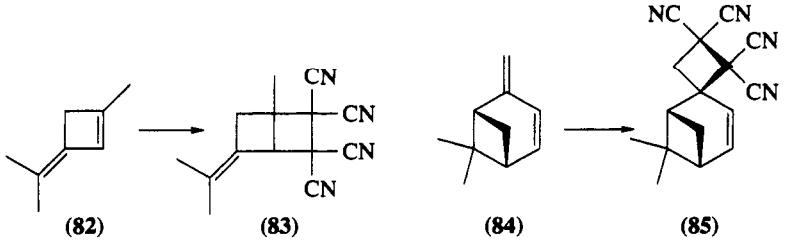
The loss of stereochemistry possible at the diradical stage, and the possible reversion of the diradical to alkenes, may lead to some loss of stereochemical integrity in recovered starting material. This occurrence is consistent with the mechanistic model, and it may be exploited by employing a reagent capable of reacting with an alkene to form a diradical, but reluctant to give a [2 + 2] adduct. 9-(Difluoromethylene)fluorene (**81**) serves well in this capacity: it will catalyze the isomerization of, but does not give cycloaddition products with, the 2,4-hexadienes.[5]



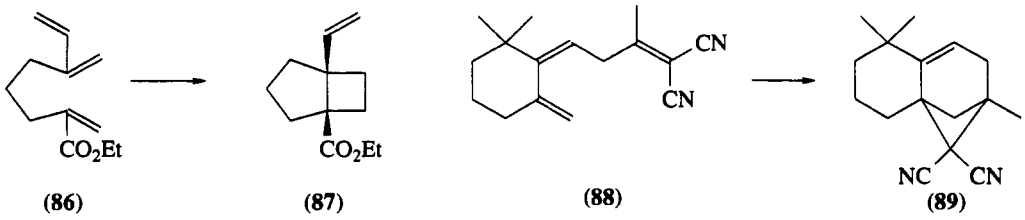
(81)

Fluorine and hydrogen appear comparable as radical-stabilizing groups, for both 1,1-difluoroethylene and trifluoroethylene react with butadiene to give mixtures of [2 + 2] regioisomers, as well as some [2 + 4] products.[109,110] Captodative substituted alkenes, not surprisingly, are well suited to [2 + 2] cycloadditions.[111–113]

For alkene–diene or diene–diene reactions, [2 + 2] additions are often in competition with Diels–Alder reactions: the balance is extremely system dependent. Only [2 + 2] products will be formed when the diene is restricted to the *(S)-trans* geometry, as in the reactions of dienes (**82**)[114] and (**84**)[115] with TCNE to give [2 + 2] adducts (**83**) and (**85**). Other conformationally mobile dienes give [2 + 2] rather than [2 + 4] adducts when reacting intramolecularly because the Diels–Alder alternative would lead to relatively unstable products, as in the isomerizations of (**86**) to (**87**)[116] and of (**88**) to (**89**).[117]



(82) (83) (84) (85)



(86) (87) (88) (89)

When the tetramethylene intermediate involved in [2 + 2] cycloadditions lacks stabilizing functionality at both termini, and the diene is free to assume, or is locked into, the *(S)-cis* conformation, the Diels–Alder process dominates: ethylene and butadiene give vinylcyclobutane and cyclohexene in 1:5000 pro-

portions.[5] While 4-methylpenta-1,3-diene[118] or bicyclopropylidene and TCNE give both [2 + 2] and [2 + 4] addition products,[119,120] only [2 + 2] cycloaddition is seen with 2,5-dimethylhexa-2,4-diene.[121]

For dienes existing as mixtures of *(S)-cis* and *(S)-trans* conformational isomers, reaction in the *(S)-trans* form will lead to [2 + 2] adducts, while reaction to generate a diradical from the *(S)-cis* form may lead to either [2 + 2] or [2 + 4] products. Temperature-dependent product ratios correlate with temperature-dependent *(S)-cis/(S)-trans* conformer populations for the reactions between 1,1-difluoro-2,2-dichloroethylene and butadiene.[122]

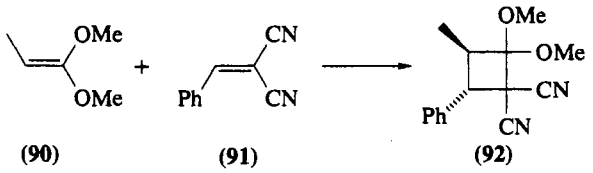
This competition between [2 + 2] and [2 + 4] cycloaddition modes presents both a fascinating mechanistic topic[123–126] and an occasionally daunting synthetic hazard, especially since many alkenes that are particularly reactive in [2 + 2] additions are also excellent dienophiles in Diels–Alder reactions. Frontier molecular orbital analysis provides useful insight regarding this parallelism in relative reactivity. Houk and others[127–129] have developed this treatment, especially for reactions between a substituted ethylene and another π-system, finding that cycloaddition rates may be increased when strong electron-withdrawing groups are present on the ethylene. Correlations between reaction rates for Diels–Alder reactions of 9,10-dimethylanthracene[130] and the ionization potentials (or LUMO energies) of cyano- and polycyanoethylenes as dienophiles validate this view. According to the FMO model, when substitution reduces the donor–acceptor HOMO–LUMO energy separation, the transition state energy may be reduced through configuration interaction. Although Diels–Alder reactions may be symmetry allowed, they still may be facilitated through configuration interaction between ground state and charge-transfer configuration. Evidence of other sorts indicative of significant charge-transfer configuration involvement in Diels–Alder reactions continues to accrue.[131–136]

For [2 + 2] cycloadditions of electron-poor and electron-rich pairs of alkenes, configuration interaction is not just marginally helpful: it is of dominant importance. Without it, activation energies would ordinarily be not just a bit higher, but drastically higher. Interestingly, the nucleophilicities of the cyanoethylenes as two-bond nucleophiles in Diels–Alder reactions and as one-bond nucleophiles in [2 + 2] cycloadditions going by way of 1,4-dipolar intermediates are projected to be approximately the same.[128]

Careful product and kinetic studies for selected electron-deficient alkenes, electron-rich dienes and vinyl-substituted aromatic systems have provided some clarification of the [2 + 2] *versus* [2 + 2] cycloaddition issue. The thermodynamically favored product can often be anticipated on structural grounds. Reactions of TCNE with vinyl-substituted benzenoid aromatics,[5] protoporphorins[137] or heteroaromatics[138] give [2 + 2] products, but for some styrenes the [2 + 4] addition may be kinetically favored. *p*-Methoxystyrene and TCNE react to form a charge-transfer complex which leads reversibly to the Diels–Alder product, and eventually to the finally isolated [2 + 2] adduct.[139–142] An isomer of dicyclopentadiene shows the same pattern, with the initially formed Diels–Alder adduct giving rise to a [2 + 2] adduct.[143]

It is not known with firm assurance if products in these reactions come directly from a charge-transfer complex. Under normal reaction conditions the kinetic behavior of these systems is not sensitive to whether the complex is on the reaction path or is just the product of a dead-end side-equilibrium process.[144] For one Diels–Alder reaction, Kiselev and Miller have demonstrated that the donor–acceptor complex is on the reaction path.[145] Similar studies for representative [2 + 2] additions remain on the agenda, for the issue is of fundamental importance even though it has proven to be a very difficult one to resolve.

Other [2 + 2] cycloadditions based on electron-rich and electron-poor alkenes, such as alkoxyethylenes and TCNE, an extremely electron-deficient alkene, were reported in the late 1950s. Dienes restricted to an *(S)-trans* geometry, thus obviating competitive [2 + 4] additions, and electron-rich alkenes of all sorts give [2 + 2] adducts with TCNE.[146–148] The scope of such additions has continued to develop impressively: TCNE has been added successfully to hundreds of substituted alkenes, and other pairs of alkenes having complementary substituents, making one electron-rich (donor substituents), the other electron-poor (acceptor substituents), have been shown to give similar facile [2 + 2] cycloadditions. Vinylcyclopropanes,[149–152] enamines,[153–157] ketene acetals[158–162] and other activated alkenes[163–165] will combine with alkenes substituted with electron-withdrawing groups. Ketene acetal (**90**), for instance, reacts with acrylic ester (**91**) to give adduct (**92**).[158]



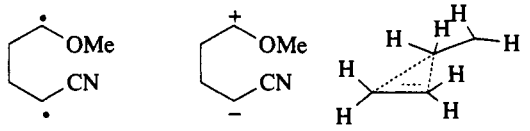
(**90**) (**91**) (**92**)

Substituent effects for typical [2 + 2] cycloadditions between electron-rich and electron-poor alkenes demonstrate a high degree of dipolar character in the transition structure; for *p*-substituted styrenes and TCNE[6] the first-order rate constants for disappearance of the π-complexes and for formation of cyclobutane products correlates well in a Hammett treatment with $[\sigma + 1.21(\sigma^+ - \sigma)]$, and $\rho = -7.1 \pm 0.5$; there is a high degree of charge transfer in the transition structure. For aryl alkenyl sulfides reacting with TCNE the ρ-value of the Hammett correlation is similarly large and negative, –5.5.[166] These and other studies lead naturally enough to consideration of whether 1,4-zwitterionic intermediates might be involved.

2.1.4 DIRADICAL *VERSUS* ZWITTERIONIC INTERMEDIATES

The 1,4-tetramethylene diradical has been subjected to numerous theoretical investigations using a full range of calculational methods[167–172], from the most rudimentary to the most computationally sophisticated. The dimerization of ethylene to generate the diradical has also been modeled theoretically. The diradical mediated path is strongly favored over the orbital symmetry allowed but geometrically awkward $[\pi 2_s + \pi 2_a]$ concerted cycloaddition.

From the perspective of theory, a tetramethylene intermediate substituted with a donor such as methoxy and an acceptor such as cyano is viewed as a resonance hybrid of a singlet diradical canonical form (**93**) and a zwitterionic form (**94**).[173–178] Alternatively, the state wavefunction for the substituted tetramethylene may be derived through configuration interaction which mixes the molecular orbital electronic configurations appropriate to forms (**93**) and (**94**). (Another, higher-energy zwitterionic configuration could be included in the calculation, but would contribute relatively little). Such tetramethylene systems would then in principle span a full range of possibilities from diradicals at one extreme to real zwitterions at the other. In between these extremes the resonance hybrid form, neither a perfectly pure diradical nor a true zwitterion, would be of lower energy than either canonical form would have by itself, and one may validly consider there to be a continuous range of possibilities between diradical and zwitterionic forms. The relative weights of diradical and zwitterionic forms will depend upon the donor and acceptor substituents, other structural factors, and probably on conformation and solvent.[179–182]



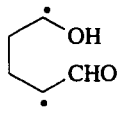
(**93**) (**94**) (**95**)

The issue here is not merely semantic, or of interest only to theoreticians, for the representations (**93**) and (**94**) imply different chemical propensities and properties to a synthetic organic chemist, and one or another style of representation will influence synthetic planning and rationalizations of observed reaction product mixtures.

Interestingly, some polar character may even be involved in what would seem to be a purely diradical mediated cycloaddition, the dimerization of ethylene. The transition structure for the first step in this addition, according to some calculations,[183] is of tricentric geometry (**95**) and it involves transfer of 0.11 electron unit of charge from the ethylene moiety in the three-membered ring to the distant CH_2 of the other ethylene, a reminder that the diradical/zwitterion dichotomy need not be absolute. Other calculations suggest other geometries for this transition structure.[171,184,185]

Calculations for substituted tetramethylene systems, using both semiempirical and *ab initio* methodologies, have been reported for several representative [2 + 2] cycloaddition reactive intermediates one might expect to have some dipolar character. Hydroxyethylene and acrolein lead to a 1-formyl-4-hydroxytetramethylene (**96**) having high diradical character and low zwitterionic character, according to spin density and charge transfer criteria.[186,187] The net transfer of electric charge from hydroxyethylene to acrolein is only 0.09 of one electron unit, suggesting that there is no essential theoretical difference between the diradical character of the intermediate of a polar and of a nonpolar [2 + 2] cycloaddition. Hydroxyethylene and TCNE similarly react to give, according to MNDO with CI calculations, an intermediate of extended conformation (**97**) that is essentially a diradical.[188]

For the [2 + 2] cycloaddition of hydroxyethylene to 1,1-dicyanoethylene the intermediate exists in a very shallow potential well and has largely diradical, but some zwitterionic, character: the charge transfer amounts to 0.2 electrons.[183] The overall transition state for the reaction, which is the transition state



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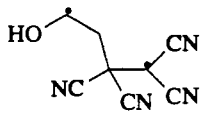
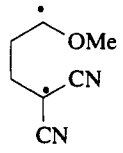


(97)

leading from intermediate to product, has more zwitterionic character, with 0.53 electrons transferred, as the second bond is just beginning to be formed.

Similar calculations of acid-catalyzed [2 + 2] cycloadditions between hydroxyethylene and acrolein show drastic alterations in reaction profile, with the catalyst lowering the overall energy requirements and changing the rate-determining step.[189,190] For the reaction catalyzed by BF_3, NH_4^+ or H^+, the formation of the first bond to give the tetramethylene becomes rate limiting; for the uncatalyzed cycloaddition the second bond formation is the slow step. The catalyst stabilizes both intermediate and second transition state as it 'amplifies' charge transfer between the cycloaddition partners. The first transition state is only slightly lowered, so by default it becomes the rate limiting step.

Other theoretical studies have been concerned with diradical or zwitterionic tetramethylenes approached from [2 + 2] cycloreversions. For 1,1-dicyano-2-methoxycyclobutane, cleavage of C-1—C-2 gives a *gauche* intermediate (**98**) which may isomerize to the *trans* intermediate (**99**). They are nearly isoenergetic, and both have predominant diradical character.[191,192]



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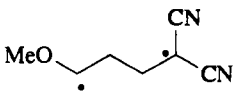
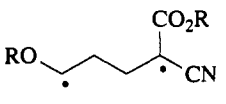


(99)

Hall has introduced an empirical test to estimate the relative importance of diradical and zwitterionic forms in tetramethylene intermediates: *trans*-1,4-tetramethylene diradical intermediates may initiate alternating radical copolymerizations if they add to another alkene faster than they undergo conformational isomerization to the *gauche* form and give a cyclobutane product through carbon–carbon bond formation, while zwitterionic 1,4-tetramethylene intermediates may initiate ionic homopolymerizations.[193–204] This empirical yardstick draws a boundary between [2 + 2] cycloadditions that occur through essentially diradical or essentially zwitterionic tetramethylenes; the resonance hybrid view which encompasses a continuous range of more or less dipolar intermediates is neglected in favor of a more decisive either/or discrimination.

Application of this postulate to a wide variety of reactions demonstrates that diradical behavior persists even with substitutents one might have expected to support zwitterionic behavior. Vinyl ethers and 1-cyano-1-alkoxycarbonylethylenes, for instance, according to the Hall hypothesis, react to give [2 + 2] adducts by way of diradical intermediates (**100**), and dimethyl cyanofumarate and *p*-methoxystyrene show the behavior expected of a reaction mediated by diradical (**101**), even though both reactions might well have been plausibly represented as involving 1,4-zwitterionic intermediates. Diradical (**101**) was successfully trapped using the 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.



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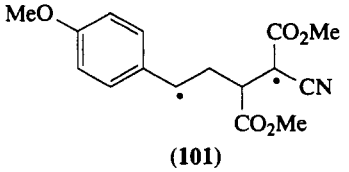
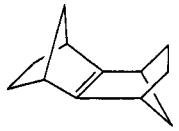


(101)

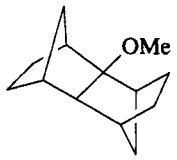
A matrix display of reactive alkenes, with more and more powerful donor and acceptor substituents arrayed in columns and rows, affords a visual representation of the transition between diradical and zwitterionic additions;[199] this 'periodic chart' of thermal [2 + 2] cycloadditions of alkenes makes vivid the wide range of acceptor- and donor-substituted alkenes which show these additions and the demarcation, as derived from the empirical rule or hypothesis given above, between diradical and zwitterionic behavior. The chart contains mostly diradical entries; zwitterionic intermediates are inferred, according to the criterion adopted, for only a few very strong donor-substituted–strong acceptor-substituted pairs of

reactants. When the donor–acceptor potency of reactants becomes somewhat more extreme, electron transfer processes intervene and products derived from radical ion pair intermediates are formed.

While this empirical approach has undeniable merits, its application through experimentation poses some potential limitations, since any extraneous initiation of an ionic homopolymerization could be misinterpreted as indicating the presence of a zwitterionic intermediate. This concern is underscored by reported instances of polymerization initiated by TCNE or by impurities in TCNE,[205,206] or by acidic products derived from an electron-poor alkene and adventitious water,[207] and by other manifestations of acid-catalyzed chemistry accompanying attempted cycloaddition reactions. The isomerization of *trans,trans*-2,4-hexadiene to 1,3-hexadiene in the presence of 1,10-difluoro-2,2-dichloroethylene,[5] and the catalyzed addition of methanol to *anti*-sesquinorbornene (**102**) to afford ether (**103**)[208] are illustrative.

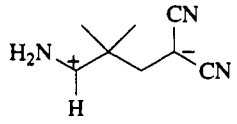


(**102**)

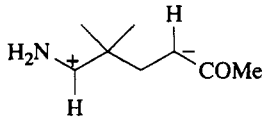


(**103**)

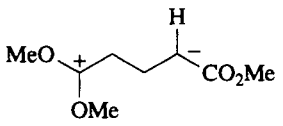
For a series of 10 donor–acceptor substituted *trans*-tetramethylenes, calculations[209,210] have shown a trend paralleling the empirical diradical/zwitterionic test proposed by Hall. Three of the ten cases, (**104**), (**105**) and (**106**), were predicted to have zwitterionic ground states.



(**104**)



(**105**)



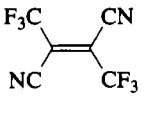
(**106**)

Some cases found empirically by Hall to fall in the zwitterionic category were redesignated as diradicals through these calculational findings, but the overall trends of the empirical scheme were duplicated.

Reviewing the various sorts of evidence employed as mechanistic criteria for cycloadditions involving dipolar intermediates, Gompper[211] concluded that detection of such intermediates through spectroscopic or kinetic methods, or through interception reactions, offers the most generally valid proof. Alternative grounds for mechanistic deductions, based on stereochemical tests, substituent effects, solvent effects on rates, kinetic isotope effects, and activation parameter comparisons, all suffer from a lack of wide-ranging applicability: they may be used only in special cases.

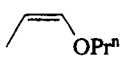
This cautionary attitude toward the standard enumeration of mechanistic criteria seems fully justified when one reflects on the sorts of evidence advanced in support of 1,4-tetramethylene zwitterionic intermediates in thermal [2 + 2] cycloadditions.

Numerous [2 + 2] cycloadditions which may proceed through dipolar intermediates (tetramethylenes which may be represented as resonance hybrids of singlet diradical and zwitterionic forms) react with partial or even complete loss of the stereochemical relationships present in starting materials. Reactions between the *cis* and *trans* isomers of 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*- and *trans*-propenyl *n*-propyl ether are not completely stereoselective. The *trans* electrophilic alkene (**107**) and the *cis* isomer of the enol ether (**108**), for instance, give rise to products (**109**), (**110**) and (**111**), the last having trifluoromethyl groups in *cis* relationship one to the other.[212]

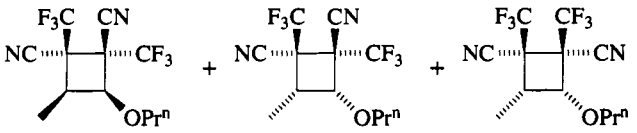


(**107**)

+

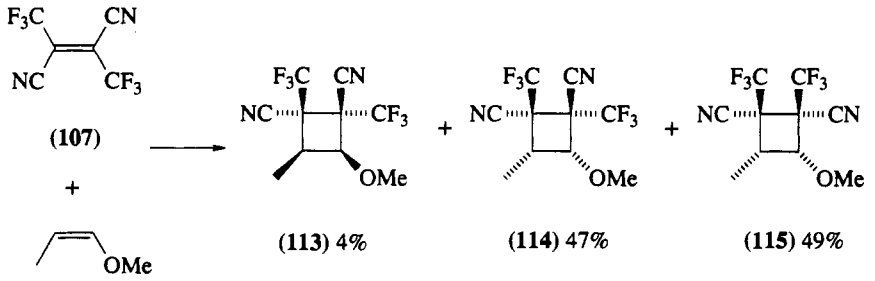


(**108**)

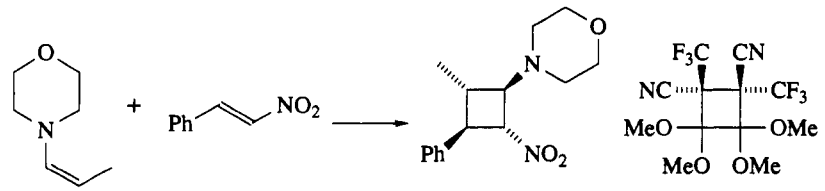


(**109**) 6% (**110**) 41% (**111**) 53%

A thorough stereochemical study of a very similar reaction with *cis*- and *trans*-propenyl methyl ether as electron-rich alkenes provides comparable findings.[213] The *trans* isomer of 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and *cis*-propenyl methyl ether (**112**) gave adducts (**113**), (**114**) and (**115**). In some cases, adducts revealing some loss of stereochemistry in the enol ether component were detected and identified.

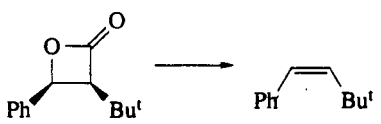


For other examples of ostensibly similar cycloadditions, however, quite different stereochemical results have been obtained, ranging from complete loss (**116** + **117** → **118**; the *trans*-propenyl enamine also gives adduct **118**!)[214,215] to complete retention of stereochemistry: tetramethoxyethylene reacts with (**107**) to give only the [2 + 2] adduct (**119**).[216,217]



(**116**) (**117**) (**118**) (**119**)

Loss of stereochemistry may be plausibly rationalized either through postulation of a diradical intermediate, or a zwitterionic intermediate, or a dipolar intermediate; an observed loss of stereochemistry in [2 + 2] cycloadditions does not help one determine the relative importance of diradical and zwitterionic forms. Complete preservation of stereochemistry, as in the reactions between the 1,2-bis(trifluoromethyl)-1,2-dicyanoethylenes and tetramethoxyethylene, does not necessarily imply a concerted reaction, one with no intermediate on the potential energy surface. There are cogent theoretical reasons for believing that [2 + 2] cycloadditions between very electron-rich and very electron-poor alkenes might be concerted pericyclic processes;[218–225] the Woodward–Hoffmann rules presuppose that a reaction under consideration may be modeled adequately from start to finish with single configuration wavefunctions, and they may be quite irrelevant here, where strong mixing of a charge-transfer configuration is probably involved.[226–230] These reactions could also involve an intermediate that collapses to product faster than it can suffer rotations about carbon–carbon single bonds. This situation may obtain in the decomposition of (**120**) to (**121**) with high stereoselectivity, even though the reaction is believed to proceed in a step-wise fashion.[231]



(**120**) (**121**)

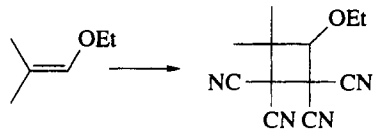
Early work on dipolar [2 + 2] cycloadditions showed that some were extremely sensitive to solvent effects. Qualitative observations for the reaction between *p*-methoxystyrene and TCNE showed that it was

faster the more polar the solvent; it proceeded about 10^5 times faster in acetonitrile than in cyclohexane![232,233]

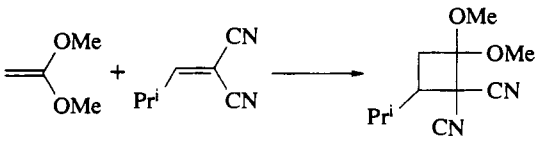
More systematic studies with *trans*-β-methyl-*p*-methoxystyrene and with alkyl vinyl ethers confirmed and extended these remarkably large solvent effects on reaction rates; the reactions of such alkenes with TCNE show large solvent effects and good correlations between solvent polarity, as represented by the E_T parameter, and reaction rates. These large effects were interpreted as support for the intervention of zwitterionic intermediates.[232–238]

The significance of such observations may be inferred from comparisons with solvent effects on the rates of other types of reactions, or on the rates of other reactions believed to be within the same mechanistic category; or one can undertake the thermochemical work necessary to determine changes in heats of solvation for reactants in various solvents and deduce then how much of the observed solvent effect on reaction rates is due to variations in ground-state energies and how much to solvent-sensitive changes in the enthalpy of solution of the transition structure.

For the reaction of (**122**) with TCNE to form (**123**) the rate increase in going from carbon tetrachloride as solvent to acetonitrile is about 4900, while for the reaction of (**124**) with (**125**) to produce (**126**) there is only about a factor of six increase in rate for reaction in acetonitrile relative to reaction in toluene;[239] there is no spectacular solvent effect. Does the latter reaction have a fundamentally different mechanism than is operative in [2 + 2] cycloadditions of enol ethers with TCNE? Are the tetramethylene intermediates of quite different dipolar character?



(**122**) (**123**)



(**124**) (**125**) (**126**)

The [2 + 2] adduct from propenylidenecyclopropane and TCNE undergoes a cycloreversion at 100 °C to give 1,1-dicyanoethylene; the solvent effect on this reaction is quite modest, a result not readily interpretable in terms of a zwitterionic transition state.[240]

Some Diels–Alder reactions have only modest rate responses to changes in solvent,[130,241] and when contrasted with a [2 + 2] addition exhibiting a strong dependence on solvent polarity, a neat mechanistic demarcation may be drawn; distinctions between concerted *versus* nonconcerted reactions, and between early and late transition states,[242] may be advanced. The large solvent effect in the [2 + 2] addition may be ascribed to solvent stabilization of a zwitterionic intermediate. However, when similar reactants, one set giving Diels–Alder product, the other [2 + 2] product, are examined for solvent effects on reaction rates, the dependencies may be virtually identical. A case in point is provided by the reactions of TCNE with 9,10-dimethylanthracene (Diels–Alder reaction) and with 2,5-dimethylhexa-2,4-diene ([2 + 2] cycloaddition).

The solvent effects on rates shown by these two reactions were determined employing the solvents chloroform, dichloromethane, acetonitrile, ethyl acetate, benzene, tetrahydrofuran and dioxane.[243,244] Solvents which react with TCNE, such as nitromethane, dimethylformamide and protic solvents, as well as cyclohexane, carbon tetrachloride and tetrachloroethylene, in which the reactants have very low solubility, were deliberately excluded from the study. The observed solvent effects were virtually identical for both Diels–Alder and [2 + 2] cycloaddition processes. Statistical correlations of rate data using a multiparameter equation with dependencies based on acceptor properties, polarizability and inherent polarity of the solvents gave nearly identical coefficients through the regression analyses for each term for both reactions, and excellent linear fits to the rate data.

Thermochemical studies on the reaction between anthracene and TCNE in various solvents show that solvent-dependent changes in reactivity are largely determined by changes in the enthalpies of solvation of the reactants.[246,247] The same is true for the [2 + 2] cycloadditions between TCNE and *n*-butyl vinyl ether, and TCNE with *trans*-β-methyl-*p*-methoxystyrene.[248] Experimental values for heats of solution and heats of sublimation of reactants allow one to calculate enthalpies of solvation of the reactants in dif-

ferent solvents; plots of $\Delta H^{\ddagger}$ against ΔH(solvation of reactants) determined for different solvents are linear with slopes of –0.8 and –0.9. The observed changes in enthalpies of solution for the transition structures in these [2 + 2] cycloaddition reactions hardly exceed experimental uncertainties. Only carbon tetrachloride gives points well off the correlation lines, which may be related to the fact that kinetic measurements defining $\Delta H^{\ddagger}$ values were made in carbon tetrachloride solutions containing high concentrations of enol ether.[249]

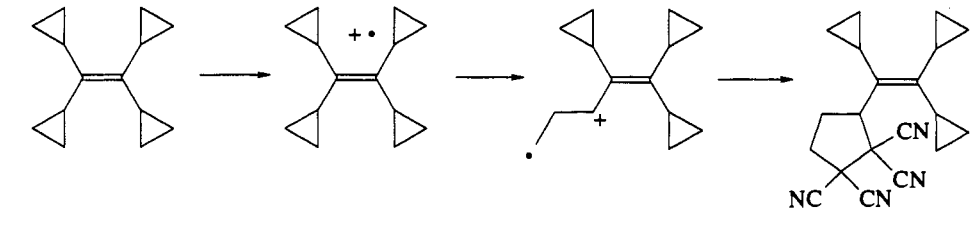
Since solvent effects are so variable, and when studied rigorously provide no support for the involvement of solvent stabilization of zwitterionic intermediates, definite mechanistic and synthetic implications follow: observed rate effects in response to changes in solvent must be interpreted with great caution, and heats of solution studies are highly desirable to distinguish solvent-induced variations in ground-state *versus* transition-state energies. At least in the immediate future, new [2 + 2] cycloadditions required to attain given synthetic objectives may be optimized most expeditiously with respect to yield and selectivity through an empirically determined choice of solvent. The importance of solvent effects for the practical exploitation of such reactions can hardly be overemphasized, even though the theoretical explanation of such effects must be approached with discretion.

There are instances when a loss of stereochemistry accompanying a [2 + 2] cycloaddition, as well as the overall rate of reaction, may change with solvent, and typically there is more loss in more polar solvents.[6,249–251] This may reflect a longer lifetime of a tetramethylene species, thus advantaging rotations about carbon–carbon single bonds relative to ring closures, which in turn could be associated with a growing importance of zwitterionic character for the intermediate. Alternatively, the effect might be the outcome of small shifts in relative importance of initial bond-making to form *gauche versus* extended *trans* tetramethylenes. The latter, whether formulated as diradical or zwitterion, should have better prospects of losing stereochemical integrity prior to forming a cyclobutane product. This possibility may be compared with the cycloaddition chemistry of cyclopropene (**47**) discussed above.

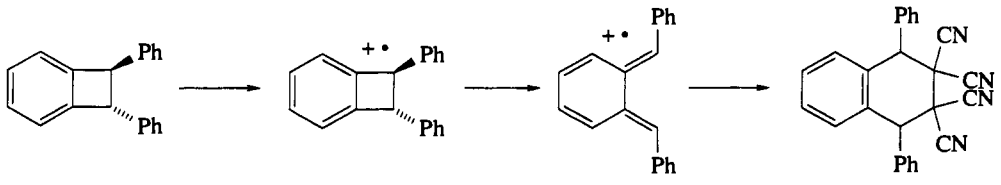
When [2 + 2] cycloadditions are followed as a function of pressure, the volume of activation, $\Delta V^{\ddagger}$, may be deduced. A number of representative [2 + 2] additions have been investigated in this way: the reactions take place with very large negative activation volumes, ranging from –25 to –45 $cm^3\ mol^{-1}$.[252–265] Intermolecular Diels–Alder reactions typically exhibit large negative volumes of activation also: from –25 to –45 $cm^3\ mol^{-1}$.[266,267] As mechanistically discriminating indicators for concerted *versus* stepwise cycloadditions, then, $\Delta V^{\ddagger}$ values are not especially telling; nor, incidentally, are $D H^{\ddagger}$ or $\Delta S^{\ddagger}$ parameters.[245]

The most curious point respecting volume of activation considerations, however, relates to synthetic applications. While high pressure is now often employed to secure intermolecular Diels–Alder adducts that could not otherwise be formed in reasonable yields, there has been little application of the same tactic to recalcitrant [2 + 2] cycloadditions. The opportunities for synthetic exploitations of the mechanistically oriented $\Delta V^{\ddagger}$ determinations for [2 + 2] cycloadditions seem essentially untapped (and enormous).

When donor-substituted and acceptor-substituted alkenes complex and suffer a one-electron transfer, the cation radical of the radical cation–radical anion pair may suffer rearrangement at rates competitive with back electron transfer or with radical ion pair recombination. Some vinylcyclopropanes show this phenomenon (**127** → **128** → **129** → **130**);[268] TCNE and the diphenylbenzocyclobutene (**131**) react similarly to form (**134**) by way of (**132**) and (**133**).[269]

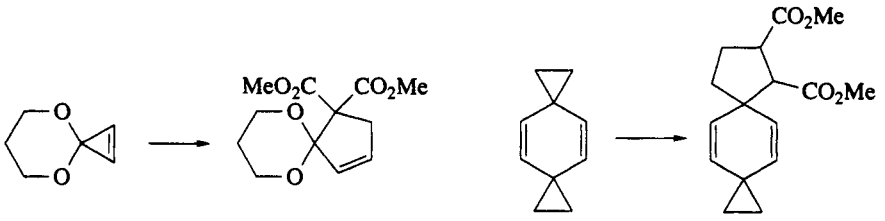


(127) (128) (129) (130)



(131) (132) (133) (134)

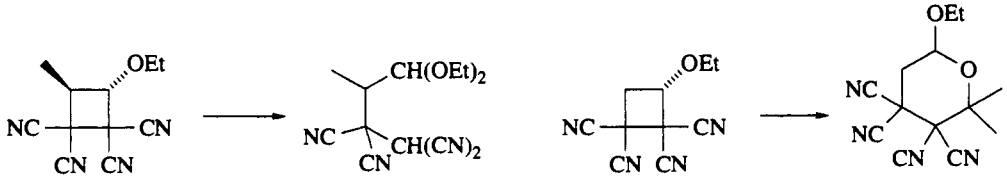
In other cases the one-electron transfer mediated mechanism for rearrangement and final adduct formation is only a conjecture, a possibility, an alternative interpretation. Might it be involved in the reaction of (**135**) with dimethyl methylenemalonate leading to (**136**)[270,271] or of dimethyl fumarate with (**137**) to give (**138**)?[272]



(**135**) (**136**) (**137**) (**138**)

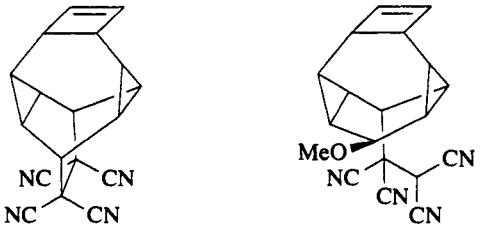
The case for 1,4-zwitterionic intermediates based on chemical trapping experiments depends on obtaining such products using reagents reactive toward the tetramethylene and unreactive toward both addends and the [2 + 2] cycloadduct.

There have been a number of unsuccessful attempts to trap 1,4-zwitterionic intermediates,[217,273–275] but there have also been some reported successes. At best, then, such trapping experiments are not uniformly diagnostic for zwitterionic intermediates. *trans*-Propenyl ethyl ether reacts with TCNE in ethanol solvent at 25 °C to give product (**140**).[276–279] The normal [2 + 2] adduct (**139**) gives this same product when allowed to react in ethanol, but at a slower rate. Just how fast this solvolysis might take place under the conditions of the cycloaddition reaction, with enol ether and TCNE present, is not clear. Acetone does not interfere with the addition of ethyl vinyl ether to TCNE, but the adduct (**141**) is converted over one week at room temperature to the six-membered ring product (**142**), which may be postulated as being derived from capture of a 1,4-zwitterionic intermediate in equilibrium with the cyclobutane structure. Alternatively, since acetone like ethanol is known to react with TCNE,[147] it may be a case of acid-catalyzed solvent-assisted solvolysis.



(**139**) (**140**) (**141**) (**142**)

Solvolyses of structures containing relatively polar C—C(CN)$_2$ bonds have been found by other workers, when the bond cleaved is in a four-membered ring[280] and in larger ring structures: adduct (**143**) gives (**144**) in methanol.[281] Acid catalysis may play a role; it may too in other cases involving cleavage of other kinds of bonds.[282]



(**143**) (**144**)

Bicyclopropylidene and TCNE give rise to structures corresponding to trapping of a zwitterionic intermediate by such agents as acetonitrile.[283]

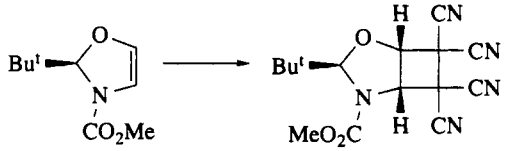
Whatever the difficulties associated with attempts to demonstrate the intervention of 1,4-zwitterionic intermediates, there are undoubtedly reactions for which the zwitterionic formalism provides a conven-

ient model for accounting for the unexpected products sometimes observed,[284–288] and this fact should assure some continuing efforts toward trapping and kinetic experiments designed to test that model.

2.1.5 STEREOCHEMISTRY AND SUMMARY

The stereochemistry of thermal [2 + 2] cycloadditions of alkenes is fairly predictable: which of two double bonds in a molecule, and the regiochemistry of addition, may be anticipated with confidence; the extent to which *cis/trans* relationships in alkene reagents will be lost in the adduct is in general not known in advance, and this factor must be taken into account in synthetic planning. The normal expedients (limiting geometrical options through employing cyclic substructures, or using reagents without *cis/trans* stereochemistry, such as 1,1-dimethoxyalkenes) can often obviate this limitation. While solvent effects on loss of stereochemistry during cycloadditions are potential variables to be utilized, the effects are often minor, and the stereochemical objectives have to be balanced against other considerations, including reaction time and yield. The great augmentation in scope of [2 + 2] thermal cycloadditions to be attained through the use of high-pressure reaction conditions may also have a benefit for stereochemical concerns: at higher pressures there may be less loss of stereochemistry accompanying the addition.

The diastereofacial selectivity of [2 + 2] cycloadditions can be quite high, as in the reaction of TCNE with diene (**82**)[115] or with the chiral alkene (**145**) which gives product (**146**) in 94% yield.[289]



(**145**) (**146**)

Substituents on the carbon atoms involved in the first bond-making step give rise to stereochemical relationships in the product with fairly high selectivity; the larger substituents are disposed in a *trans* orientation in the product, as in the reaction (**90**) + (**91**) → (**92**). Models and theoretical rationales for this favored mode of combination of the two trigonal centers have been advanced.[290–292]

In summary, then, the diradical *versus* zwitterionic issue seems to have shifted in recent years, away from an either/or dichotomy and toward a more integrated view, one seeing tetramethylene intermediates as more or less dipolar diradicals. A small amount of zwitterionic character does not obviate the essentially diradical nature of these intermediates, any more than monoradicals forego radical character if they are more or less electrophilic or nucleophilic.

A little bit of zwitterionic character goes a long way energetically, especially in transition states for cyclobutane formation. 1,4-Zwitterionic tetramethylene intermediates in [2 + 2] cycloadditions may well be important in some reactions, where donor and acceptor substituents are so strong that diradical character is overshadowed and yet one-electron transfer does not take over, but they do not at this point seem common.

The stereochemical characteristics of thermal [2 + 2] cycloadditions of alkenes seem fairly well defined, but substantial further developments and elaborations on stereochemical aspects of the reaction may be anticipated. The ground work has been done, but full development of the potential of the reaction for stereocontrolled synthetic operations still lies ahead.

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2.2
Formation of Four-membered Heterocycles

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2.2.1 INTRODUCTION

Among the four-membered heterocycles, 2-azetidinones have received considerable attention due to the presence of a β-lactam ring as an important structural feature for the biological activity of penicillins, cephalosporins and related antibiotics.[1,2] Recent reviews of β-lactam syntheses have been given by Sammes,[3] Isaacs,[4] Mukerjee,[5,6] Hegedus,[7] Labia[8] and Barrett.[9] The most complete and exhaustive ac-

counts covering the chemistry of small heterocyclic rings are found in the well-known series edited by Weissberger[10] and Hassner.[11]

The replacement of carbon atoms of cyclobutane by heteroatoms introduces functionalities which show increased reactivity resulting from the ring strain. This often leads to unusual properties which make four-membered heterocycles useful as synthetic intermediates.[12–18] However, it also adds a new dimension of difficulty concerning the synthesis of these heterocycles. A valuable source of four-membered heterocycles uses the combination of π-bonds. This section is devoted to a survey of these reactions with special focus on selectivity in all of its forms. Photochemical cycloadditions are not discussed here since they are covered elsewhere. In several instances, reactions will be described which can formally be considered as combinations of π-systems but probably take alternate pathways. However, since the real mechanisms are often unknown, these very useful reactions will be discussed here.

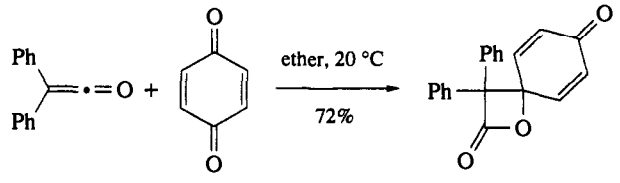
2.2.2 2-OXETANONES FROM KETENES AND CARBONYL COMPOUNDS

2-Oxetanones (β-lactones)[19,20] are useful synthetic intermediates which have been most often prepared by cyclization[21,22] of β-halo or β-hydroxy acid derivatives or by addition of ketenes[23–26] to carbonyl compounds. They are starting materials for useful polymers and copolymers[27,28] and have been used for the synthesis of alkenes[26,29] and carboxylic acid derivatives.[30,31] β-Lactones possessing antimicrobial activity have recently been found in bacterial cultures.[32–34]

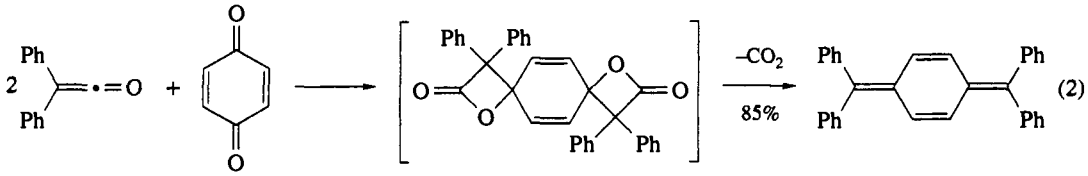
2.2.2.1 Chemo- and Regio-selectivity

The carbonyl π-bond has been found to add chemo- and regio-selectively across the alkenic π-bond of ketenes.[24] Thus diphenylketene readily reacts with benzoquinone to yield a stable [2 + 2] adduct (equation 1).[25] With an excess of diphenylketene the bis-adduct is formed, which decomposes into tetraphenylquinodimethane and carbon dioxide (equation 2).[25] With the less stable ketene, thermal [2 + 2] cycloadditions are observed with highly electrophilic carbonyl compounds (equation 3).[25] With unactivated aldehydes and ketones, yields are much lower due to a faster oligomerization of the ketene reagent. However, in the presence of a Lewis acid catalyst, most aldehydes or ketones form β-lactones with ketene (equation 4).[35] Cycloadditions with ketones usually require more active catalysts than with aldehydes. The catalyzed reaction of ketene with methyl vinyl ketone is chemoselective,[25] yielding a 10:1 ratio of [2 + 2] *versus* [4 + 2] adducts (equation 5). In the absence of catalyst, methyl vinyl ketone reacts with ketene to give exclusively the [4 + 2] adduct.

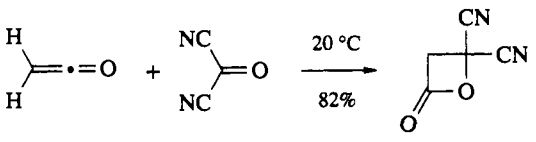
A practical extension of the reaction uses ketenes generated *in situ*[36] in the presence of a carbonyl compound. Thus the highly reactive dichloroketene generated *in situ* from the reaction of dichloroacetyl chloride with triethylamine has been trapped by aldehydes (equation 6) or activated ketones (equation 7)



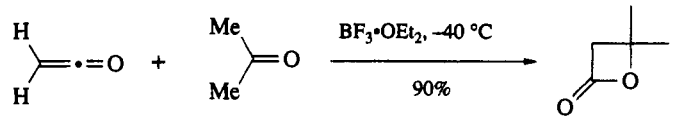
(1)



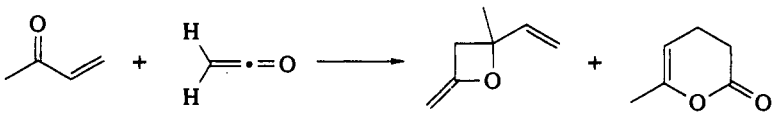
(2)



(3)



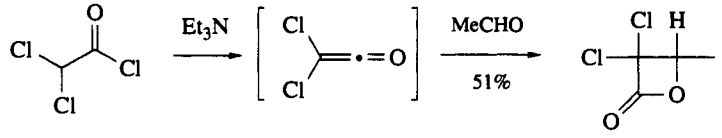
(4)



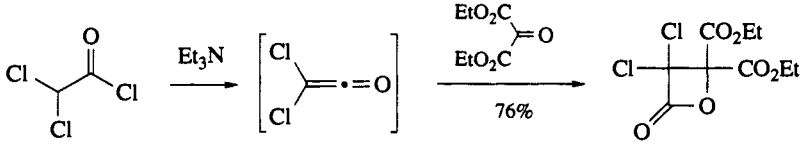
(5)

$ZnCl_2$ (20 °C)	91	9
no catalyst (Δ)	0	100

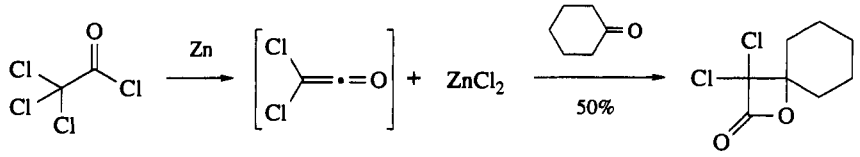
to give β-lactones.[37-39] Simple ketones do not react under these conditions. However, β-lactones are formed when ketones are reacted with dichloroketene generated from trichloroacetyl chloride and zinc (equation 8). Zinc chloride formed *in situ* activates the ketone partner.



(6)



(7)



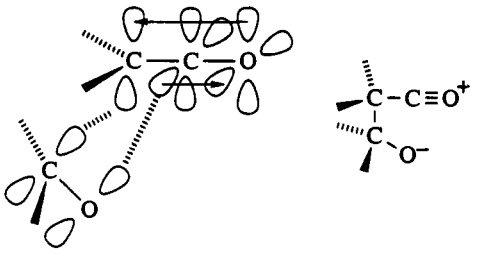
(8)

There is ample evidence[40] that, in these reactions, the ketene is behaving as the nucleophilic partner. Ketenes are ambiphilic molecules[41] which are characterized by a low-energy LUMO but also by a high-energy HOMO resulting from the interaction of an oxygen lone pair with the alkenic π- bond. Thus the dominant interaction between the two partners occurs *via* the highest occupied molecular orbital of the ketene and the lowest unoccupied molecular orbital of the carbonyl compound. This readily accounts for the regiochemistry of the reaction, the C-2 carbon atom of the ketene being always linked to the carbon atom of the carbonyl compound. From the information available it is not possible to ascertain whether these reactions are stepwise or concerted cycloadditions. Formation of the β-lactone could well occur in a single step involving a transition state (**1**) similar to that of the ketene–alkene reaction[41] but in which bonding is more advanced between C-2 of the ketene and the carbon of the carbonyl compound. However, the formation of a 1,4-dipolar intermediate (**2**) cannot be rejected. Complexation of the carbonyl compound with a Lewis acid catalyst will lower the LUMO, thus favoring the reaction.

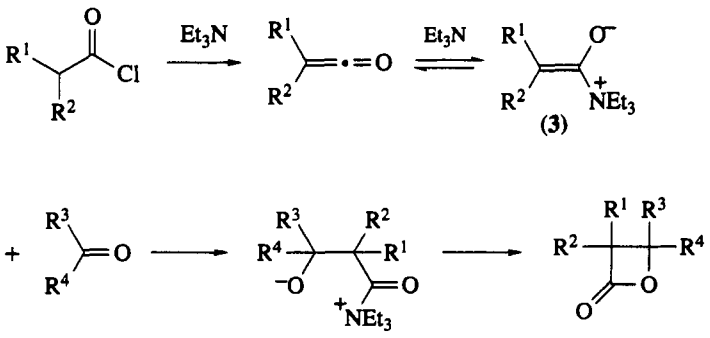
Alternatively, when the ketene is generated in the presence of triethylamine, one cannot exclude the formation of a nucleophilic intermediate (**3**) which would then add to the carbonyl compound (Scheme 1).[42]

2.2.2.2 Stereoselectivity

The diastereoselectivity of addition of ketenes to carbonyl compounds is moderate (equations 9 and 10). Mixtures of *cis* and *trans* β-lactones are usually formed.[43,44]

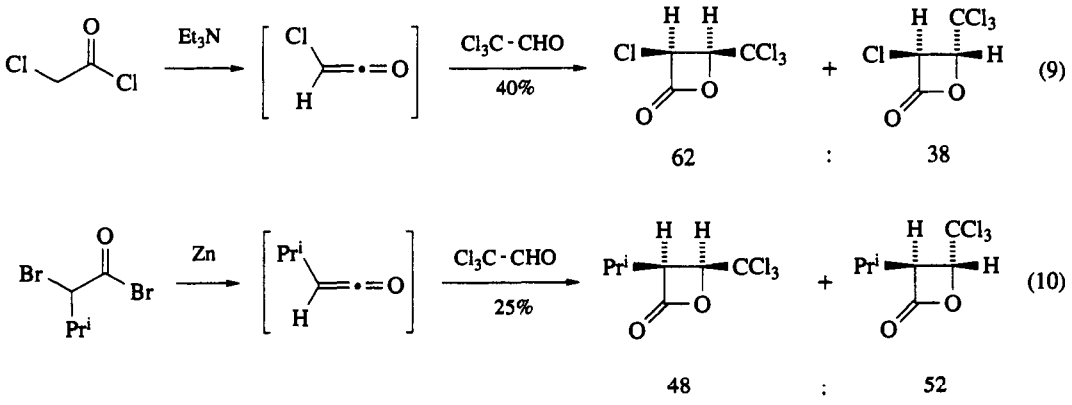


(1) (2)



(3)

Scheme 1



(9)

62 : 38

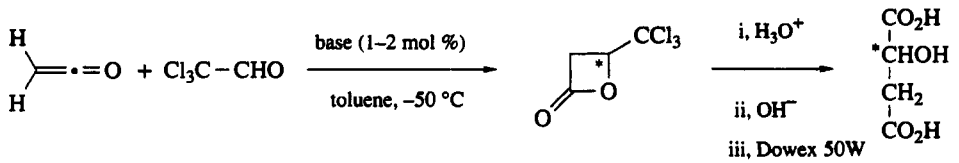
(10)

48 : 52

Enantiopure β-lactones have been obtained from the reaction of acid chlorides[45] or ketene[30,46–49] with aldehydes in the presence of optically active tertiary amines. The reaction of ketene with chloral has been studied in considerable detail (Scheme 2). In the presence of 2 mol % of quinidine at –50 °C the β-lactone is formed in virtually quantitative chemical and optical yield.[47] By proper choice of the catalyst, either enantiomer of the β-lactone can be obtained. The transition state picture (4) has been proposed[50] for the ketene–chloral addition in the presence of quinidine. Hydrolysis converts the β-lactone to malic acid with inversion of configuration (Scheme 2).[47]

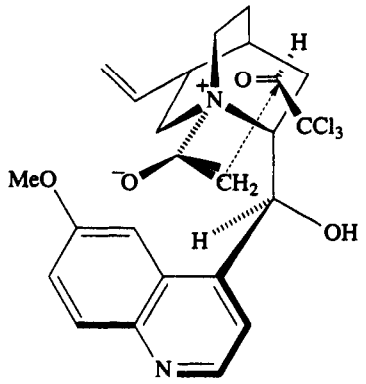
Similarly, the quinidine-catalyzed cycloaddition of ketene to 2,2-dichloro aldehydes gives β-lactones of high optical purities which are easily converted to the corresponding methyl (3*S*)-hydroxyalkanoates (Scheme 3).[30]

In the presence of catalysts such as $ZnEt_2/H_2O$ or $AlEt_3/H_2O$, optically active 2-substituted β-propiolactones readily polymerize[48,49] to give optically active stereoregular polyesters exhibiting quite unique properties compared with the corresponding racemic polymers (Scheme 4).



Base	*Yield (%)*	*ee (%)*	*Configuration*
(R)-1,2-Dimethylpyrrolidine	87	60	*(S)*-(+)
(S)-*N*,*N*-Dimethyl-α-phenylethylamine	90	77	*(R)*-(–)
Quinine	89	76	*(S)*-(+)
Quinidine	95	98	*(R)*-(–)

Scheme 2



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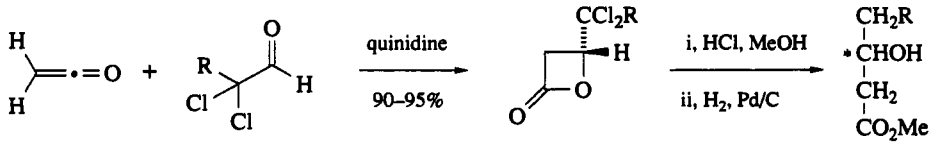
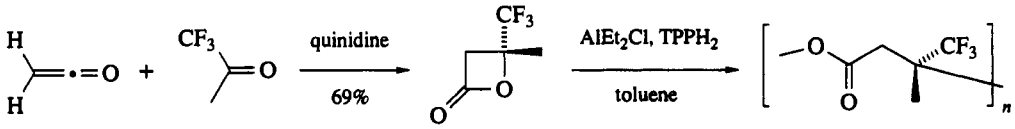


R = Et, Bu^n, n-hexyl

ee 92% (crude)
ee 98% (cryst.)
(R)-(+)

(S)-(+)

Scheme 3

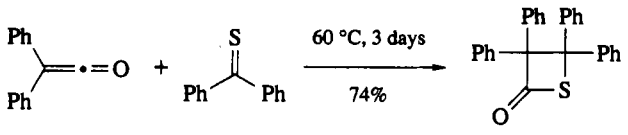


ee 89%
(R)-(+)

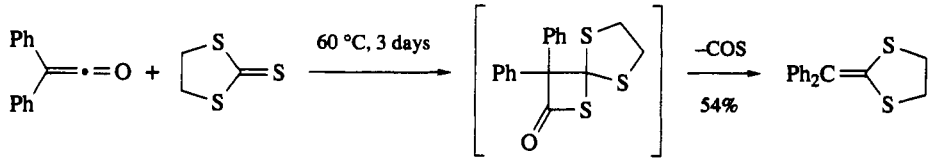
Scheme 4

2.2.3 2-THIETANONES FROM KETENES AND THIOCARBONYL COMPOUNDS

These reactions, first described by Staudinger,[24] have received little attention. A more recent investigation shows[51] that the C=S bond of the thiones regioselectively adds across the C=C bond of the ketenes (equation 11) to form 2-thietanones (β-thiolactones). Primary adducts have been isolated only in a few cases. Most often they spontaneously decompose to yield an alkene and COS (equation 12).



(11)

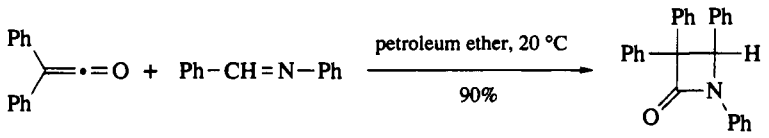


(12)

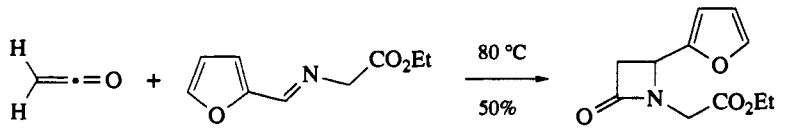
2.2.4 2-AZETIDINONES FROM KETENES AND IMINES

2.2.4.1 Direct Combination of Ketenes with Imines

The first 2-azetidinone (β-lactam) was obtained by Staudinger[52] from the reaction of diphenylketene with benzylideneaniline (equation 13). Most of the β-lactams prepared by this method have been made from imines derived from aromatic carbonyl compounds and ketoketenes.[23–26,53–55] The reaction of ketene itself with imines has been recently reinvestigated.[56] Good yields of β-lactams are obtained when a stream of ketene gas is passed through the imine in the absence of solvent (equations 14 and 15). No [4 + 2] cycloadduct is formed with *N*-cinnamylideneaniline.



(13)



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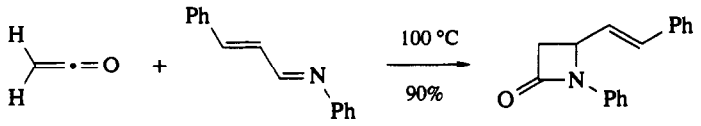


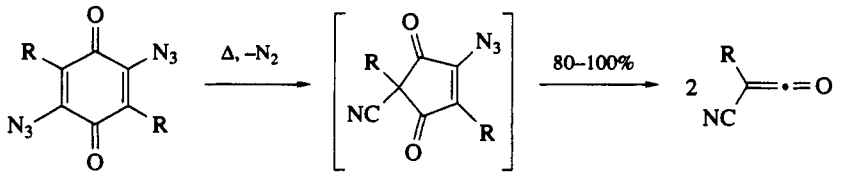
(15)

Cyanoketenes are conveniently prepared[54,57] by thermolysis of 2,5-diazido-1,4-quinones or 4-azido-3-halo(or phenoxy)-5-methoxy-(5*H*)-furan-2-ones in refluxing benzene (Scheme 5).

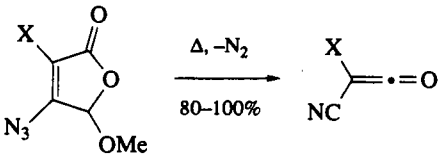
With the exception of *t*-pentyl- and *t*-butyl-cyanoketenes, which are stable to self-condensation, cyanoketenes are generally generated *in situ*.[54] Reactions with imines, formimidates and thioformimidates yield the corresponding 3-cyano-2-azetidinones (equations 16–18). The reactions proceed stereoselectively, yielding β-lactams having the 3-cyano and 4-protio substituents in a *trans* relationship.[57]

There is ample evidence[57] that these cycloadditions involve the initial formation of a dipolar intermediate (**5**; Scheme 6). Conrotatory cyclization of (**5**) leads to the β-lactam. Intermediates of type (**5**) can be trapped by another molecule of ketene to yield (**6**)[24] or by sulfur dioxide to yield sulfone (**7**).[58] This mechanism also explains the formation of [4 + 2] adducts (**8**) which are sometimes observed with conjugated imines.[57,59]

Intermediates of type (**5**) have been independently generated[54] and found to yield β-lactams (Scheme 7). The stereochemistry of the β-lactams has been rationalized[57] on the basis of a conrotatory ring closure of the intermediate dipole in a way which minimizes steric interactions (equations 19 and 20). However, this explanation is weakened by the fact that configurations proposed for dipoles are purely speculative.

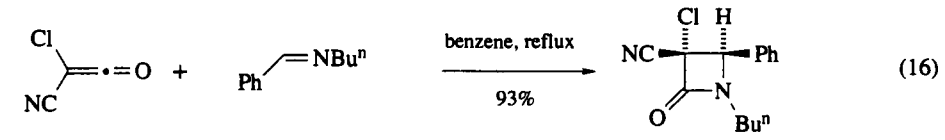


R = Bu^t, Pr^i, Me, Ph, CN

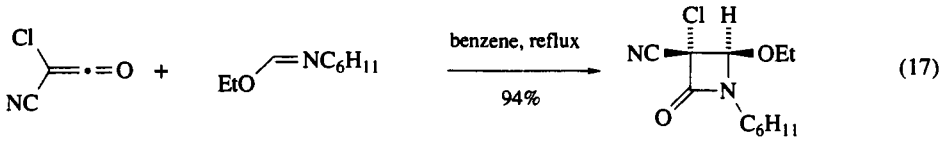


X = Cl, Br, I, PhO

Scheme 5



(16)



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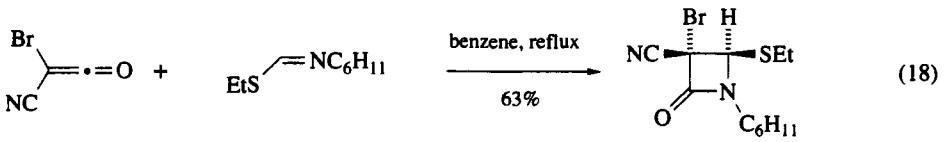

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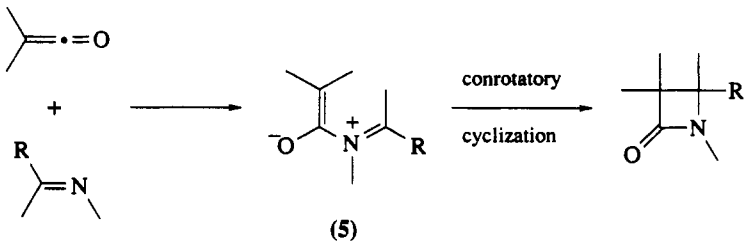
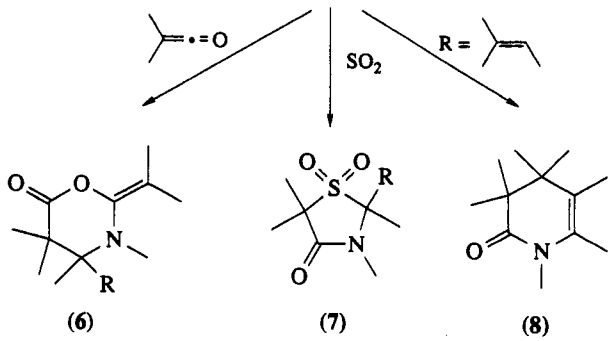
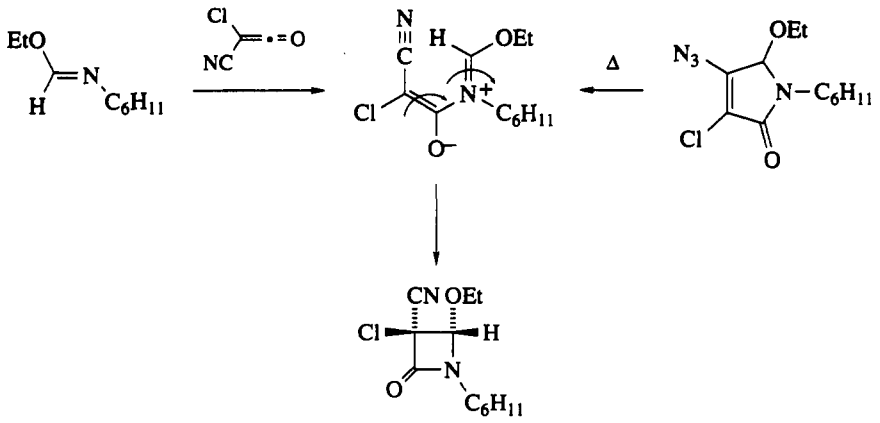


(5)



(6) (7) (8)

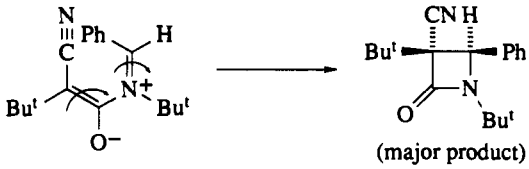
Scheme 6



Scheme 7

(19)

(single product)



(20)

(major product)

The preparation of β-lactams by the direct combination of isolated ketenes with imines is severely limited by the instability of monosubstituted and heterosubstituted ketenes, which show a great tendency to polymerize.[41] The discovery that ketenes can be readily generated by the reaction of an acid chloride with tertiary amines offers a practical solution to this problem.[60]

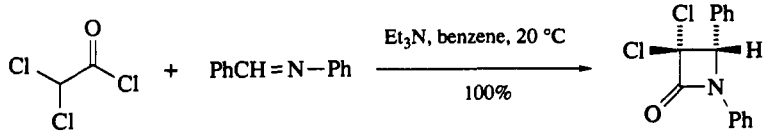
2.2.4.2 Reactions with Ketene Precursors

2.2.4.2.1 Chemo- and regio-selectivity

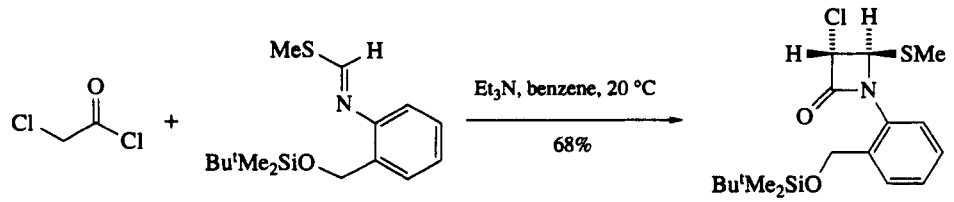
β-Lactams are readily prepared by reaction of acid chlorides or bromides with imines in the presence of a tertiary base, usually triethylamine. The method is extremely versatile. Conditions are very mild (inert solvent, room temperature) and sensitive functional groups are tolerated on both the imine and acid chloride partners (equations 21–24).[61–64]

Particular attention has been focused on cycloadditions of acid chlorides bearing a masked amine function[65–75] since they are potential precursors of penicillin or cephalosporin analogs (equations 25–27).

Thiazines have been successfully used as cycloaddition partners (equation 28)[76] but only thiazolines bearing a substituent at C-2 were found to yield β-lactams.[77,78] In this context, thio and, even better, seleno groups are useful as precursors of a protio group in the resulting β-lactams (Scheme 8).[79–81]



(21)



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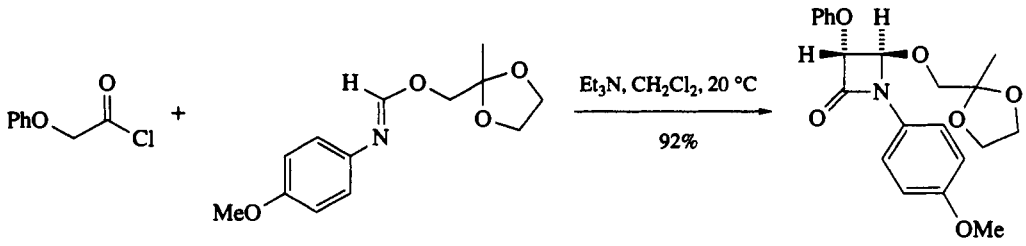

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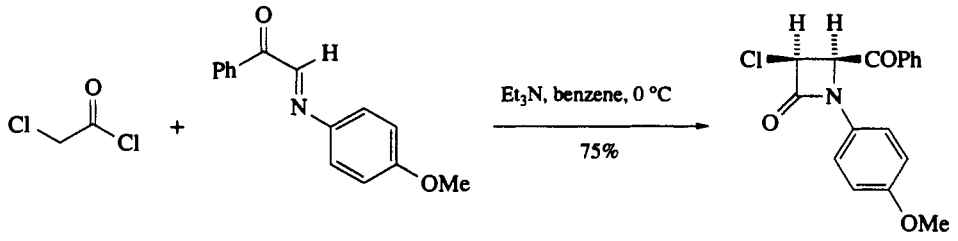
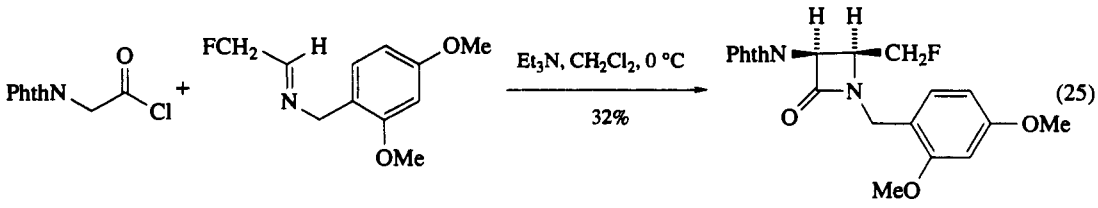


(24)



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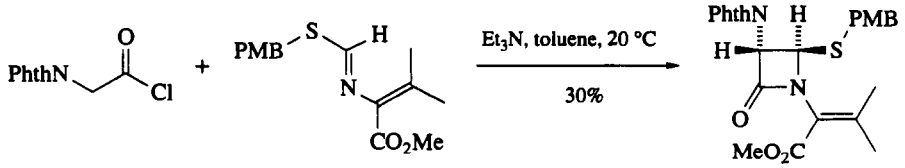
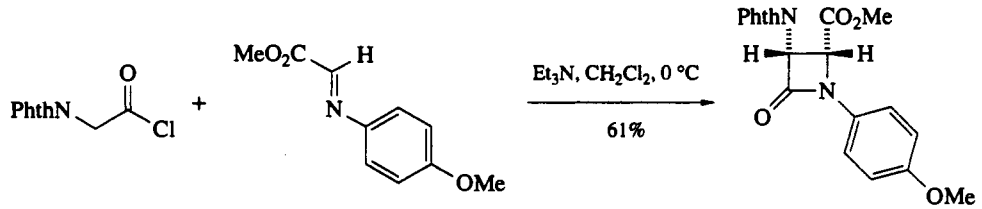


(26)

PMB = —CH_2—⟨⟩—OMe



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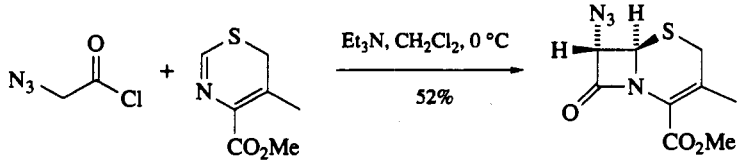

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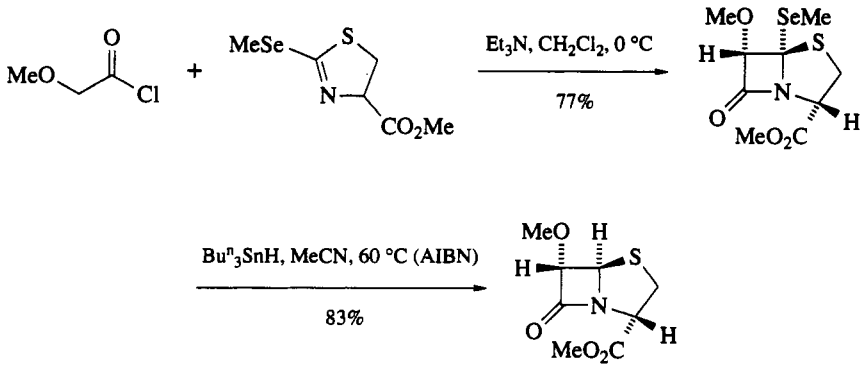
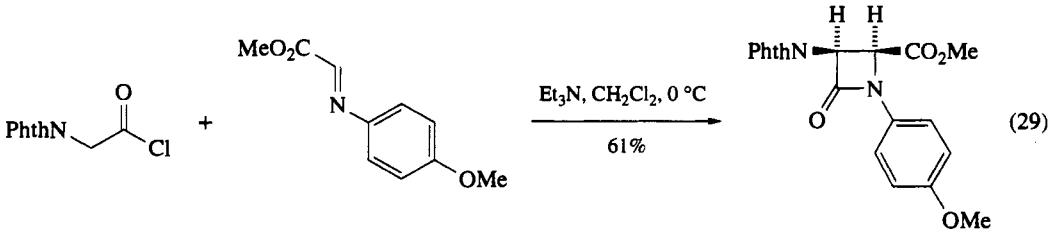


Scheme 8

Imines derived from glyoxylic acid derivatives[66,82] successfully lead to β-lactams which are potential precursors of various antibiotics (equation 29). Conjugated imines have also been used in this context: they give exclusively [2 + 2] cycloadducts with azido-,[66,83–86] phthalimido-,[87] phenoxy-[87] and vinylketene[88] precursors (equations 30 and 31). However, [4 + 2] adducts are the only observed products with haloketene precursors (equation 32).[59,61]



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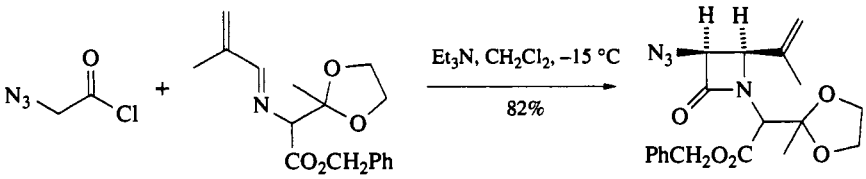

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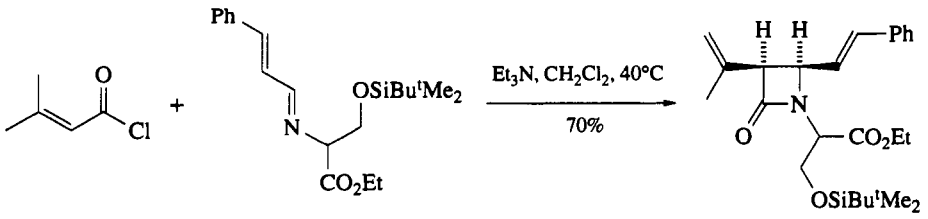
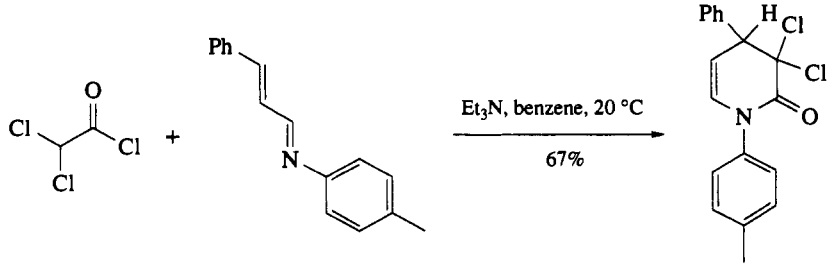
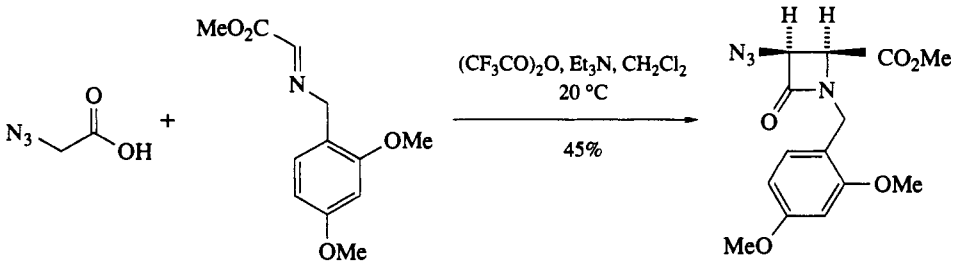


(31)



(32)

Alternative syntheses of β-lactams which circumvent the use of acid halides involve carboxyl group activating reagents (equations 33–35).[89–98] These are more practical when the corresponding acid chlorides are unstable or unsafe.[89]



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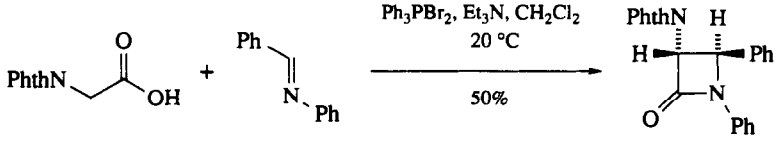

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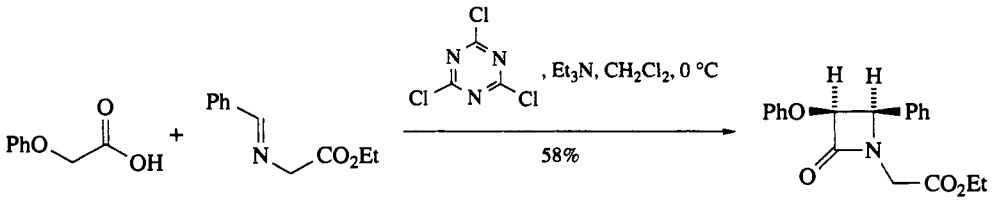
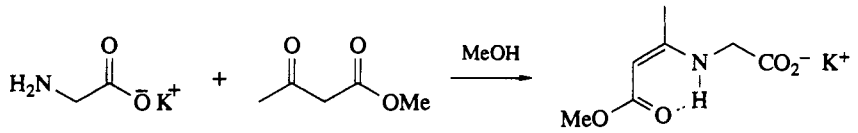
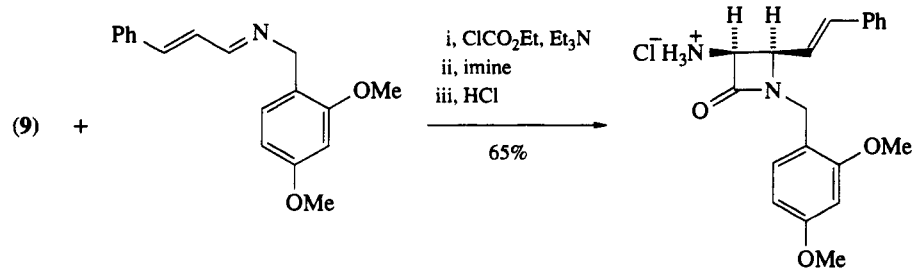


(35)

A practical synthesis of α-amido β-lactams uses a 'Dane salt' (**9**) formed by the reaction of a methanolic solution of the potassium salt of glycine with methyl acetoacetate (Scheme 9). The salt (**9**) readily reacts with a Schiff base in the presence of triethylamine and *e.g.* a chloroformate ester.[89] Other activating agents such as phenyl dichlorophosphate[90,99,100] or phosphorus oxychloride[101,102] have also been successfully used.



(**9**)

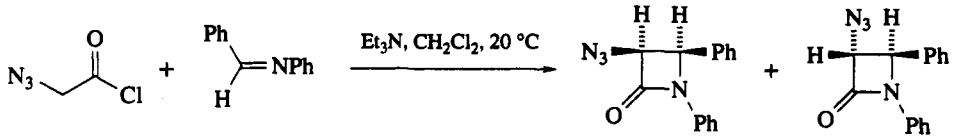


Scheme 9

2.2.4.2.2 Stereoselectivity

The stereochemical course of the reaction varies with the nature of the substituents on both the ketene precursors and imines and also with experimental conditions.[57,68,73,88] Under the usual conditions (addition of the acid chloride to a solution of imine and Et_3N, in CH_2Cl_2 at 0–20 °C), α-functionalized acetyl

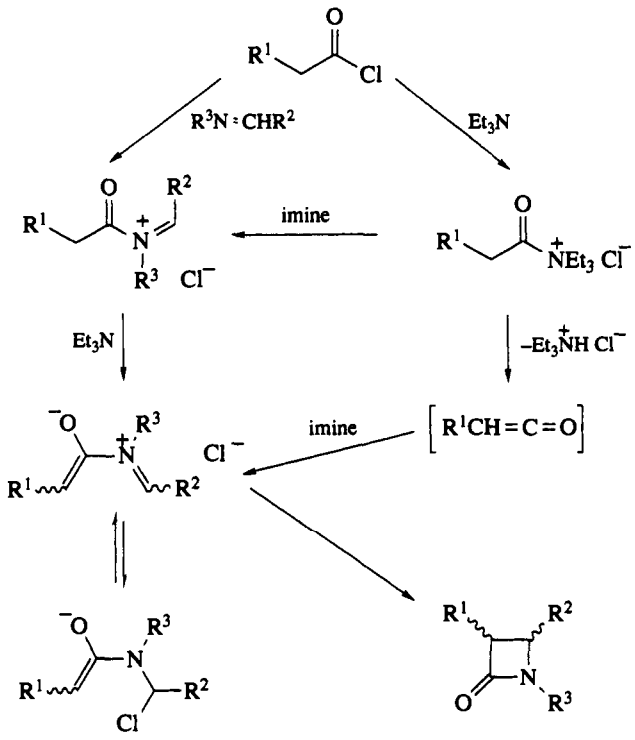
chlorides yield *cis* β-lactams as major or often single stereoisomer (equations 24, 25, 27, 29, 30, 31, 33 and 35) except with imidates or thioimidates (equations 22, 23, 26 and 28). The sequence of addition of the reactants can also influence the isomer ratios (Scheme 10).[68] Both *cis* and *trans* β-lactams appear to be stable under the experimental conditions.



	cis	*trans*
addition of acid chloride (to imine + Et_3N)	66%	34%
addition of Et_3N (to imine + acid chloride)	33%	67%

Scheme 10

Tentative rationalizations of these stereochemical results have been offered on the basis of a mechanism involving a ketene intermediate reacting with an imine.[103–107] However, it is by no means proven that all these reactions involve an intermediate ketene. Several pathways can lead from an acid chloride, an imine and triethylamine to a β-lactam (Scheme 11). Thus the origin of the stereochemical selection in these multistep processes is not very well understood.

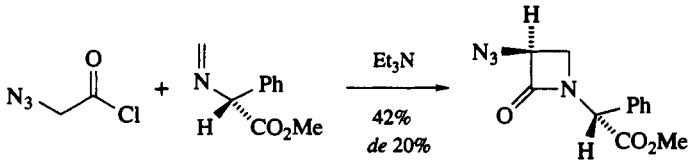


Scheme 11

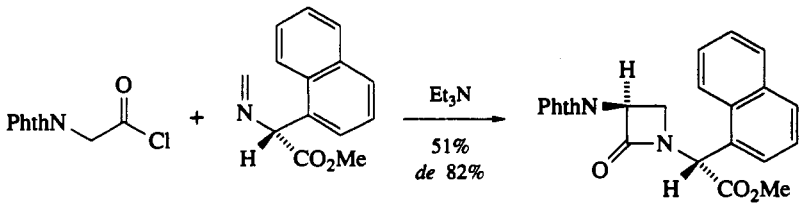
Enantiopure β-lactams have been prepared using chiral ketene precursors or chiral imines.[103,107,108]

Acyclic imines derived from optically active α-amino acid derivatives have been used in the Staudinger reaction.[105,106,109,113,114,117,118] Variable levels of diastereoselection have been reported (equations 36 and 37). In several cases the poor diastereoselectivity has been shown to result from some racemization of the imine synthon under the experimental conditions.[109,110] Only a few examples of high levels of diastereoselection have been reported (equations 38 and 39).[111,112,115,116]

The condensation of imines derived from glyceraldehyde acetonide[104,119–121] or α,β-epoxy aldehyde[122] with phthalimidoacetyl chloride proceed with high diastereoselection. Thus the addition of phthalimido acetyl chloride to the aldimine (**10**) derived from (*S*)-glyceraldehyde acetonide in the presence of triethylamine yields a β-lactam (**11**) which possesses the (3*S*,4*S*) configuration (Scheme 12). Compound



(36)



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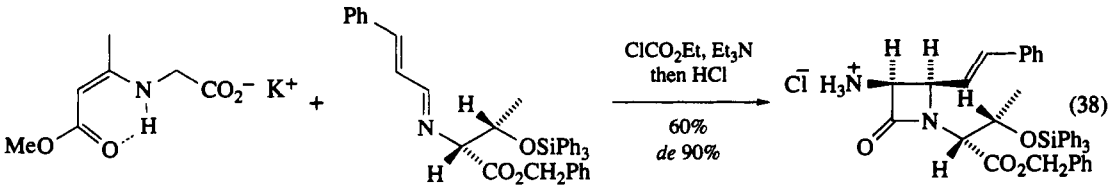
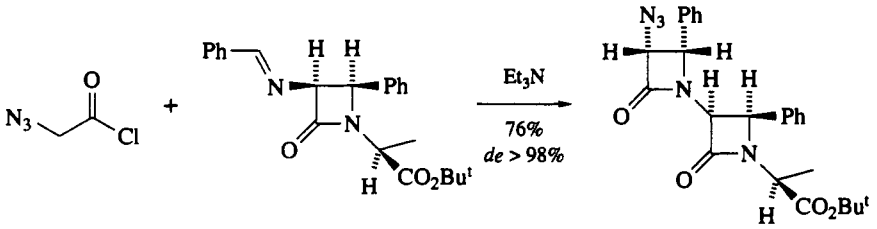
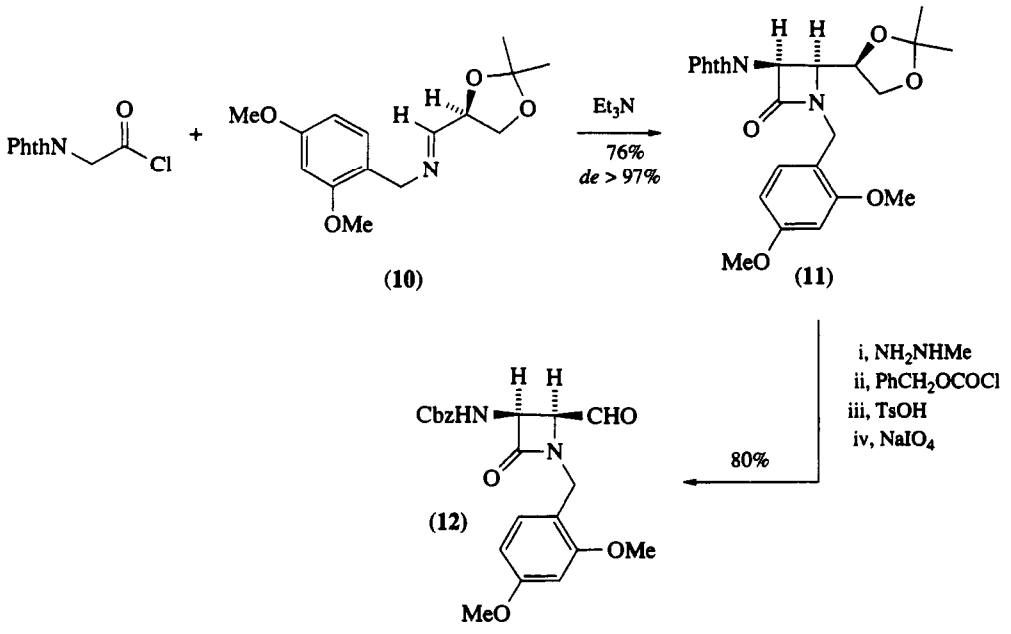


(38)



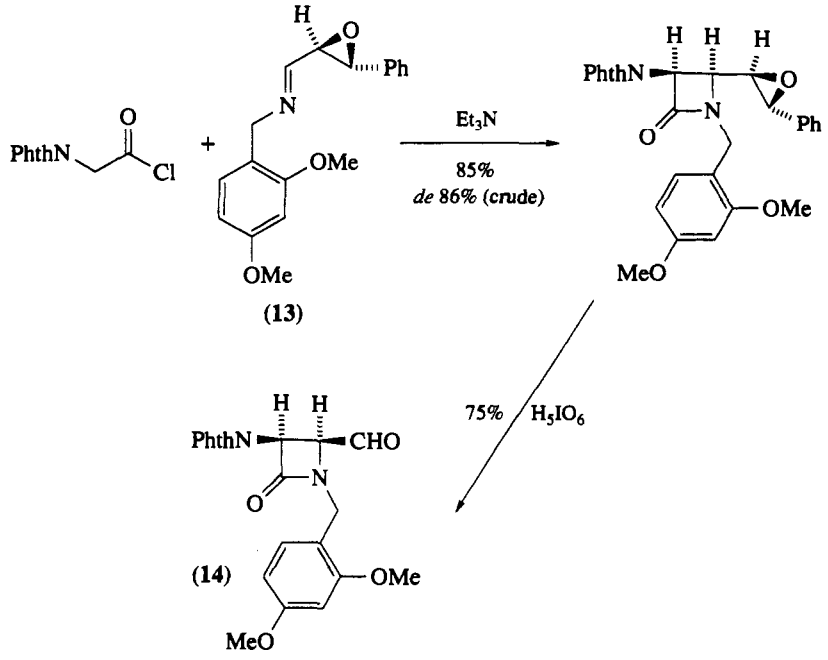
(39)

(**11**) is readily transformed into β-lactam (**12**), a useful chiral synthon for the production of new analogs of β-lactam antibiotics (Scheme 12).[104]

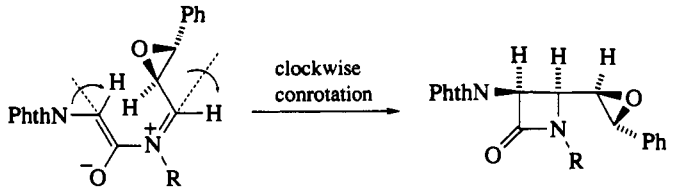


Scheme 12

Sharpless asymmetric epoxidation provides direct access to epoxy alcohols which are precursors of the required epoxy imines for the cycloaddition process.[122] Reaction of (**13**) with a protected glycine acid chloride yields the *cis* azetidinone which can be isolated in >98% diastereoisomeric purity by either chromatography or crystallization. Oxidation gave aldehyde (**14**; Scheme 13). The mode of asymmetric induction correlates with that of the corresponding reaction from (*S*)-glyceraldehyde acetonide. The π-facial discrimination imposed by the α-oxygen substituent of the imine is at least in part stereoelectronic in nature.[121] Accordingly, the preferred orientation of the C—O bond should be antiperiplanar to the forming C(3)—C(4) β-lactam bond for transition state stabilization by delocalization into the C—O antibonding orbital. In addition, 1,3-allylic strain interactions might be expected to force the electrocyclization to be initiated from a nonplanar reactant conformation (Scheme 14).[103] These effects appear to be maximal when the C—O bond is part of a ring since lower levels of diastereoselection are usually obtained with imines derived from chiral α-alkoxy aldehydes.[104,123,124]



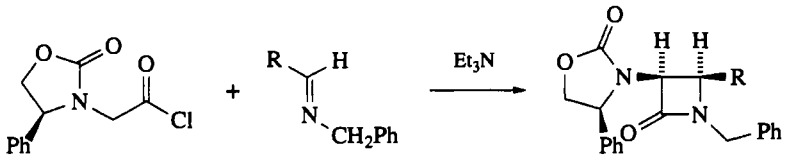
Scheme 13

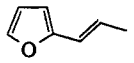


Scheme 14

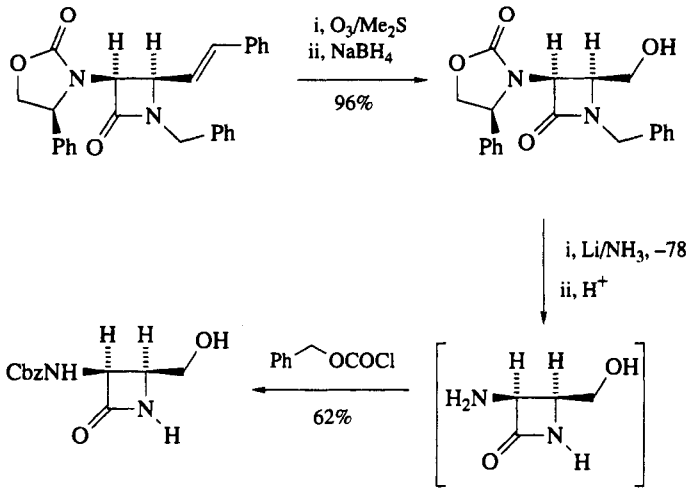
Significant progress has been made in the development of asymmetric syntheses of the biologically important 3-amino-β-lactams from homochiral ketene precursors.[103,123–128] High levels of diastereoselection have been observed with chiral 1,3-oxazolidinones. Thus (4*R*)-phenyloxazolidylacetyl chloride, readily prepared from (*S*)-phenylglycine, reacts with *N*-benzylaldimines in the presence of triethylamine to yield the *cis* β-lactams in high diastereoisomeric excesses (Scheme 15).[126]

In addition to providing excellent diastereoselection in the cyclocondensation process, the chiral oxazolidinone auxiliary can be reductively removed to give the enantiomerically pure 3-amino-β-lactam in good overall yields (Scheme 16).[126] Homochiral 1,4-imidazolidinones also give *cis* β-lactams with excellent induction when the asymmetric carbon atom is next to the nitrogen atom (**15** in Scheme 17).[129] High inductions can also be observed with a γ-lactam (**16**),[125] but the cycloaddition yields a mixture of *cis* and *trans* isomers. The level of diastereoselection is much lower with imide synthons (**17**).[103,125]

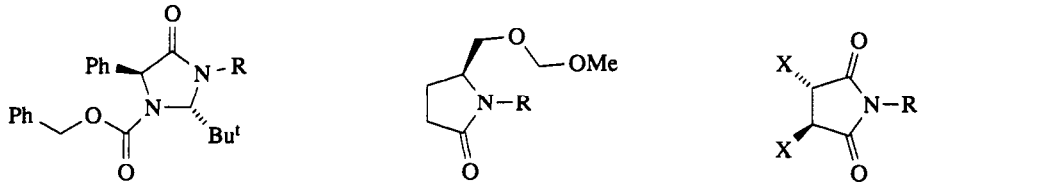


R	*Yield (%)*	*de (%)*
Ph	90	94
trans-PhCH=CH–	82	90
	80	94

Scheme 15



Scheme 16



(**15**) R = CH_2COCl (**16**) R = CH_2COCl (**17**) R = CH_2COCl; X = OMe, $OCOCH_2Ph$, OCOMe

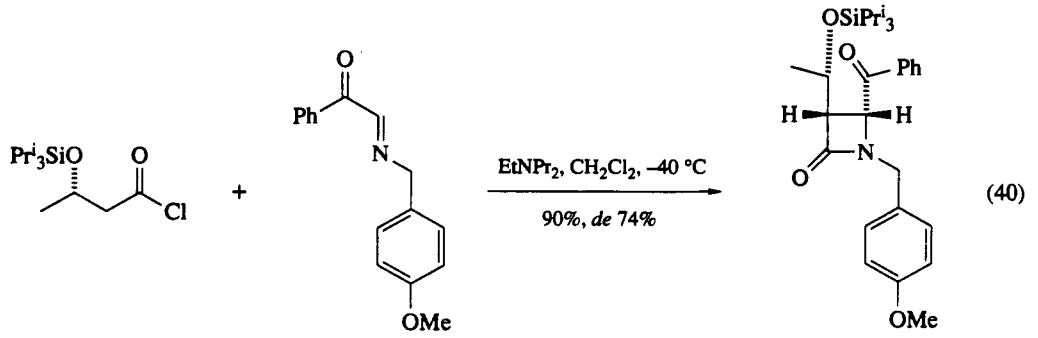
Scheme 17

A good level of diastereoselection has also been obtained with (3*S*)-triisopropylsilyloxybutyric acid chloride as chiral precursor (equation 40).[130]

Finally, all attempts to develop an asymmetric cyclocondensation of an acid chloride with an imine in the presence of a chiral tertiary base have failed.[103] No induction was observed when the reaction between diphenylketene and benzylideneaniline was effected in cholesteric liquid crystals.[131]

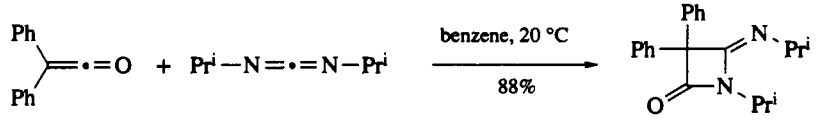
2.2.4.3 Cycloadditions of Ketenes to Carbodiimides

Ketenes readily react with carbodiimides[132–139] to yield 1:1 adducts (equation 41). The formation of 2:1 adducts (**18**) is observed[139] when the C=N double bond of the 1:1 adduct is activated by strain



(40)

(Scheme 18). The reaction occurs at the most nucleophilic imine bond:[136,138] C=NMe > C=NBu^t > C=N-aryl > C=NSiR$_3$ (equation 42). The reaction takes place by an ionic mechanism[133,135] in which ring closure is the slowest step. In the reaction of prochiral ketenes with chiral carbodiimides,[137] ring closure creates a new chiral center with good selectivity (equation 43).



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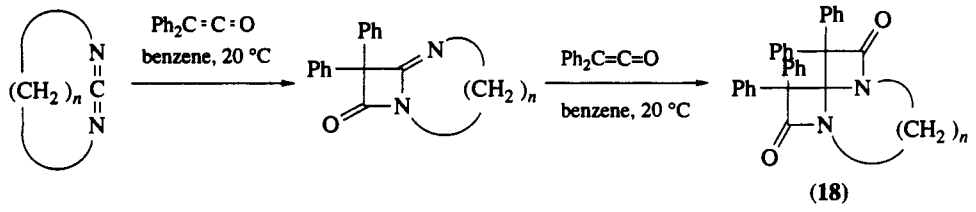
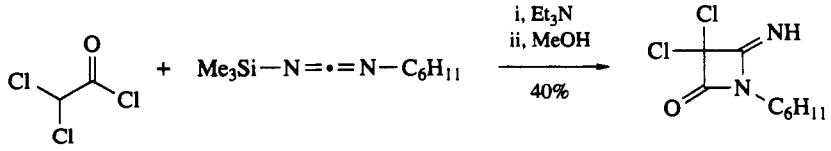


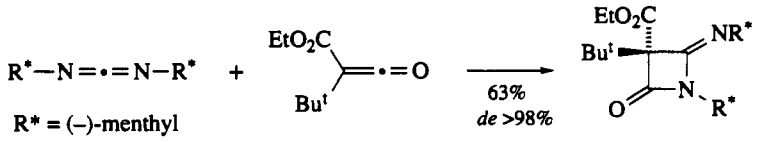
(18)

$n = 5$	–	91%
$n = 11$	90%	–

Scheme 18



(42)



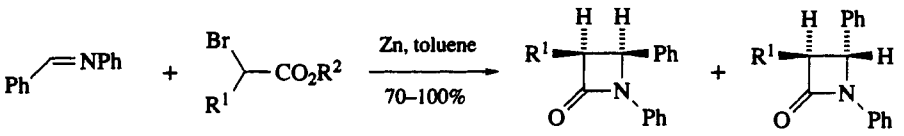
(43)

2.2.5 2-AZETIDINONES FROM ENOLATES OR ENOL ETHERS AND IMINES

Zinc enolates (Reformatsky reagents), generated from α-bromo esters and zinc, react with imines derived from aromatic amines to yield β-lactams (Scheme 19).[140–142] The stereoselectivity of the reaction varies[143–146] with the nature of ester substituents R^1 and R^2: the bulkier the groups, the more *trans* isomer is produced.

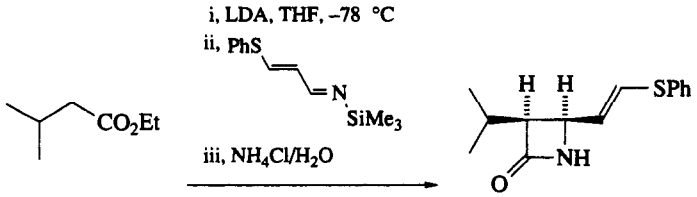
A useful variation of this reaction involves lithium enolates derived from esters.[147,148] They react with imines derived from non-enolizable aldehydes to form β-lactams (equations 44 and 45).[149–158]

The *cis* stereoselectivity can be explained[150] by a six-membered chair-like transition state model (**19**) resulting from the interaction of an (*E*)-enolate with an imine in its *trans* configuration (Scheme 20). Conditions favoring (*E*)-enolate formation (LDA, THF) predominantly yield *cis* β-lactams.[150,152,155,156,158] Addition of HMPA[152,159] or reactions at higher temperature[151,160] favor the forma-

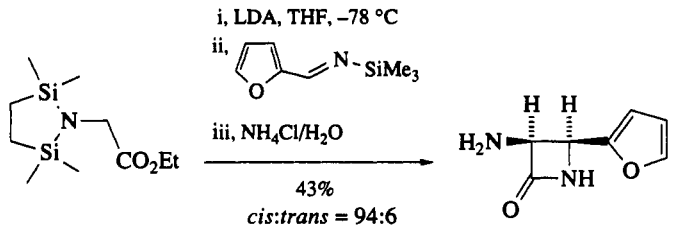


R^1	R^2	% *cis*	% *trans*
Me	Me	73	27
Bu^t	Me	25	75
Bu^t	Pr^i	2	98

Scheme 19

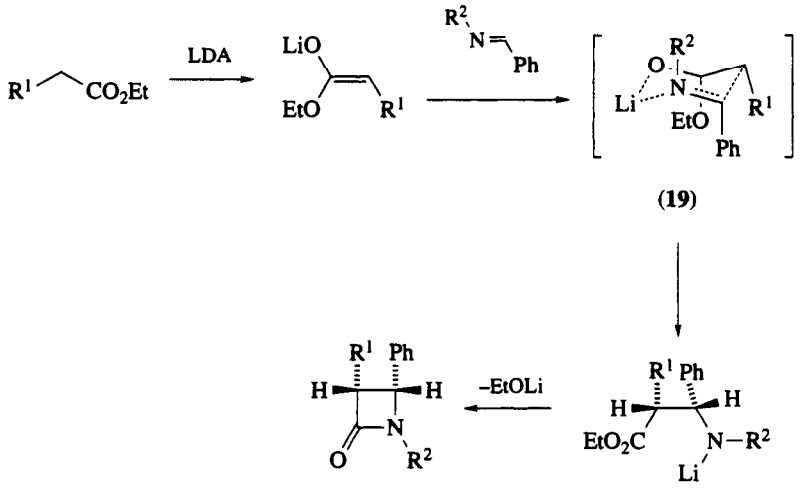


(44)



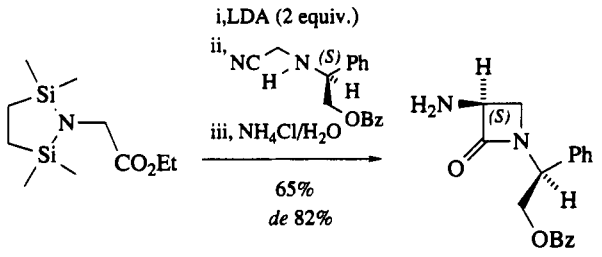
(45)

tion of *trans* β-lactams. In several cases this has been shown to result from a change in enolate geometry but in other cases, *e.g.* with imines derived from aromatic amines, isomerization of the β-lactam occurred under the reaction conditions.[150,160] *Trans* β-lactams were also obtained in the presence of $ZnCl_2$[161] or Et_2AlCl[162] while $AlMe_3$[163] was reported to enhance *cis* selectivity.



Scheme 20

Attempts to prepare homochiral β-lactams using chiral reactants under Reformatsky conditions described above gave poor results.[143,164] Good diastereoselectivities are observed in the reaction of lithium enolates with imines bearing a chiral group on either a nitrogen (equation 46)[154] or carbon atom (equation 47).[165] Esters derived from isoborneol-10-diisopropylsulfonamide give enolates which condense with cinnamaldimines to yield *cis* β-lactams with excellent enantioselectivity (equation 48).[166]



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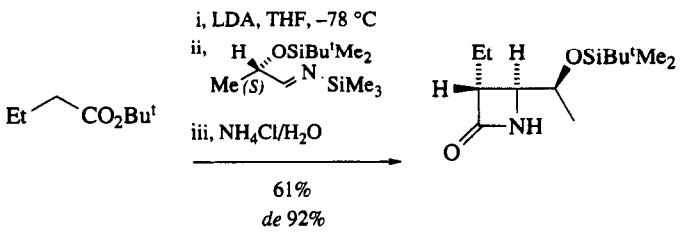

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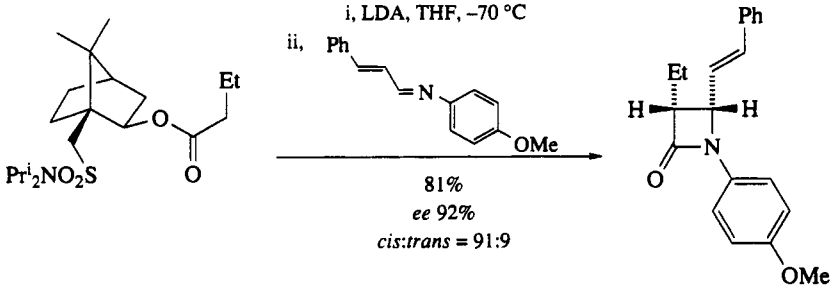


(48)

Using (3*R*)- or (3*S*)-hydroxybutyric esters as chirons, it was possible to construct β-lactams with some control on three contiguous asymmetric centers.[165,167–174] Chelation maintains the dilithium derivative of ethyl (3*S*)-hydroxybutyrate in the (*Z*) configuration (Scheme 21). Approach of the imine from the less-hindered β-face leads to the (3*S*)-β-lactam with a high degree of facial selectivity but to a much lower degree of diastereoselectivity at C-4. The corresponding reaction using ethyl (3*R*)-hydroxybutyrate gave, as expected, high diastereofacial selection in favor of the (3*R*)-β-lactam.

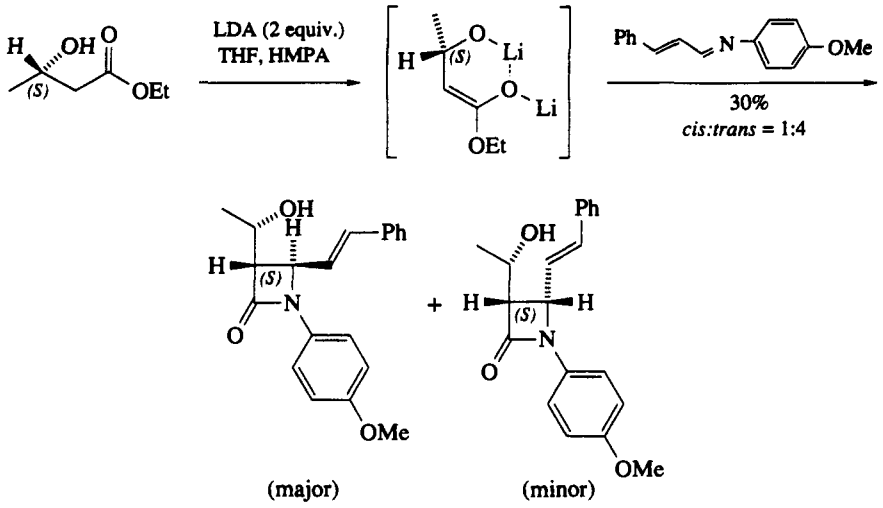
Silylketene acetals react with imines under acidic conditions (Scheme 22). With *N*-alkylimines in the presence of a stoichiometric amount of $TiCl_4$, β-lactams are formed[175] in good yields. *N*-Aryl-[176–178] and *N*-trimethyl-silylimines[179] also react under acidic conditions but yield only open-chain products. On the other hand, bis(trimethylsilyl)ketene acetals yield β-lactams with both *N*-alkyl- and *N*-aryl-imines (Scheme 22).[180]

High diastereoselectivities have been observed[181] for the reaction of dimethylketene methyl trimethylsilyl acetal with imines derived from (2*S*)-amino esters (equation 49). However, the scope of this method must be further investigated.

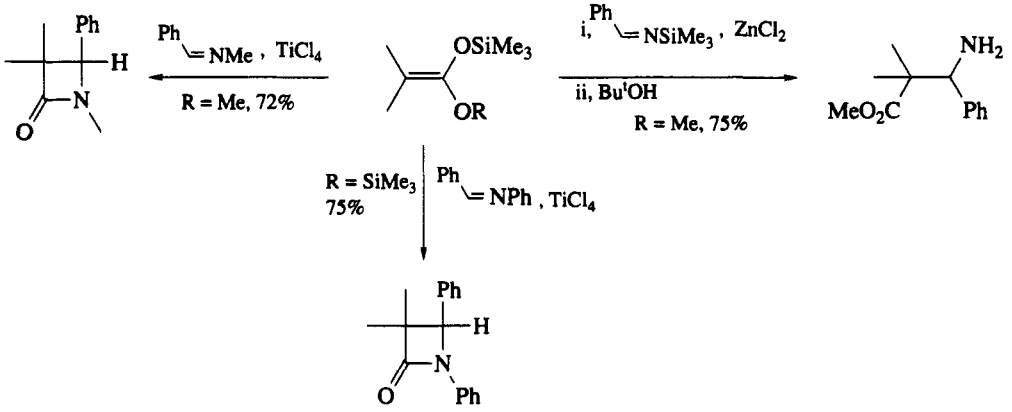
2.2.6 2-AZETIDINONES FROM ISOCYANATES AND ALKENES

2.2.6.1 Scope

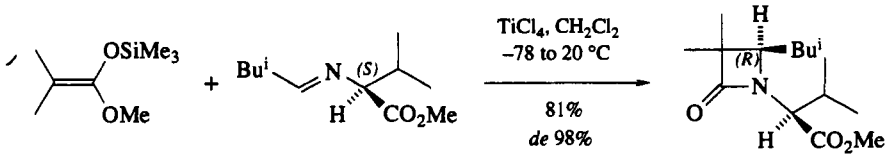
The cycloaddition of an alkene across the C=N bond of an isocyanate is a useful method of synthesis of β-lactams (equation 50).[24,182] The reaction requires the activation of the alkene by electron-releasing



Scheme 21

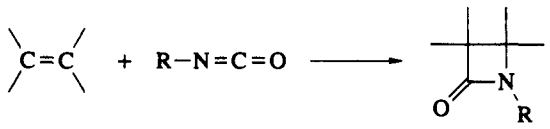


Scheme 22

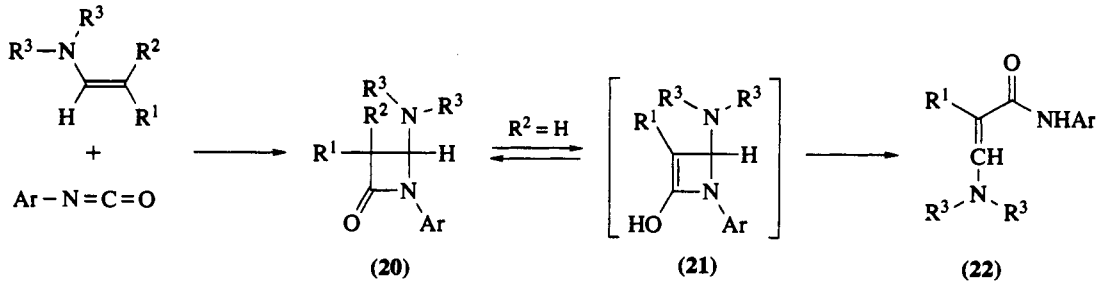


(49)

substituents or that of the isocyanate by electron-withdrawing groups. Alkyl and aryl isocyanates do not react with alkenes or enol ethers but cycloadd to enamines, ketene acetals and ketene aminals. The initial product is a β-lactam (**20**) which is stable when there is no available hydrogen at C-3 (Scheme 23). However, when R^2 = H, enolization yields intermediate (**21**) which undergoes a fast electrocyclic rearrangement to give the open-chain isomer (**22**). Ketene acetals behave similarly (Scheme 24). In both cases the rearrangement is driven by the release of strain and the presence of an electron-releasing group at C-4.

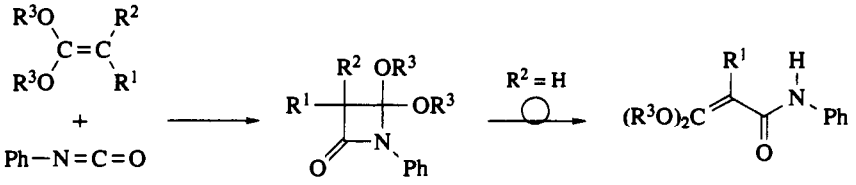


(50)



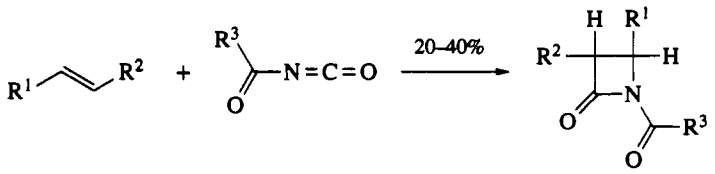
(20) (21) (22)

Scheme 23



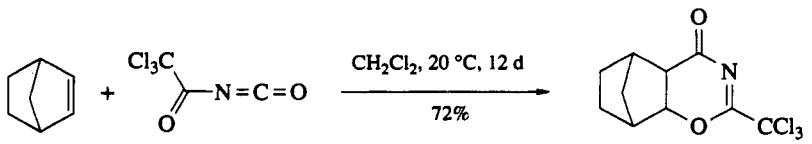
Scheme 24

Acyl isocyanates[183–185] are more reactive than alkyl or aryl isocyanates. However, the presence of an additional π-bond conjugated to the C=N bond of the isocyanate opens the possibility for [4 + 2] cycloadditions to compete with normal [2 + 2] additions. Reactions with alkyl and aryl substituted alkenes are rather slow. Propene, *trans*-2-butene, styrene and conjugated dienes give only β-lactams, albeit in moderate yields (Scheme 25). The strained double bond of norbornene, a reactive dienophile, adds across the conjugated 4π-system of trichloroacetyl isocyanate (equation 51).



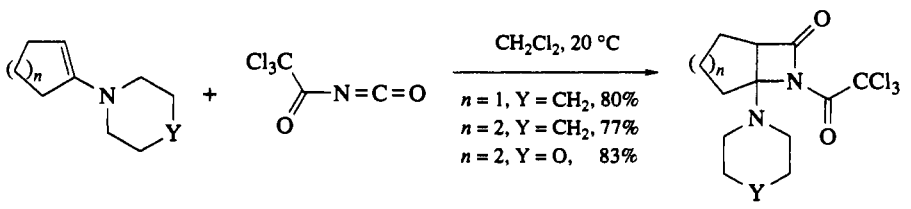
R^1 = Me, Ph, $CH{=}CH_2$; R^2 = H, Me; R^3 = Cl_3C, Ph

Scheme 25



(51)

More nucleophilic alkenes such as enamines or enol ethers react faster with acyl isocyanates but the reaction is of little value for the preparation of β-lactams since it often produces [4 + 2] or open-chain adducts. The chemoselectivity apparently varies with subtle changes in the structures of the reactants as well as experimental conditions (equations 52–55).



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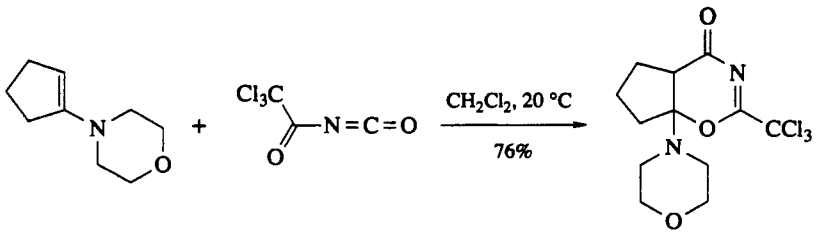

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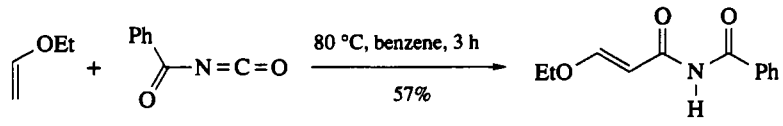

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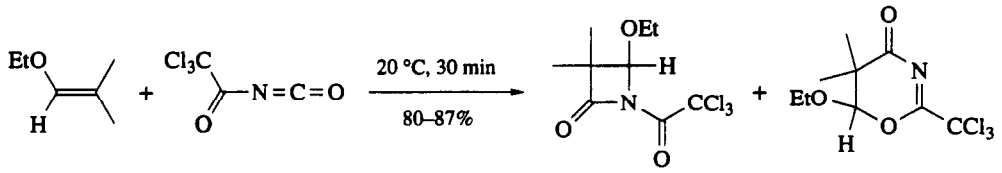
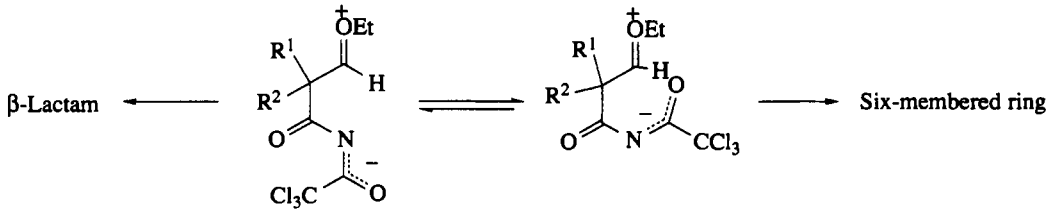


(55)

60% (in CCl_4) 40%
40% (in MeCN) 60%

These results are best explained by the formation of 1,4-dipolar intermediates which can cyclize from two conformations (**23**) or (**24**) leading respectively to a β-lactam or to a six-membered heterocycle (Scheme 26). When R^1 or R^2 = H, open-chain adducts can also be formed.



(**23**) (**24**)

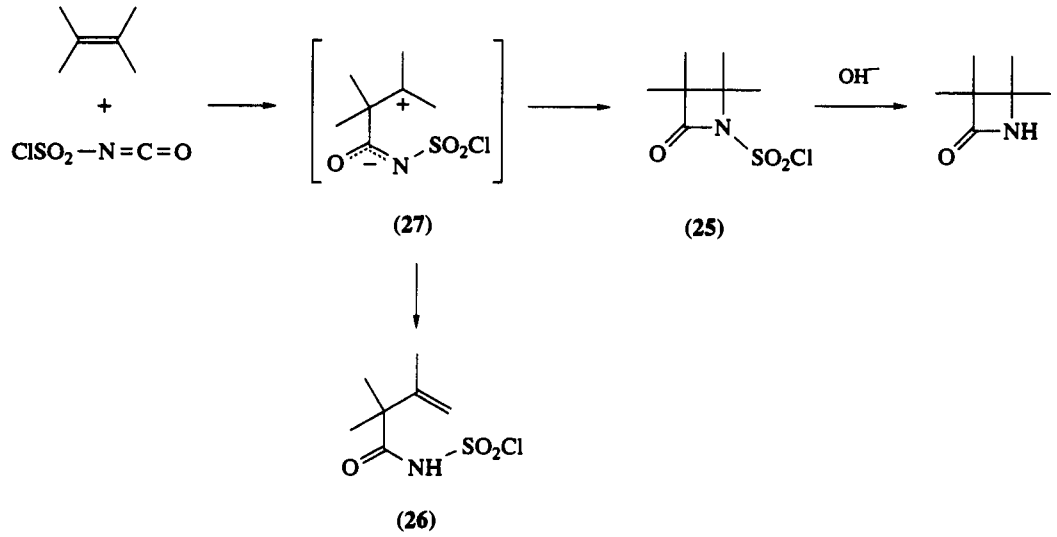
Scheme 26

A more general and practical approach towards β-lactams utilizes the cheap chlorosulfonyl isocyanate (CSI),[186-191] which was first described by Graf[192] more than 35 years ago. The chlorosulfonyl group offers several advantages over the acyl groups described above: (a) it has a stronger activating effect on the isocyanate function; (b) it does not offer the possibility for competing [4 + 2] cycloadditions; (c) it can be smoothly removed by simple basic hydrolysis or even more effectively *via* unstable sulfinic acids produced by reduction with zinc dust, iron powder or sodium sulfite. A two-phase system consisting of an organic solvent and aqueous sodium sulfite kept slightly basic by addition of KOH has been recommended.[193]

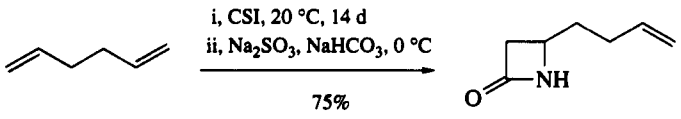
Chlorosulfonyl isocyanate reacts with a wide range of alkenes under mild conditions to produce β-lactams (**25**) accompanied[186,189] by variable but usually minor amounts of open-chain adducts (**26**; Scheme 27). In most cases, β-lactams and open-chain products are formed independently. Thus *N*-chlorosulfonyl amide by-products are not formed by further reaction of *N*-chlorosulfonyl-β-lactams.

A large number of β-lactams have been prepared[188,189,191] by this method (equations 56–61). Cycloadditions of CSI with 1,5-hexadiene,[194] allyl iodide[195] and vinyl acetate[196,197] yield azetidinones which have been used as starting materials in the synthesis of carbapenems and penems. In some cases the cycloaddition must be conducted at low temperature to avoid open-chain products (equations 61 and 62).

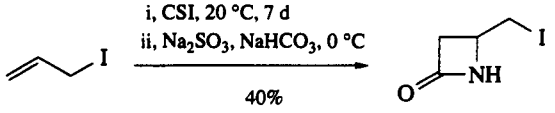
Conjugated dienes react with CSI to yield[198] *N*-chlorosulfonyl-β-lactams as the primary products (Scheme 28). These [2 + 2] adducts undergo stepwise thermal rearrangements with variable degrees of ease to thermodynamically more stable [2 + 4] adducts, cyclization occurring at oxygen or nitrogen of the intermediate ambident zwitterion. These rearrangements can be avoided by *in situ* reduction of the *N*-



Scheme 27



(56)



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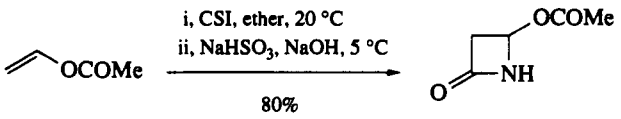

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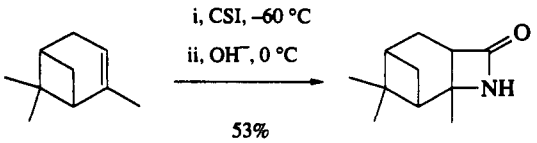

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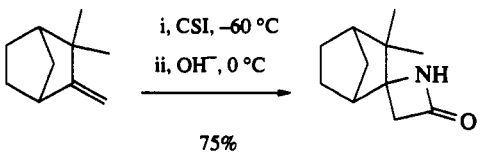

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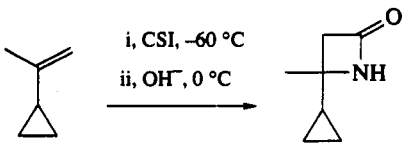

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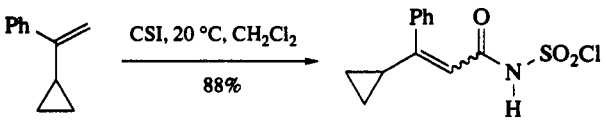

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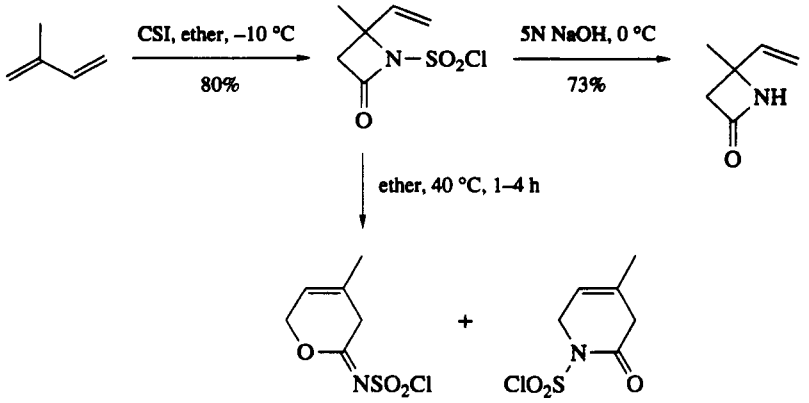
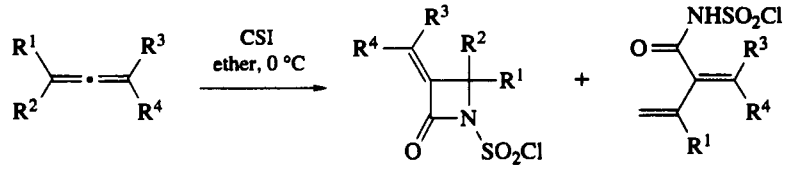


Scheme 28

chlorosulfonyl-β-lactams to the more stable NH β-lactams.[199,200] CSI reacts with allenes[201–203] to give 3-alkylidene-β-lactams accompanied by variable amounts of 2-vinylacrylamides when the R^2 substituent is a methyl group (Scheme 29).



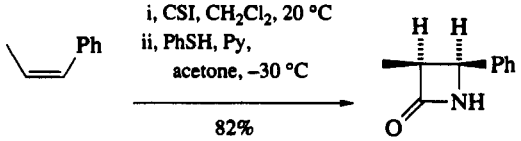
R^1	R^2	R^3	R^4	%	%
Me	Me	Me	Me	67	28
Me	Me	H	H	23	36
H	Ph	H	H	60	0
H	OAc	Me	Me	50	0

Scheme 29

Both concerted[204] and stepwise[192] mechanisms have been proposed for these reactions although the experimental facts can be readily accounted for by the formation of a 1,4-dipolar intermediate (**27**; Scheme 27). The reaction rates are markedly increased in polar solvents.[188] The cycloadditions of isocyanates to alkenes are always regiospecific, the reaction taking place so as to form the most stable 1,4-dipole.

2.2.6.2 Stereochemical Aspects

Reactions of activated isocyanates with alkenes are highly stereospecific (equations 63 and 64).[183,187,201]



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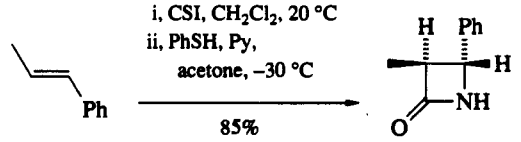
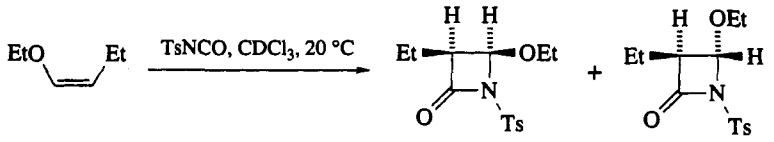


(64)

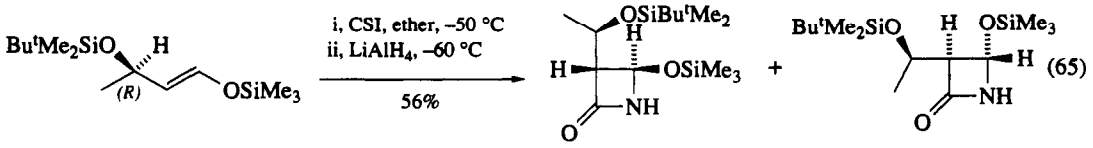
In a few cases it was found that the primary adduct epimerized[205] under the reaction conditions (Scheme 30).



Reaction time (min)	*cis*	*trans*
1	>95%	<5%
18	65	35
1440	27	73

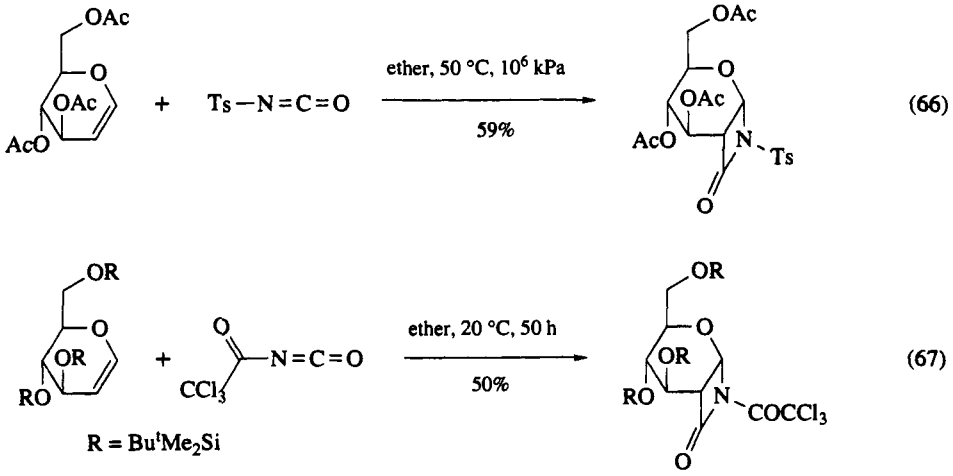
Scheme 30

Excellent stereoselectivity is also obtained in the cycloaddition of CSI with the optically active enol ether (**28**).[206] The reaction gives the *trans* β-lactams (**29**) and (**30**) in a 10:1 ratio (equation 65).



(**28**) (**29**) 91% (**30**) 9% (65)

[2 + 2] Cycloadditions of activated isocyanates to 3,4-dihydro-2*H*-pyran derivatives are highly sensitive to the nature of substituents attached to the dihydropyran ring.[207,208] Thus, at normal pressure, the reaction of tosyl and trichloroacetyl isocyanates to give acetylated glycals is entirely shifted toward starting materials. Application of 10 kbar (10^6 kPa) pressure led to the formation of unstable β-lactams (equation 66). The cycloadditions proceed regio- and stereo-specifically, yielding adducts resulting from a *trans* addition relative to the acetoxy group at C-3. Glycals having nonpolar blocking groups react at normal pressure. Again the cycloadditions proceed regio- and stereo-specifically with formation of the β-lactam ring *anti* to the C-3 substituent (equation 67).



(66)

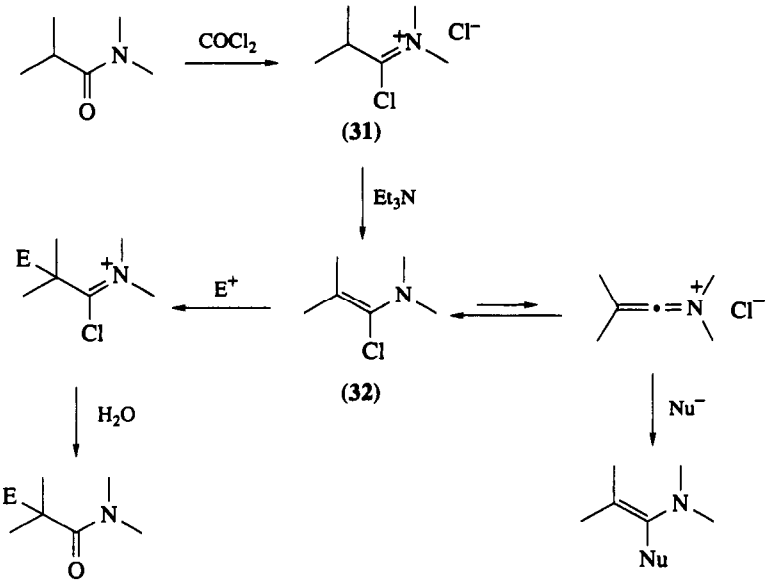
(67)

2.2.7 2-AZETIDINIMINIUM SALTS FROM KETENIMINIUM SALTS AND IMINES

2.2.7.1 Scope

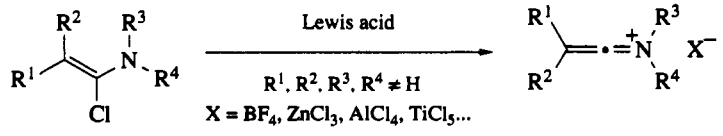
2-Azetidiniminium salts[209,210] are available from the reaction of imines with iminium salts derived from tertiary carboxamides. These smoothly react with phosgene[211,212] to yield α-chloroiminium

chlorides (**31**; Scheme 31). Elimination of HCl with a tertiary base forms[213,214] the corresponding α-chloroenamines (**32**) in good yields. These are ambiphilic molecules[215] which exhibit nucleophilic reactivity at C-2 and electrophilic reactivity at C-1 (Scheme 31). Thus they can react either as enamines or as keteniminium chlorides. Consequently, they readily undergo self-condensation reactions and have often to be prepared *in situ*. However, when they bear no hydrogen at C-2, their nucleophilic reactivity is reduced and they are stable enough to be purified by distillation.[214]



Scheme 31

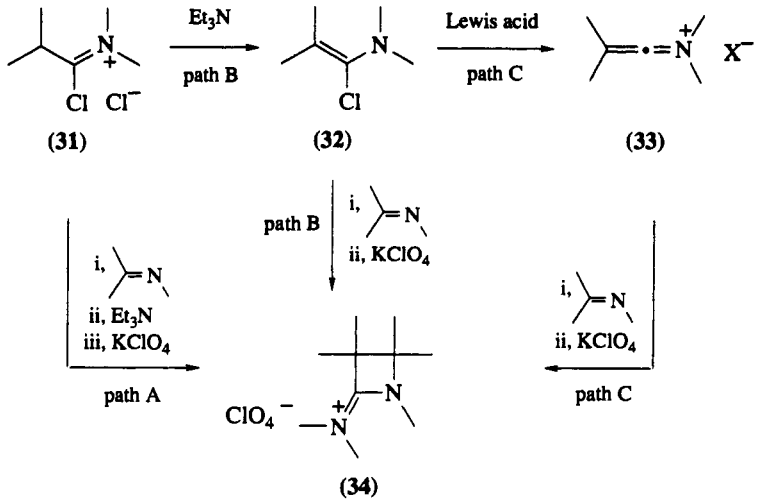
β-Disubstituted α-chloroenamines are readily converted into the corresponding keteniminium salts (**33**)[216,217] in the presence of a Lewis acid (equation 68). Silver tetrafluoroborate, zinc, tin and aluminum chlorides have been successfully used. β-Disubstituted keteniminium salts have been isolated and characterized.[211] Unlike the corresponding ketenes, they do not dimerize or polymerize. However, they readily undergo [2 + 2] cycloaddition reactions with unsaturated substrates.[41]



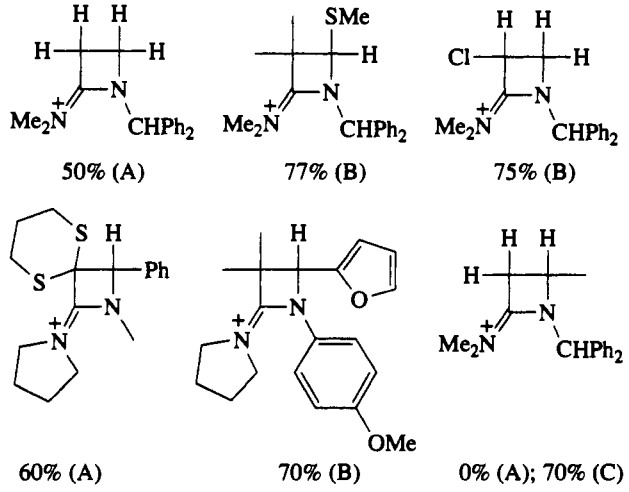
(**32**) (**33**) (68)

While alkenes and alkynes only react with the most reactive keteniminium salts, imines are nucleophilic enough to cycloadd[210,218,219] to α-chloroenamines (**32**) which then behave as keteniminium chlorides (Scheme 32). The latter are often conveniently prepared *in situ* from the corresponding α-chloroiminium chlorides (**31**). A wide variety of 2-azetidinimimium salts (**34**) has been prepared by this method.[222] They are conveniently purified as perchlorates (Scheme 33). Paths A and B (Scheme 32) usually give similar results. In general, path B, which does not involve the isolation of (**32**), is more practical. However, neither path A nor path B allows the preparation of 4-alkyl substituted azetidiniminium salts: open-chain products are formed. This limitation is overcome by using a keteniminium salt generated from the corresponding α-chloroenamine and a Lewis acid (path C).[222]

Basic hydrolysis[209,210] of azetidiniminium salts proceeds *via* a tetrahedral intermediate which can fragment in two ways (Scheme 34): cleavage of the exocyclic C–N bond yields a β-lactam; alternatively, cleavage of the endocyclic C–N bond leads to an open-chain product devoid of any strain. Experimentally it is found[220–222] that β-lactams are the major hydrolysis products of 2-azetidiniminium salts bearing alkyl groups on the endocyclic nitrogen. When this substituent is an aryl group, the course of hydrolysis is pH dependent: at pH ≤ 10, β-lactams are the major products; at higher pH, β-amino amides are formed predominantly (Scheme 35).



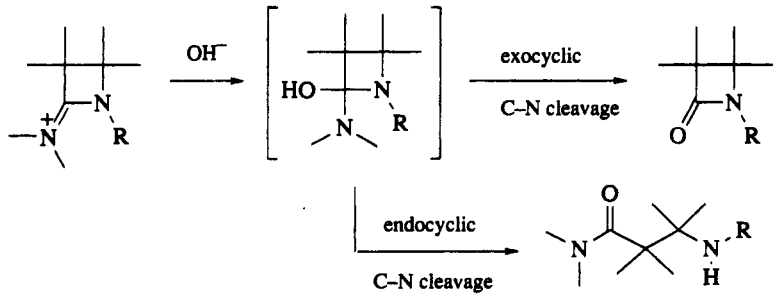
Scheme 32



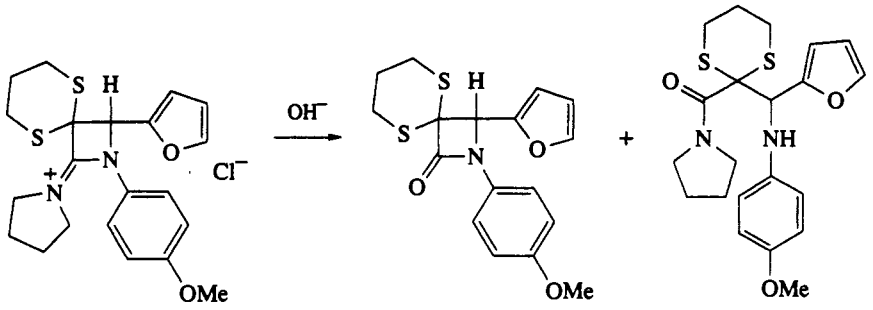
Scheme 33

Azetidiniminium salts have also been converted[222,223] into azetidine-thiones, -imines or -hydrazones (Scheme 36). Yields of imine derivatives are high when the azetidiniminium salts bear no hydrogen atom at C-3. Otherwise the reaction is best effected by first forming the corresponding 2-azetidinethione which is further treated[223] with an amine in the presence of mercury(II) acetate (Scheme 37).

The high reactivity of these strained amidinium salts (**34**) is further illustrated by their unusual ability to react with nucleophilic peroxides (equation 69).[210,222] None of the above transformations is observed with the corresponding 2-azetidinones.

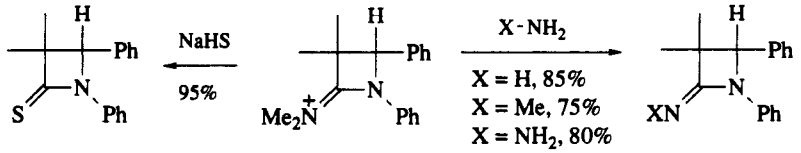


Scheme 34

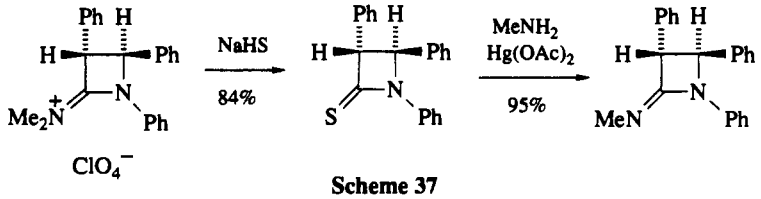


pH		
9.5	48%	0%
13	0%	60%

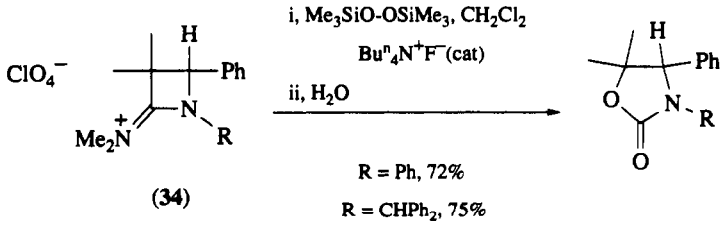
Scheme 35



Scheme 36



Scheme 37



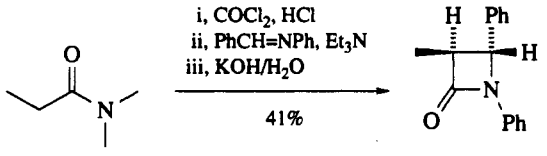
(69)

2.2.7.2 Stereochemistry

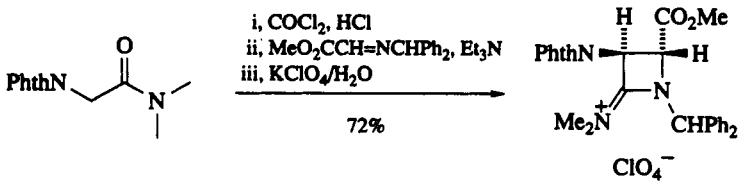
While cycloadditions of imines with ketenes or their precursors often produce *cis* β-lactams, the corresponding reactions of keteniminium salts are *trans* stereoselective (equations 70 and 71).[210,222] It is not clear whether the *trans* stereoselectivity is kinetic or results from an equilibration of 2-azetidiniminium salts under the basic conditions used in both cycloaddition and hydrolysis steps.

Use of chiral imines[224,225] produces β-lactams with low diastereoselection (Scheme 38).

A potentially more interesting application of the method for asymmetric synthesis[210,222] uses chiral α-chloroiminium chlorides as starting material. Best results are obtained with iminium salts derived from (2*S*)-(methoxymethyl)pyrrolidine. They react with imines in the presence of triethylamine to give opti-



(70)



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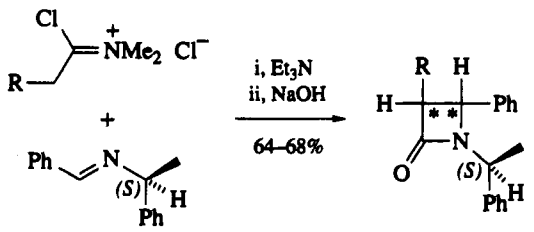
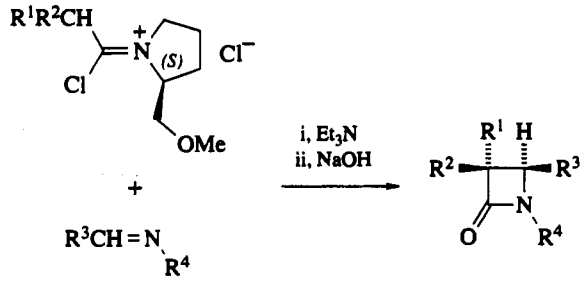


R	*trans* (%)		*cis* (%)	
	(3*S*,4*R*)	(3*R*,4*S*)	(3*R*,4*R*)	(3*S*,4*S*)
Me	35	32	22	11
Ph	30	50	5	15

Scheme 38

cally active β-lactams after hydrolysis (Scheme 39). The bulk of the C-3 substituents R^1 and R^2 plays a decisive role in the diastereoselectivity. When R^1 and R^2 are different from hydrogen, the diastereoselection is very high. However, it drops dramatically when R^1 and/or R^2 are hydrogens.

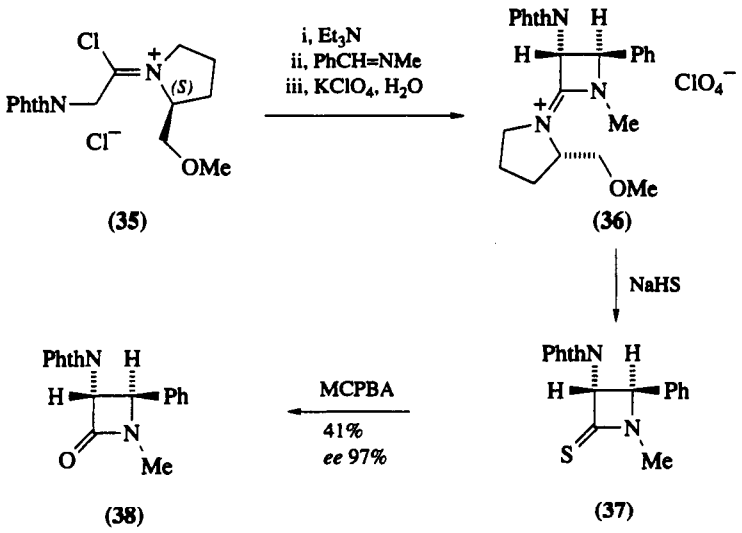


R^1	R^2	R^3	R^4	*Yield* (%)	*cis/trans*	*ee* (%)
Me	Me	Ph		42	–	98
Me	Me	SPh	CH_2Ph	65	–	99
Ph	Me	Ph	Me	29	0/100	97
Me	H	Ph	Me	30	20/80	40
H	H	Ph	Me	47	–	4

Scheme 39

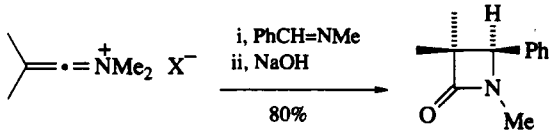
A notable exception is found in the reaction of iminium salt (**35**) derived from *N*-phthaloylglycinamide with imines (Scheme 40). The presence of the phthalimido substituent requires a modification of the procedure[222,223] converting the adduct (**36**) into the β-lactam (**38**). While basic hydrolysis destroys compound (**36**), treatment with sodium hydrogensulfide smoothly gives the azetidinethione (**37**) which is readily oxidized to the corresponding β-lactam (**38**) with modest overall chemical yield but high enantiomeric purity.

The nature of the anion associated with the iminium salt appears to play an important role in the diastereoselectivity of the reaction.[222] Thus while tetramethyl-α-chloroenamine (**39**) gives a β-lactam in high optical purity, the corresponding tetramethylketeniminium tetrafluoroborate (**40**) reacts with almost no diastereoselection (Scheme 41).



(35) (36) (37) (38)

Scheme 40



X	*ee*
Cl (39)	98%
BF_4 (40)	4%

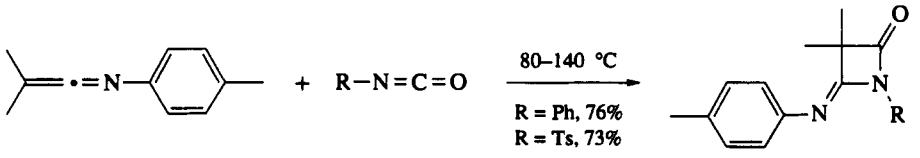
Scheme 41

2.2.8 CYCLOADDITIONS OF KETENIMINES

There are only few reports of [2 + 2] cycloadditions with ketenimines.[226–232] In most cases, reactions occur across the C=C bond. Only ynamines[233] and polyfluorinated alkenes[234] cycloadd to the C=N bond.

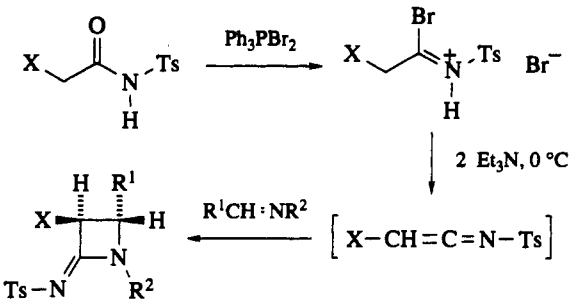
2.2.8.1 2-Iminoazetidines from Ketenimines and C=N Bonds

The nucleophilic C=C bond of ketenimines reacts[235] with isocyanates to yield a single [2 + 2] adduct (equation 72).



(72)

N-Alkyl- and *N*-aryl-ketenimines are poor electrophilic partners and do not react with benzylideneaniline[236] or dicyclohexylcarbodiimide.[237] The introduction of an electron-withdrawing substituent (tosyl[236,238] or cyano[239]) on the nitrogen atom enhances the electrophilic character of the cumulene and cycloadditions to imines occur under very mild conditions (Scheme 42). In most cases, the reactions are *trans* stereoselective.

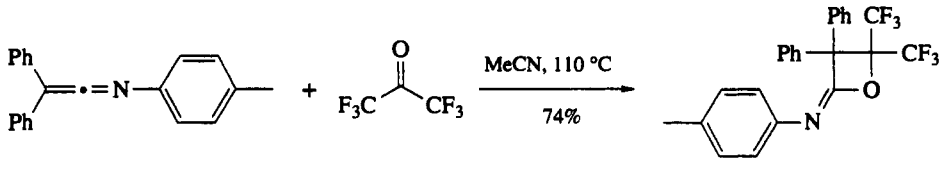


X	R^1	R^2	Yield (%)	cis:trans
H	Ph	Ph	50	-
Cl	Ph	Ph	38	0/100
N_3	CO_2Me	$CHPh_2$	47	50/50
Phth	SCH_2–C$_6$H$_4$–OMe	MeO_2C	57	0/100

Scheme 42

2.2.8.2 2-Iminooxetanes from Ketenimines and C=O Bonds

Thermal cycloadditions of ketenimines to carbonyl compounds requires activation of the C=O bond. The highly electrophilic bis(trifluoromethyl) ketone reacts[240] at high temperature with diphenyl-*N*-tolylketenimine (equation 73). Lanthanide shift reagents[241] such as tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium or -ytterbium [Eu(fod)$_3$ or Yt(fod)$_3$] are efficient catalysts for the cycloaddition of ketenimines with aldehydes (equation 74). The use of chiral catalysts such as tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium or -ytterbium [Eu(hfc)$_3$ or Yt(hfc)$_3$] has been found to generate only moderate enantiomeric excesses (20–40%).[241]



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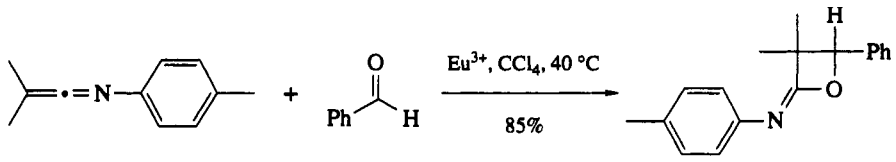
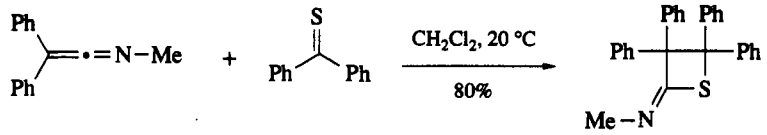


(74)

2.2.8.3 2-Iminothietanes from Ketenimines and C=S Bonds

Thermal reactions of ketenimines with thiobenzophenone have been investigated in detail.[242–245] Trisubstituted ketenimines bearing an alkyl or an *o,o'*-disubstituted aryl group on nitrogen give 2-iminothietanes (equation 75). When there are no *ortho* substituents on the aromatic ring, the C=S bond adds across the conjugated system involving the C=N bond of the cumulene and one C=C bond of the aromatic ring (equation 76). With aldoketenimines, and irrespective of the nature of the nitrogen substituent, the initially formed 2-iminothietanes isomerize to give the more stable conjugated thioamides (equation 77).



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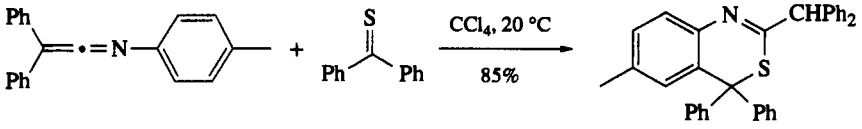
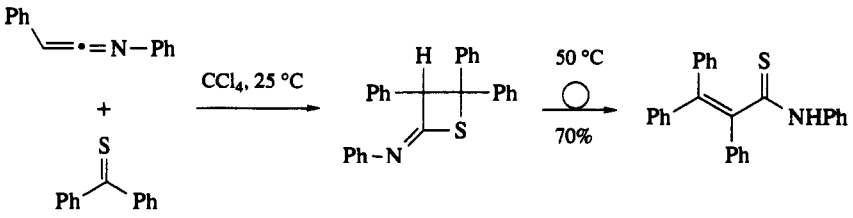


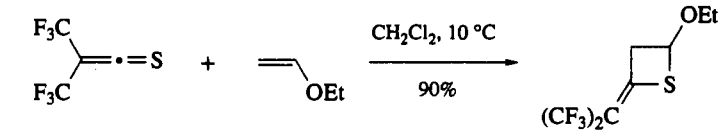
(76)



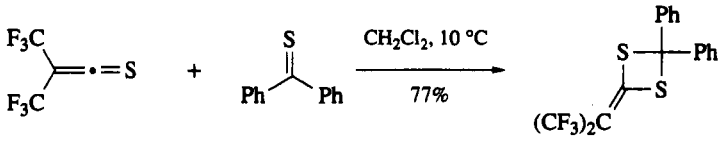
(77)

2.2.9 CYCLOADDITIONS OF THIOKETENES

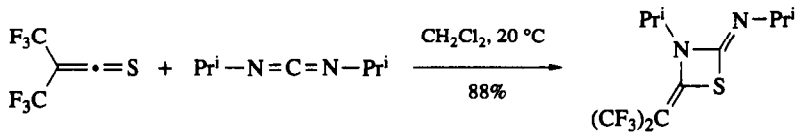
Thioketenes are generally unstable and difficult to prepare. Therefore only few compounds have been studied.[246] Bis(trifluoromethyl)thioketene reacts[247] with a wide range of C=C and C=X bonds (equations 78–80). The products always result from addition across the C=S bond of the cumulene.



(78)

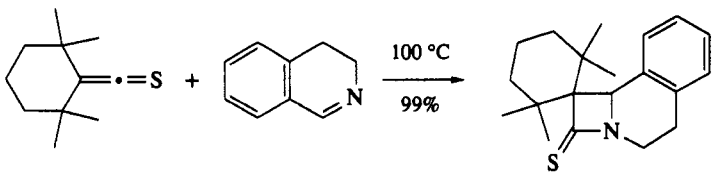


(79)

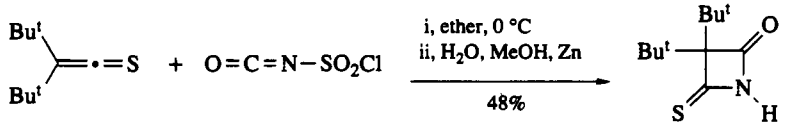


(80)

2-Azetidinethiones are formed[248,249] in the reaction of imines with dialkylthioketenes (equation 81). These also react across the C=N bond of electrophilic isocyanates (equation 82).[250,251]



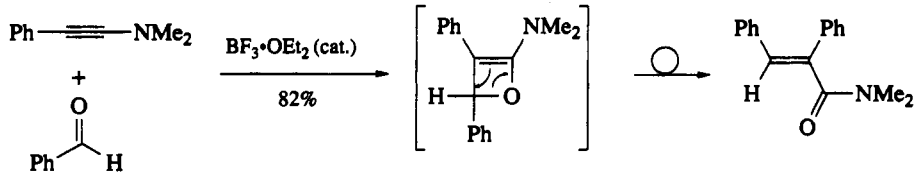
(81)



(82)

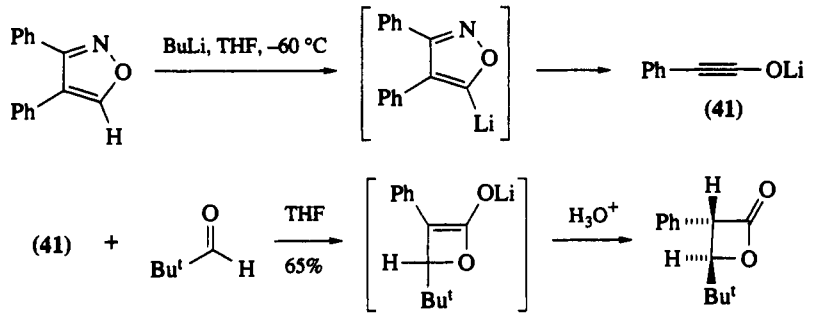
2.2.10 FOUR-MEMBERED HETEROCYCLES FROM ACTIVATED ALKYNES AND C=X BONDS

Few reactions of alkynes with C=X bonds are valuable for the preparation of four-membered heterocycles. Ynamines[252,253] react with aldehydes and ketones in the presence of Lewis acids to give unstable oxetene derivatives[254] which undergo electrocyclic opening (Scheme 43). Open-chain products are also obtained with thiocarbonyl compounds,[255] Schiff bases[256] and iminium salts.[257] Reactions of ynamines with carbon dioxide,[258] ketenes,[259,260] ketenimines[261,262] and isocyanates[263–266] often give mixtures of products and are of little preparative value.



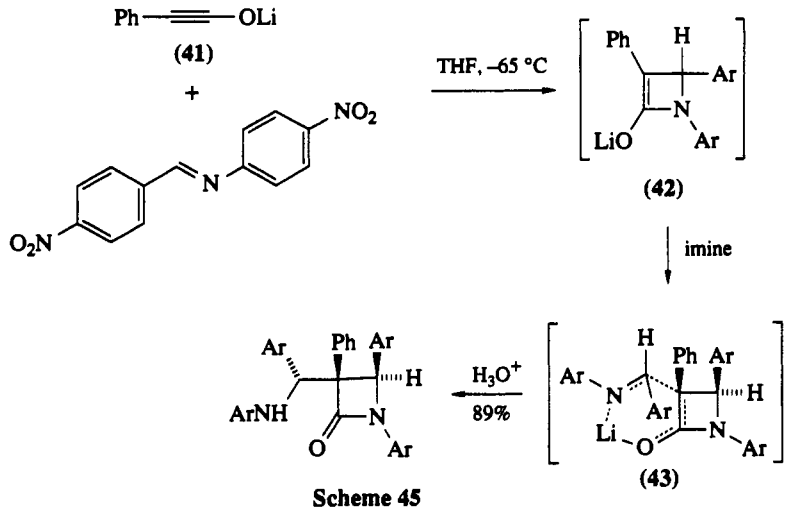
Scheme 43

Lithium phenylethynolate (**41**), which is readily obtained from 3,4-diphenylisoxazole and butyllithium, reacts[267,268] with aldehydes and ketones to yield 2-oxetanones after protonation (Scheme 44).

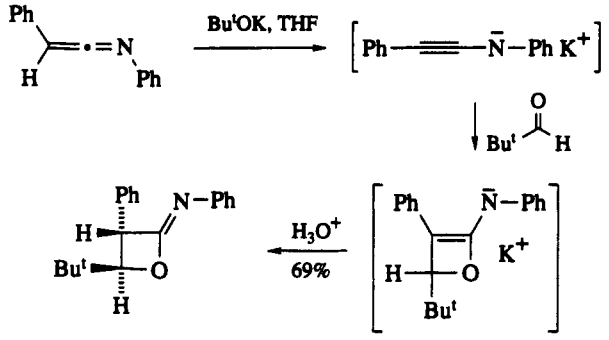


Scheme 44

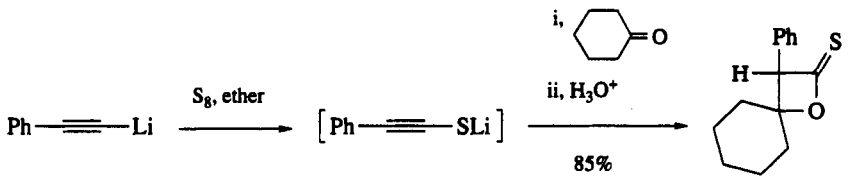
The reaction of (**41**) with electron-deficient imines yields 2-azetidinones resulting from a 1:2 addition (Scheme 45).[269,270] The total stereoselectivity of the reaction has been explained on the basis of steric approach control and chelation in transition state (**43**). The intermediate β-lactam enolate (**42**) is more nucleophilic than the starting ynolate. This unfavorable nucleophilicity ratio is responsible for the formation of a 1:2 adduct. This represents a severe limitation of the reaction as a general route toward β-lactams.



Scheme 45



Scheme 46

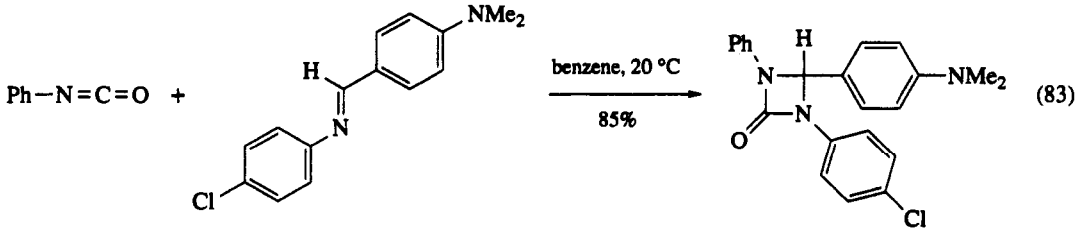


Scheme 47

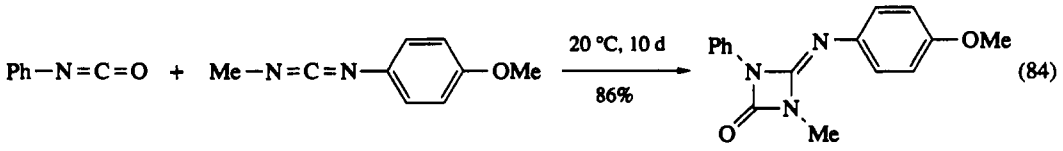
2-Iminooxetanes have been prepared from aldehydes and lithium (*N*-phenyl)phenylethynamide (Scheme 46).[271,272] 2-Thionooxetanes are similarly formed from carbonyl compounds and lithium thioalkynolates (Scheme 47).[273] None of these reactions is of general preparative value.

2.2.11 MISCELLANEOUS

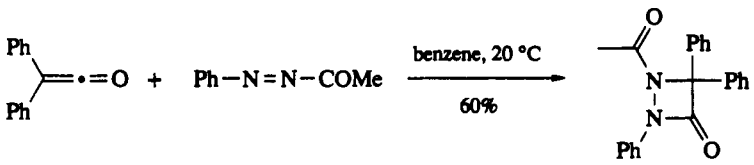
There are many other cases of combination of π-bonds leading to four-membered heterocyclic rings. Few of these are of great preparative value and most have been little studied. Some representative examples are shown in equations (83),[274] (84),[275] (85),[276] (86)[277] and (87).[278]



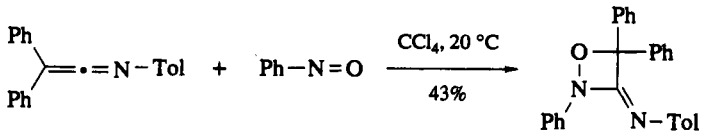
(83)



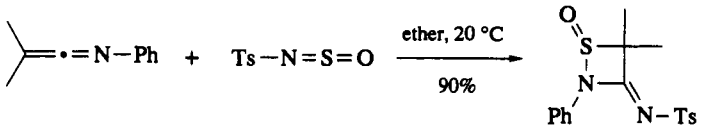
(84)



(85)



(86)



(87)

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2.3
Photochemical Cycloadditions

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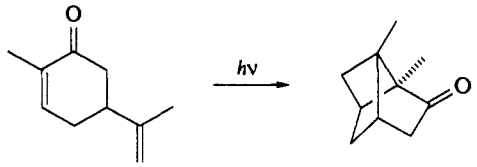
2.3.1 INTRODUCTION

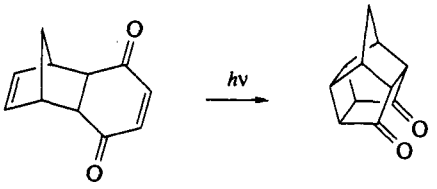
The photochemical [2 + 2] cycloaddition reaction of alkenes, the light-induced cycloaddition of two carbon–carbon π-bonds to produce a cyclobutane, is a potentially highly useful reaction in organic synthesis since two new carbon–carbon bonds are formed and a maximum of four new stereocenters are introduced in the process.[1] Ciamician reported the first example in 1908 when he observed the formation of carvone camphor (**2**) on prolonged exposure of carvone (**1**) to Italian sunlight (equation 1).[2]



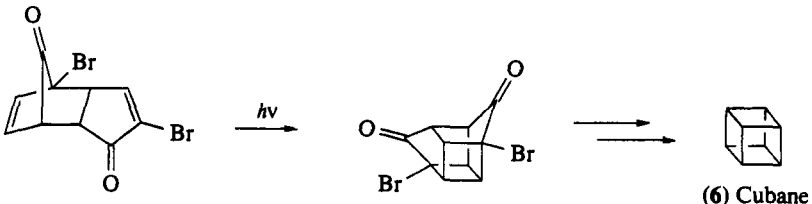
(1)

(1) (2)

After Buchi confirmed this finding in the 1950s,[3] numerous other investigators immediately recognized the rapidity with which complex molecular architectures could be constructed by this reaction. Cookson irradiated the Diels–Alder adduct (**3**) of cyclopentadiene and benzoquinone to produce the caged diketone (**4**) (equation 2)[4] while Eaton utilized a photochemical cycloaddition of diene (**5**) in a synthesis of the platonic solid cubane (**6**) (equation 3).[5]



(3) (4) (2)

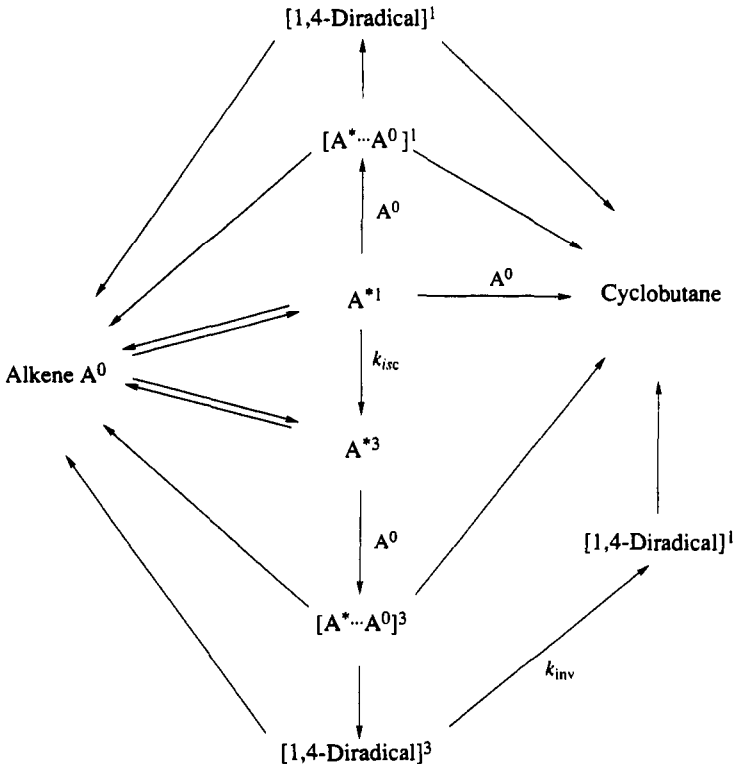


(5) (6) Cubane (3)

Corey,[6] Eaton,[7] de Mayo[8,9] and many others began to investigate the various synthetic and mechanistic ramifications of the photocycloaddition which resulted in the total synthesis of caryophyllene[10] and bourbonene[11] as well as a proposed mechanistic rationale for the reaction.[6] Subsequently, numerous natural and unnatural products have been prepared by synthetic routes which have a [2 + 2] photocycloaddition as a crucial step in their synthesis, and the reaction has become recognized as an important transformation in the repertoire of the synthetic organic chemist.

2.3.2 MECHANISM

While there is still much which is not well understood about the mechanism of the photochemical cycloaddition, several points about a working hypothesis (Scheme 1)[6,8–10] are worthy of note and serve as a basis for the discussions which follow.



Scheme 1

Excitation of the ground-state alkene A^0 (either $n\rightarrow\pi^*$ or $\pi\rightarrow\pi^*$)[12,13] normally produces the excited singlet A^{*1} which can (1) combine with a ground-state alkene A^0 to form a singlet exciplex $[A^*...A^0]^1$, (2) undergo a concerted cycloaddition with A^0 to form a cyclobutane, (3) intersystem cross to an excited triplet A^{*3}, or (4) collapse back to the ground state. The singlet is fairly short lived, particularly in enone systems, and will decay back to the ground state if *cis–trans* isomerization can occur.[14] The singlet exciplex can decay back to the ground state or generate a cyclobutane directly, or produce a 1,4-diradical which can also collapse to the ground state or proceed to cyclobutane. The triplet A^{*3}, which can result from the singlet A^{*1} or from sensitized excitation of the ground state A^0, can either decay to the ground state or combine with a ground-state alkene to generate a triplet exciplex $[A^*...A^0]^3$.[6] The exciplex can then form a carbon–carbon bond and produce a triplet 1,4-diradical which can undergo spin inversion to the singlet diradical followed by production of the cyclobutane. Additionally, at any point along the path to cyclobutane, *i.e.* (1) the triplet exciplex $[A^*...A^0]^3$, (2) the triplet diradical or (3) the singlet diradical, the ground-state alkenes can be regenerated. While it is convenient to invoke the intermediacy of exciplexes in photocycloadditions, Schuster has recently presented kinetic evidence which is inconsistent with exciplex formation.[15]

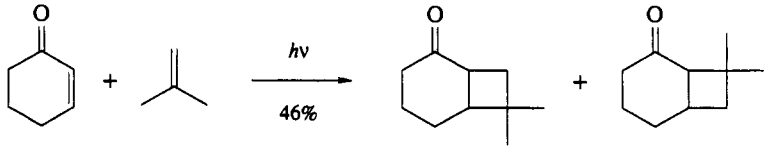
In the majority of cases the pathway which leads to cyclobutane adducts is most likely excitation to a short-lived singlet A^{*1}, followed by crossing to the longer-lived triplet A^{*3} which forms an exciplex and then a triplet diradical. The triplet diradical spin inverts to the singlet and closes to the cyclobutane. If the singlet can undergo rotation, energy wasting *cis–trans* isomerization will compete with intersystem crossing and subsequent photocycloaddition. This occurs primarily in acyclic systems which are not rigidly held by hydrogen bonding or in cyclic systems which are larger than six members.[16]

2.3.3 INTERMOLECULAR PHOTOCYCLOADDITIONS

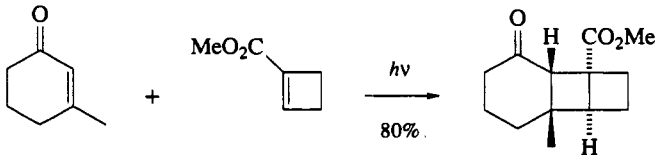
2.3.3.1 Regiochemical Control

When two unsymmetrical alkenes undergo [2 + 2] photocycloaddition, two regiochemical isomers, the head-to-head and head-to-tail isomers, can result. For example, when cyclohexenone is irradiated in the presence of isobutene the head-to-head product (**8**) is produced along with the head-to-tail isomer (**7**) (equation 4). The preponderence of the head-to-tail isomer (**7**) is generally thought to be controlled by electronic interactions. The excited enone is assumed to have a charge distribution which is the opposite of its ground-state configuration and thus the enone β-carbon bears a partial negative charge.[6,17] During the exciplex formation the ground-state alkene and the excited-state enone are oriented to maximize electrostatic interactions. This interpretation is supported by results with more highly polarized alkenes and enones which both show significantly higher regioselectivity (equations 5–7).[6,18,19] While this electrostatic interpretation is a useful predictive tool, regioselectivity may be greatly influenced by the rate with which each initially formed exciplex proceeds to products or reverts to the ground state.

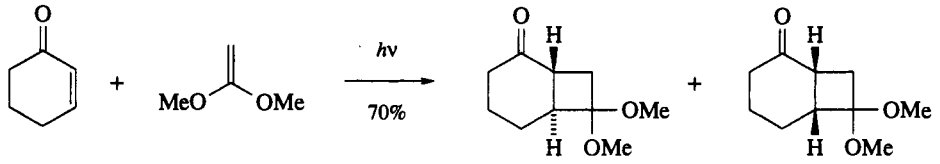
Steric interactions can dramatically affect regioselectivity as well. This is demonstrated by the result that cyclohexenone reacts with vinyl acetate to give exclusively the head-to-tail regioisomer (**9**)[20] while 3-methylcyclohexenone produces a 1:4 mixture of the head-to-head:head-to-tail isomers (**10**):(**11**) (equation 8).[21] Additionally, 3-*n*-butylcyclopentenone undergoes photocycloaddition with vinyl acetate to give a 3:1 mixture of head-to-tail:head-to-head photoadducts while 1-acetoxy-1-hexene gives rise to exclu-



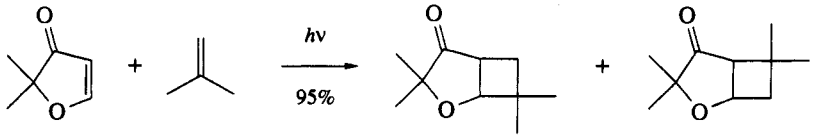
(7) 86:14 (8) (4)



(5)

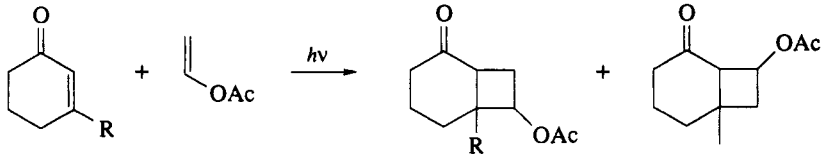


(6)



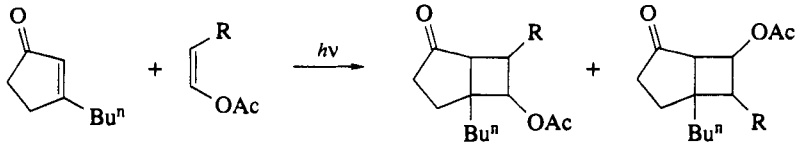
(7)

sively the head-to-tail adduct, presumably due to the steric interaction between the two alkyl chains (equation 9).[22]



(8)

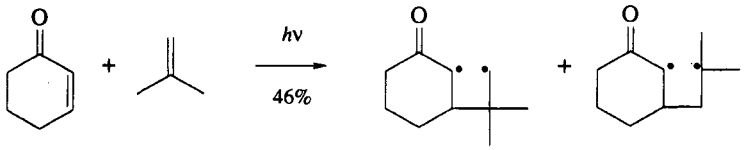
R = H	90%; 100:0	(9)	
R = Me	68%; 20:80	(10)	(11)



(9)

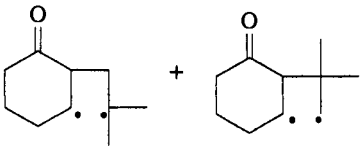
R = H	75:25
R = Pr^n	100:0

Regioselectivity in photocycloadditions may also depend on the production and partitioning of various 1,4-diradicals as has been proposed by Bauslaugh (equation 10).[1] In this treatment, unstable 1,4-diradicals are presumed not to form to any appreciable extent while the more stable diradicals are presumed to revert to starting alkenes preferentially. The diradicals of intermediate stability thus determine the selectivity of the reaction. While the product ratio may clearly depend in some instances on the rates of partitioning of the diradicals to cyclobutane *versus* ground-state alkenes, it is often very difficult even qualitatively to determine which diradicals are more or less stable, making this interpretation somewhat difficult. Overall, the polar exciplex theory serves as a useful model for predicting regioselectivity in most photocycloadditions.



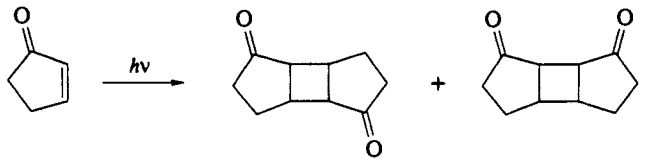
(10)

most stable



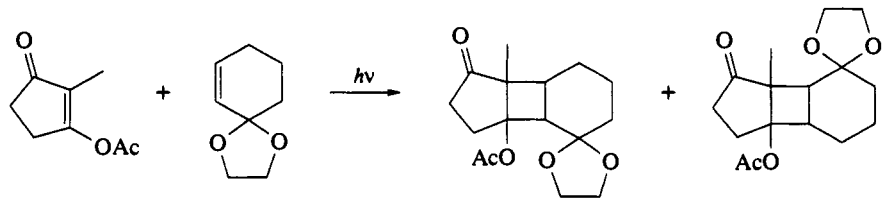
least stable

The observed regioselectivity can be perturbed to varying degrees by choice of reaction parameters. Solvent polarity can play a role in the control of regioselectivity, as would be predicted by the polar exciplex model. The regioselectivity of the dimerization of cyclopentenone (equation 11) produces a larger proportion of the head-to-head adduct in more polar solvents.[23] The photoaddition of enone (**11**) to alkene (**12**) also displays a pronounced solvent dependence (equation 12).[24] A consequence of the solvent effect is that nonpolar solvents tend to produce products which would be predicted from the polar exciplex model, while more polar solvents result in somewhat more of the minor product but do not cause complete reversal of the regioselectivity.



(11)

neat 57:43
cyclohexane 85:15

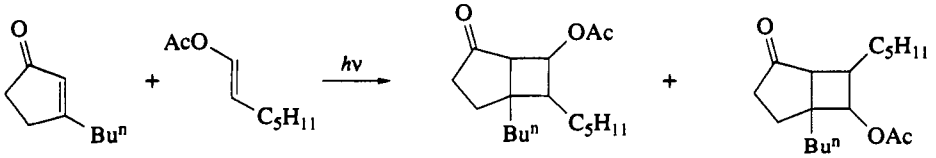


(12)

(**11**) (**12**)

cyclohexane 2:98
methanol 55:45

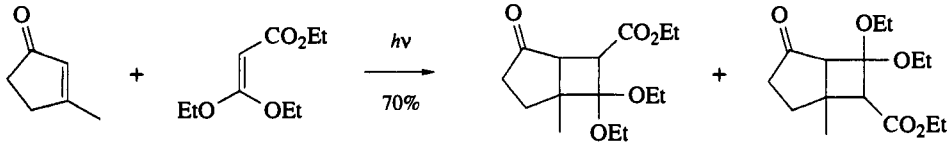
Organized media have also been used to influence the regiochemical outcome in the reactions.[22] Photoaddition of 3-*n*-butylcyclopentenone with various terminal alkenes has shown a pronounced preference for the alignment of the enone and the alkenes with their polar groups toward the surface of the micelle. This effect is most pronounced in the case of 1-acetoxy-1-heptene, which gives exclusively the head-to-tail adduct in cyclohexane solvent but a 2.3:1 mixture in favor of the head-to-head isomer in the presence of potassium dodecyl sulfate (equation 13).



(13)

cyclohexane 0:100
potassium dodecyl sulfate 70:30

Varying the temperature of the photoaddition reaction can also produce minor changes in the regioselectivity. Typically, lowering the temperature tends to enhance the selectivity in favor of the major regioisomer, as seen in equation (14).[25]

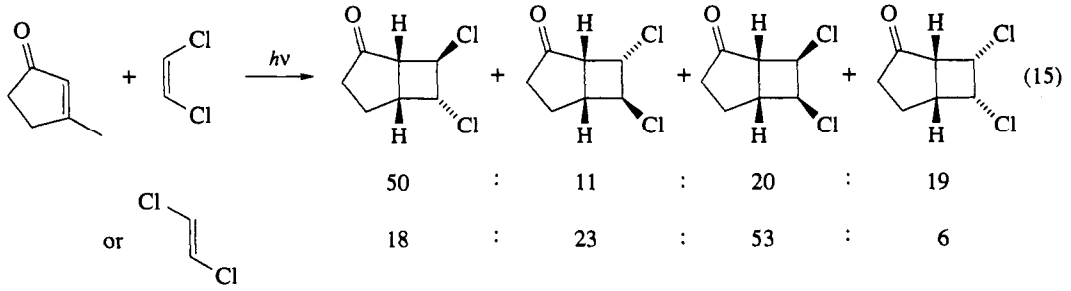


(14)

25 °C 29:71
−40 °C 0:100

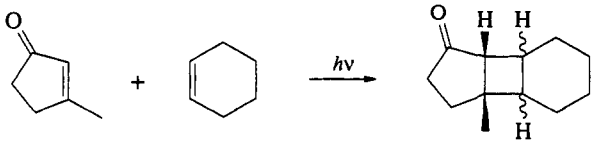
2.3.3.2 Stereochemical Control

Since up to four new stereogenic centers can be produced in a photocycloaddition reaction, prediction of stereoselectivity becomes extremely important with regard to the use of [2 + 2] photoadditions in synthesis. Stereoisomerism in the products of photoaddition can manifest itself in several different ways. First of all there is the question of geometry about the cyclobutane ring. In the addition of acyclic alkenes to cyclic enones, the geometry of the alkene is normally scrambled during the cycloaddition as a result of the rotational freedom in the intermediate long-lived 1,4-diradical. Thus *cis*- and *trans*-2-butene produced the same mixture of three stereoisomeric photoadducts when irradiated with cyclohexenone.[6] Similarly, cyclopentenone and 1,2-dichloroethylene produced all four possible *cis* photoadducts when either the *cis* or *trans* alkene was used.[26] Here the ratios of the products are somewhat different depending on the geometry of the alkene, but this may simply be a result of different rates of cyclobutane closure of the initially formed diradicals (equation 15).

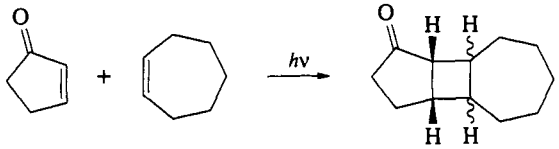


(15)

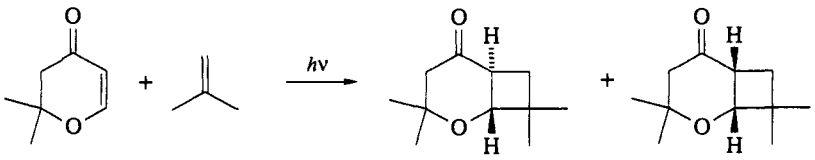
Loss of geometric integrity is not observed with cyclic alkenes which have ring sizes of five members or less since *cis–trans* isomerization is inhibited. Larger rings, however, can result in loss of alkene stereochemistry (equations 16, 17).[22,27] The cyclobutane ring juncture derived from the excited-state alkene is always *cis* if the enone is contained in a five-membered ring (or smaller), since the excited state is not substantially twisted (equations 7, 15–17).[19,22,26,27] Conversely, cyclohexenones often produce significant amounts of *trans* products at the cyclohexane–cyclobutane ring juncture (equations 6, 18, 19).[6,28,29] This has been attributed to the spectroscopic observation that some cyclohexenone triplets are substantially twisted, allowing bond formation on one side of the ring at the α-carbon and bond formation from the opposite face at the β-carbon.[13] Cyclohexenones which are conformationally more rigid tend to produce predominantly or exclusively *cis* ring fusions (equations 20–22).[21,30] The *cis* product is also obtained with cyclohexenones if the product cyclobutane contains an unusual amount of ring strain, *e.g.* with cyclobutenes, alkynes or allenes as the ground state alkene (equations 5, 23, 24).[18,31,32] As can be seen in equations (5), (11), (12) and (20), if the *cis* product is obtained the *cis-anti-cis* geometry as opposed to the *cis-syn-cis* geometry is by far the dominant product, presumably as a result of the steric interactions between the two rings.



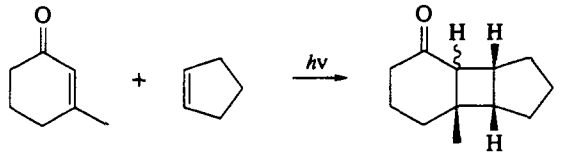
(16)



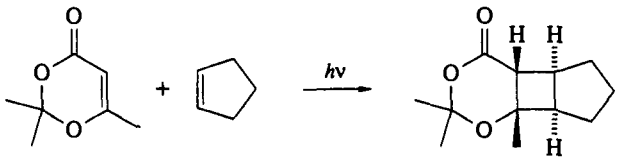
(17)



(18)



(19)



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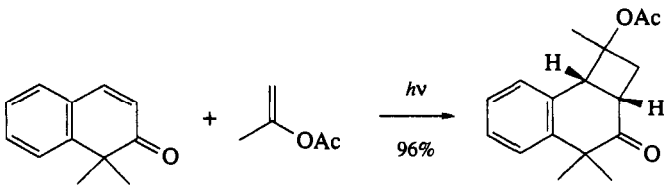

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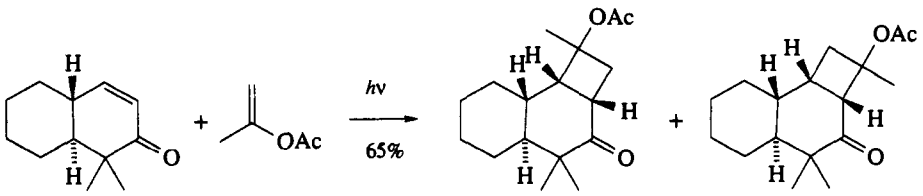
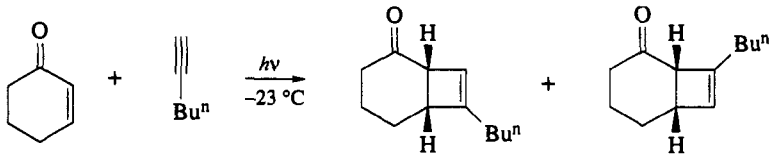


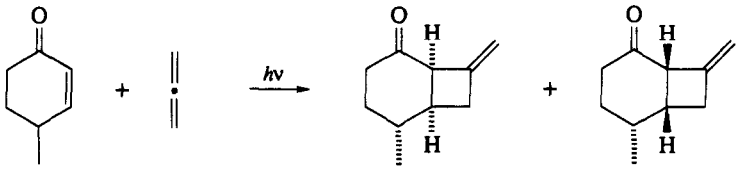
5.5:1

(22)



10:90

(23)

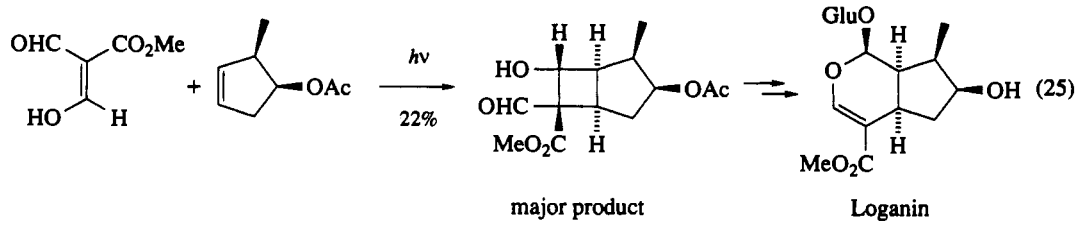


20:80

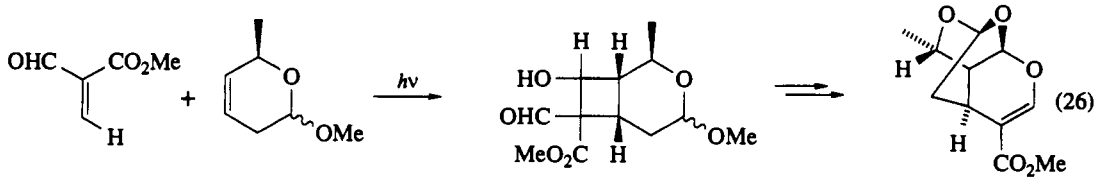
(24)

The remaining stereochemical point which must be addressed is the effect of a preexisting stereogenic center on either the excited-state or ground-state alkene. As a general rule, a stereogenic center in the ground-state alkene will affect the stereochemical outcome of a photocycloaddition reaction much as it would be expected to affect any other chemical reaction. That is, the excited state enone normally adds to the sterically most accessible face of the ground-state alkene, as in the photoadditions utilized in the syntheses of loganin (equation 25),[33] sarracenin (equation 26),[34] acorenone (equation 27)[35] and bourbonene (equation 28).[11] The addition of the dimethylfuranone (**13**) to enol derivatives (**14–18**) (equation 29) produces the product which would appear to result from approach from the more hindered face of the alkene.[36] This can perhaps be rationalized by $A_{1,2}$ strain in a similar manner to the epoxidation of 1,5-dimethylcyclopentene.[37]

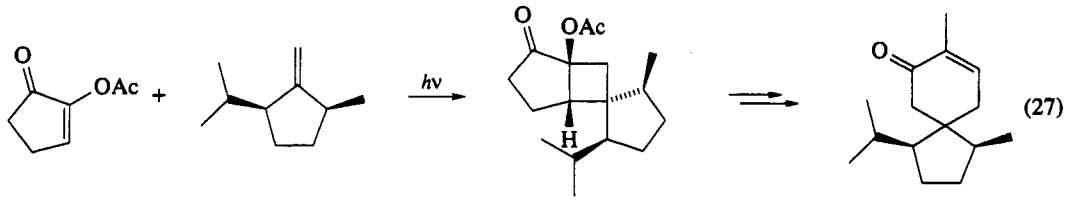
Stereochemical induction by a stereogenic center on the excited state enone, particularly cyclohexenones, has been rationalized by Wiesner as resulting from attack of the ground-state alkene on the most



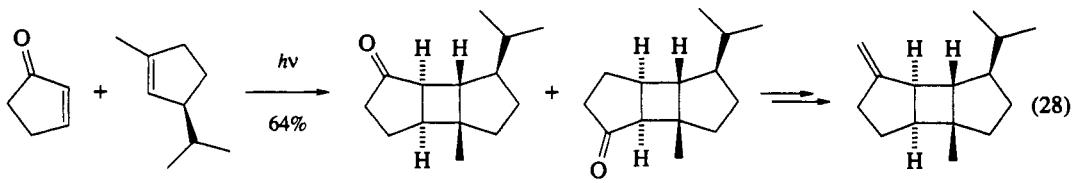
major product Loganin



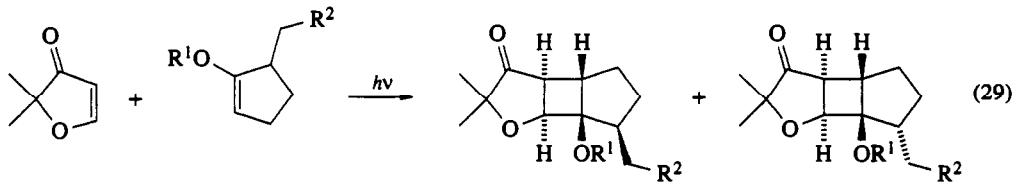
Sarracenin



Acorenone



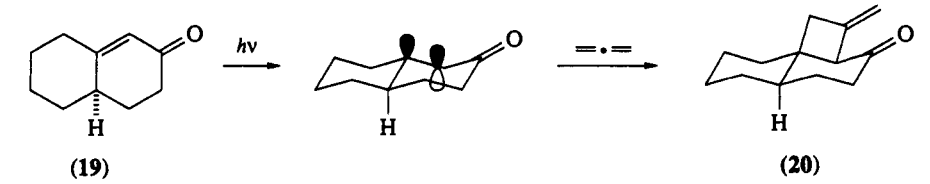
50:50 Bourbonene



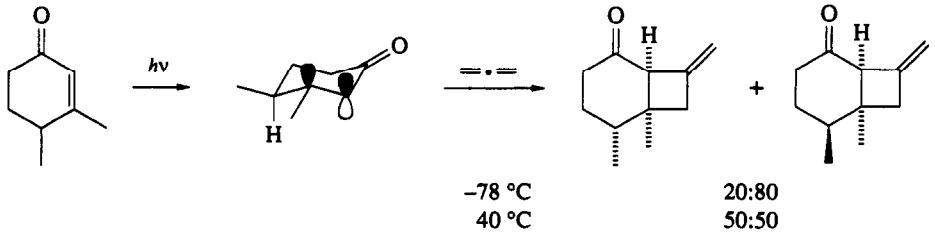
(13)		
(14)	$R^1 = SiMe_3$, $R^2 = H$	1:5
(15)	$R^1 = SiMe_3$, $R^2 = OCH_2Ph$	1:5
(16)	$R^1 = SiMe_3$, $R^2 = OSiMe_3$	1:10
(17)	$R^1 = Ac$, $R^2 = H$	1.8:1
(18)	$R^1 = Ac$, $R^2 = OCH_2Ph$	1.8:1

stable conformation of an excited enone which has a substantially pyramidalized β-carbon.[38,39] For example, addition of allene to octalone (**19**) produces (**20**) which results from addition of allene opposite the angular substituent (equation 30).[39] Similar results are obtained in the dissolving metal reductions of (**19**), which are presumed to proceed through a species in which the β-carbon is pyramidalized.[40] Results for the addition of allene to 3,4-dimethylcyclohexenone (equation 31) support this model since the predicted product should arise from *cis* approach to the C-4 methyl.[32] However, an alternative explanation which invokes $A_{1,2}$ strain, as in the epoxidation of 1,6-dimethylcyclohexene, is also plausible. Conversely, 4-isopropylcyclohexenone shows no selectivity[10,41] while 4-*t*-butylcyclohexenone yields the *trans* adduct as the major isomer,[42] albeit with ethylene as the ground-state alkene (equations 32, 33). Thus it

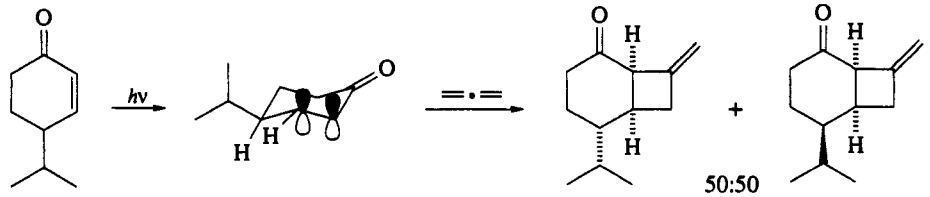
would appear that most examples might be better rationalized as proceeding through an excited state with a trigonal β-carbon with pyramidalization occurring during the reaction with the ground-state alkene, which conforms more closely to theory, and that cases such as 3,4-dimethylcyclohexenone are somewhat distorted due to torsional strain induced in a conformation with a trigonal β-carbon. It should also be noted that Dauben has recently proposed that photoadditions involving allenes as ground-state alkenes may be very different mechanistically from ordinary alkenes, at least in intramolecular cases.[43]



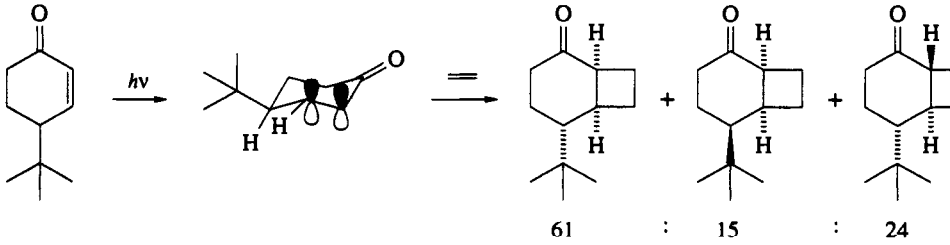
(19) (20) (30)



−78 °C 20:80
40 °C 50:50 (31)

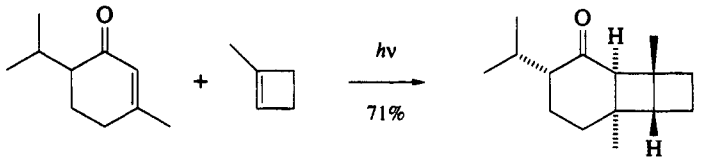


50:50 (32)

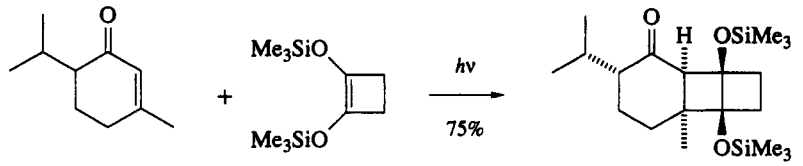


61 : 15 : 24 (33)

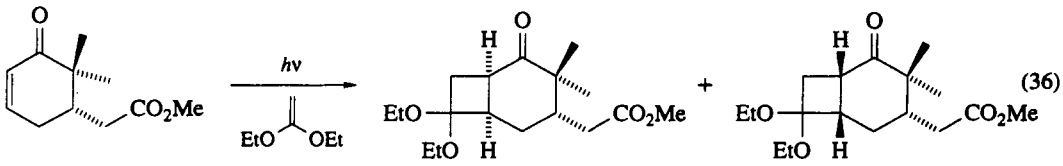
Cyclohexenones with substituents at the 5- and 6-positions tend to give the product which would be predicted by steric approach control to an excited state with a trigonal β-carbon (equations 34–36).[44–46] As a final cautionary note, while these hypotheses are often useful for prediction of stereochemical results, the true source of the selectivity may involve the rates of cleavage of the intermediate diradicals to the ground state *versus* rates of cyclobutane ring closure. Insufficient data are currently available to explain these results completely.



71% (34)



(35)

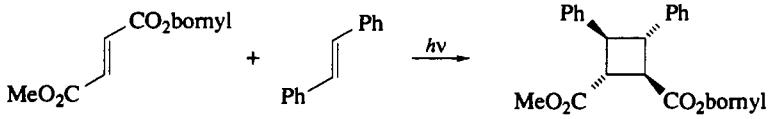


(36)

37:63

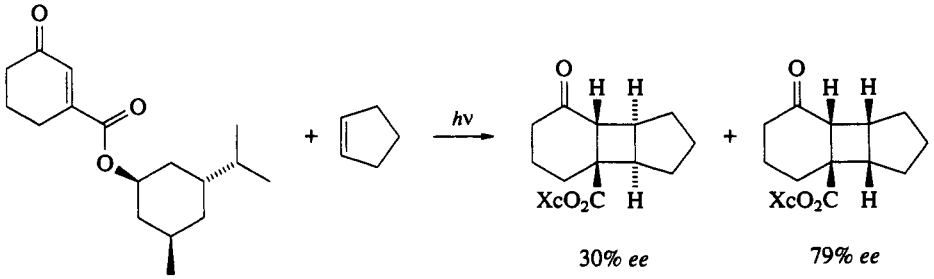
2.3.3.3 Enantioselectivity

Control of absolute asymmetry is a relatively untouched area for [2 + 2] photochemical cycloaddition reactions despite the recent advances in the field of asymmetric synthesis. The first example of the use of a 'removable' chiral auxiliary was reported by Tolbert,[47] who obtained impressive enantioselectivity in the photocycloaddition of bornyl fumarate to stilbenes (equation 37). More recently, Lange[48] has shown that menthyl cyclohexenonecarboxylates are useful in control of absolute stereochemistry (equation 38). Baldwin[49] and Meyers[50] have also obtained excellent facial selectivity in systems where the stereogenic center which controls the diastereoselectivity can be excised to afford products of high enantiomeric purity (equations 39, 40).



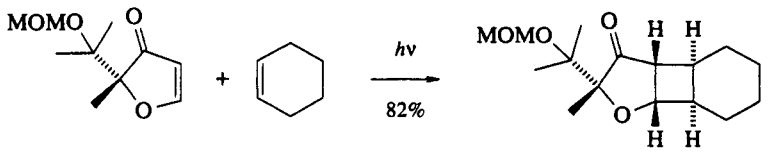
(37)

94% *ee*



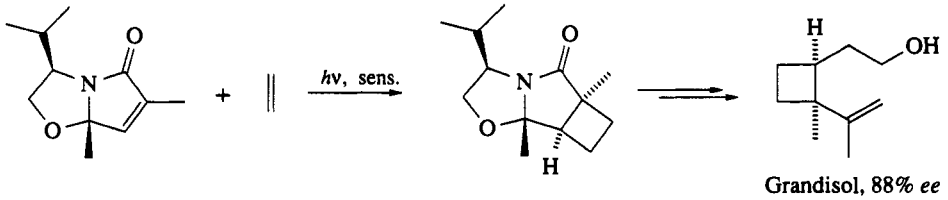
(38)

30% *ee* 79% *ee*



(39)

96:4 face selectivity



(40)

Grandisol, 88% *ee*

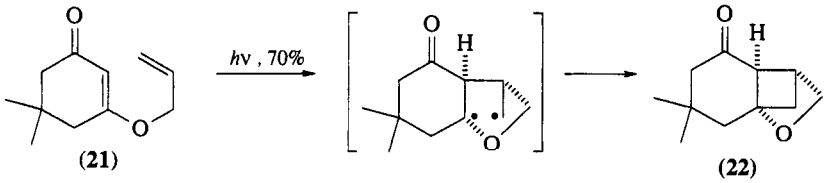
2.3.4 INTRAMOLECULAR PHOTOCYCLOADDITIONS

Regiochemical and stereochemical control can be excellent in many examples of the intermolecular photochemical [2 + 2] cycloaddition, but the frequency of cases where selectivity is low, or worse, unpredictable, has inhibited the use of this powerful reaction. While the major disadvantage of the *inter*molecular photocycloaddition is its low selectivity in some systems, this problem can be substantially overcome by incorporating the two sites of unsaturation into the same molecule. Although many of the early examples of the [2 + 2] photocycloaddition were *intra*molecular, this variation of the reaction saw only limited use until the 1970s when its potential for the rapid construction of complex polycyclic carbon skeleta was recognized by Oppolzer, Pattenden and others.

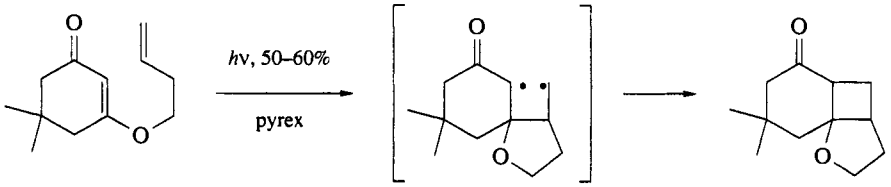
2.3.4.1 Regioselectivity

Regioselectivity in the intramolecular photocycloaddition reaction is generally higher and more predictable than in the intermolecular version. This derives primarily from the geometric constraints which are placed on the transition states during initial ring closure. Formation of five-membered rings, if possible, is favored in the initial ring formation by attack of the excited-state on the ground-state alkene. This empirical observation was termed 'the rule of five' by Hammond and Srinivasan[51] and is similar to the observation by Beckwith[52] that the 5-hexenyl radical undergoes cyclization to the cyclopentylmethyl radical 75 times faster than to the cyclohexyl radical. An excellent illustration of this model is seen in the cyclization of enol ether (**21**) to the crossed adduct (**22**), presumably proceeding through the intermediate diradical formed by the closure of a five-membered ring (equation 41).[53] The system (**23**), with a three-atom tether, produces exclusively the straight adduct (**24**) also by initial formation of a five-membered ring (equation 42).[54] While there are exceptions to this generalization, systems with two- and three-atom tethers give either exclusively or predominantly the product predicted by the 'rule of five' (equations 43–47).[55–59] Cyclohexenones and cyclopentenones with tethers of two and three atoms attached at C-2 or C-3 are particularly reliable with respect to their regiochemistry. Of particular note is the interesting case of the furan (**25**), which cyclizes to (**26**) in accord with the above rule while completely overcoming the normal electronic preference observed for intermolecular photocycloadditions (equation 47).[59] The major exceptions to the 'rule of five' in these systems have an allene as the ground-state alkene and Dauben has presented convincing evidence which indicates that photocycloadditions involving allenes may be quite different mechanistically.[43]

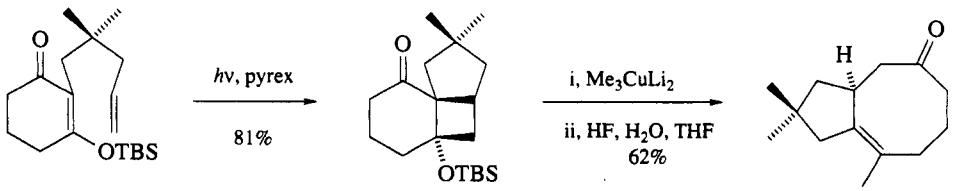
When the two alkenes are tethered by four or more atoms, the favored product is typically the straight adduct. For example, systems with a four-atom tether give products derived from initial formation of a



(21) (22) (41)



(23) (24) (42)



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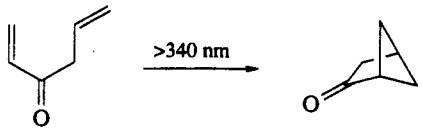

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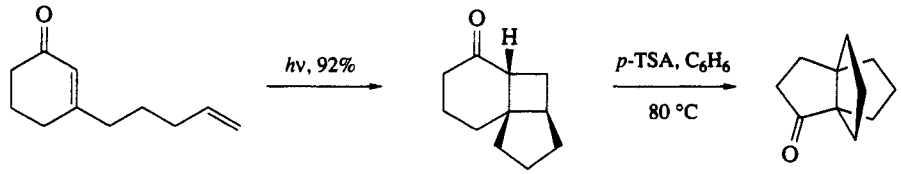

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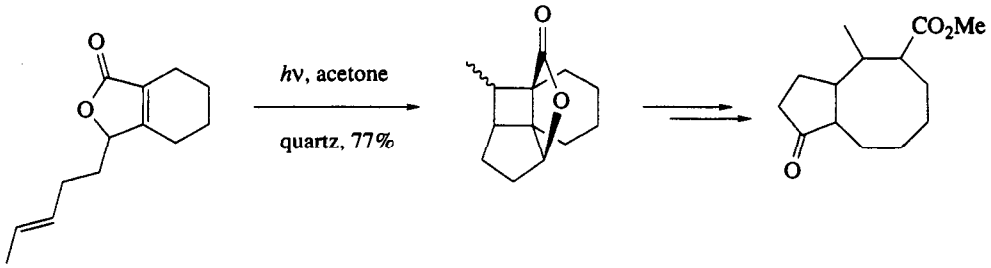

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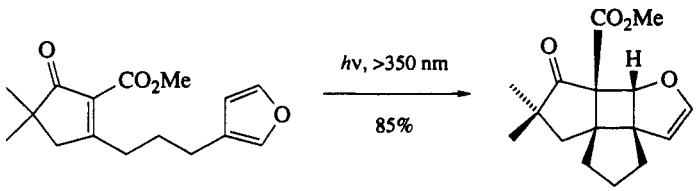
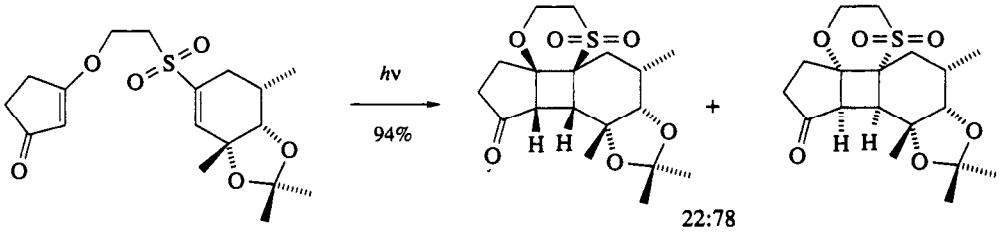


(47)

(25) (26)

six-membered ring, as in equations (48)–(53).[60–65] Winkler has studied a variety of tether lengths in the photocycloadditions of dioxolenones and observed only the straight adduct in all cases (equations 54, 55).[66] However, Baldwin has pointed out that the regiochemistry in these dioxolenone systems is particularly sensitive to subtle steric and electronic effects (equations 56–58).[30]



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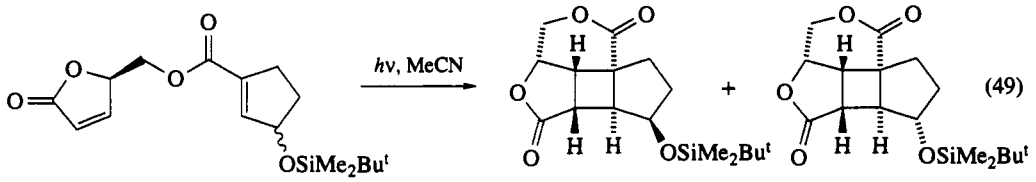

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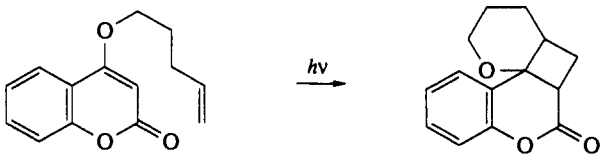

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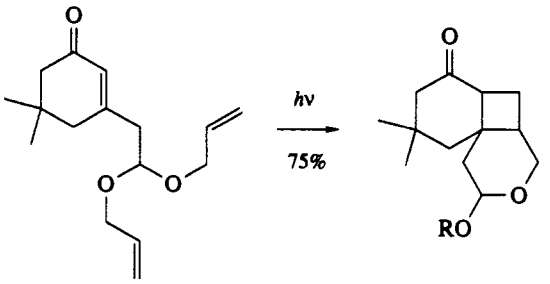

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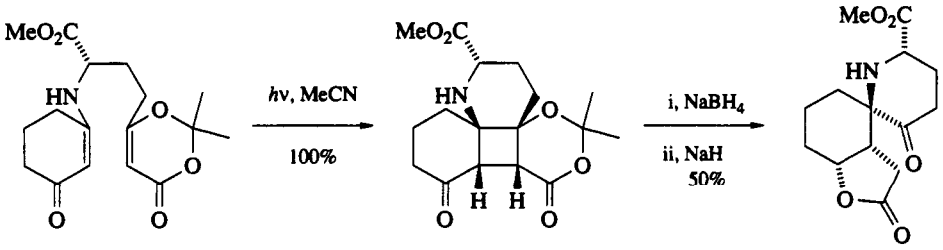

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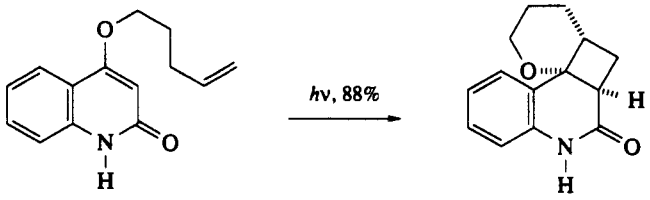

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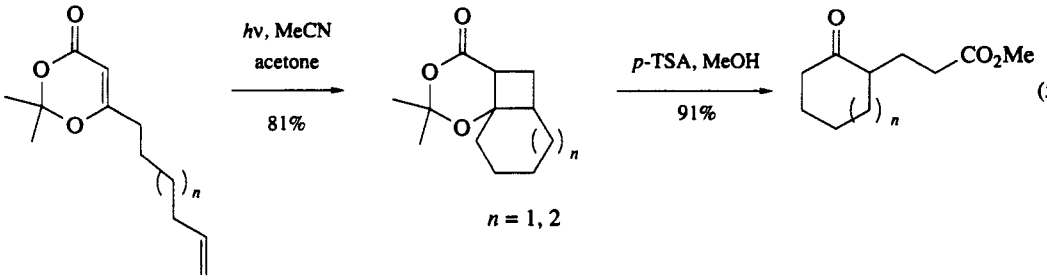

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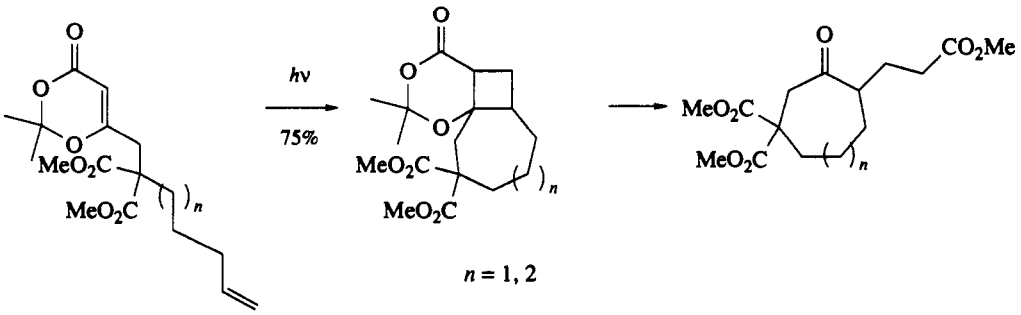

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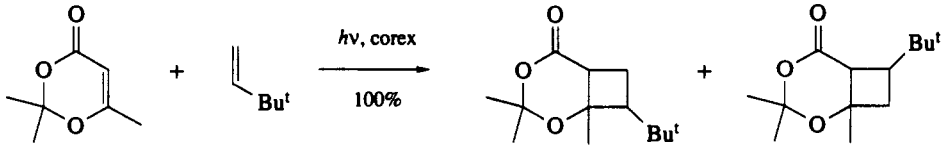

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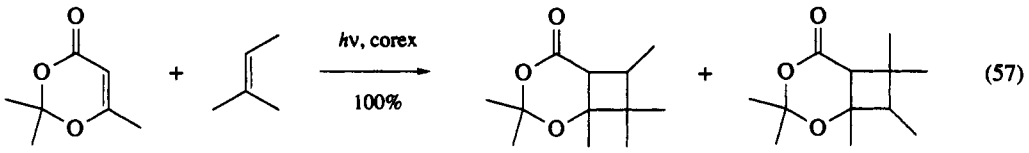
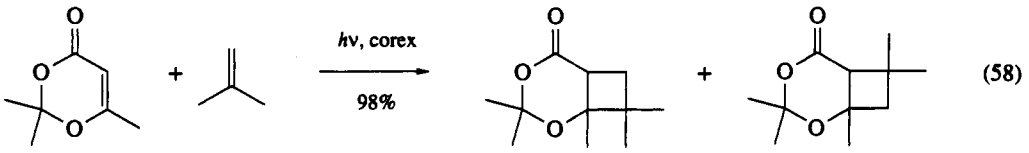
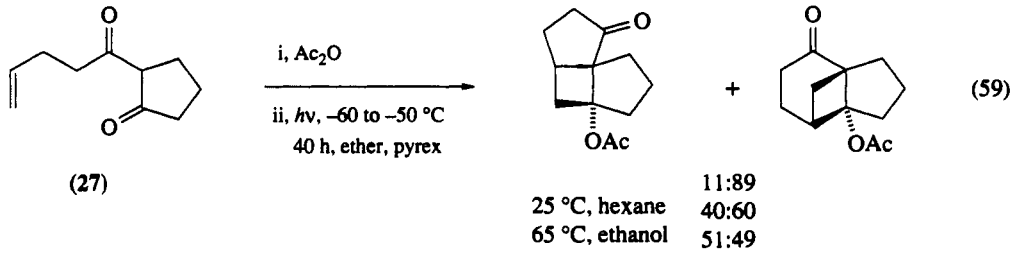
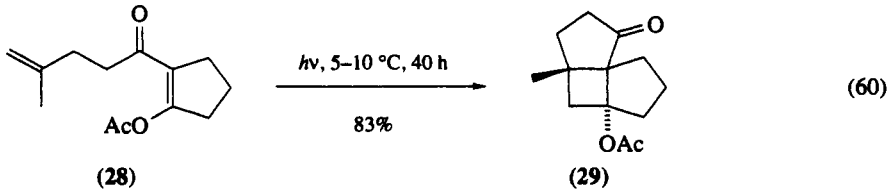


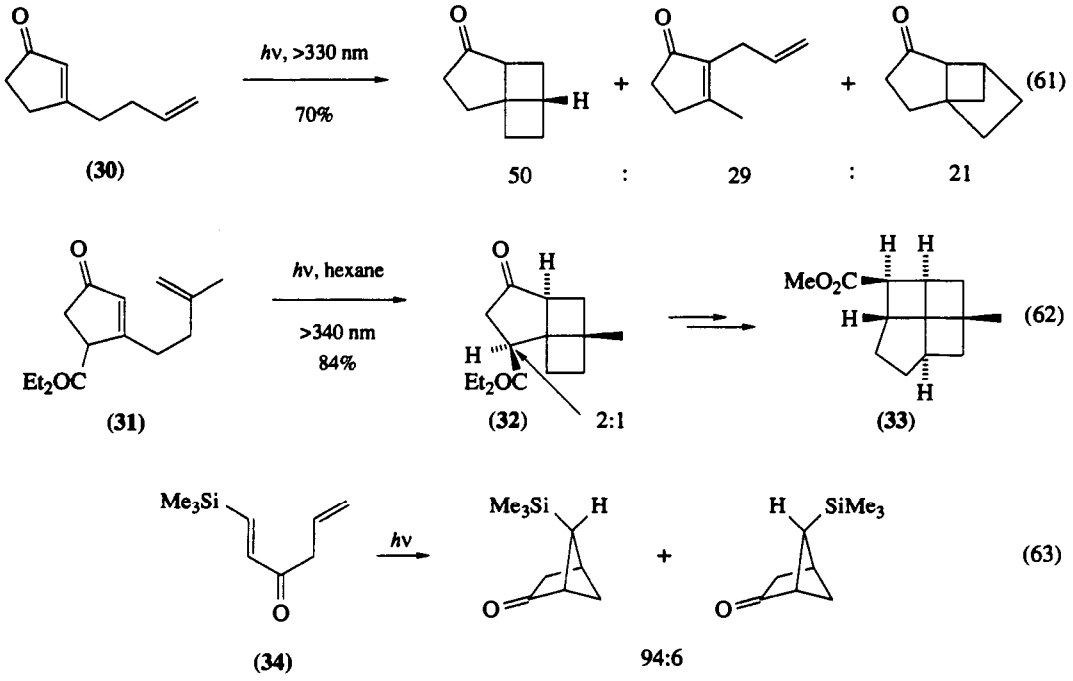


One very unusual case which does not follow the 'rule of five' is shown in equation (59). Enone (**27**) produced a 1:1 mixture of straight and crossed adducts at 65 °C and a 9:1 ratio in favor of the crossed adduct at –50 to –60 °C. The result was completely reversed when the methyl substituted alkene (**28**) was utilized, producing exclusively the straight adduct (**29**) (equation 60).[67,68]





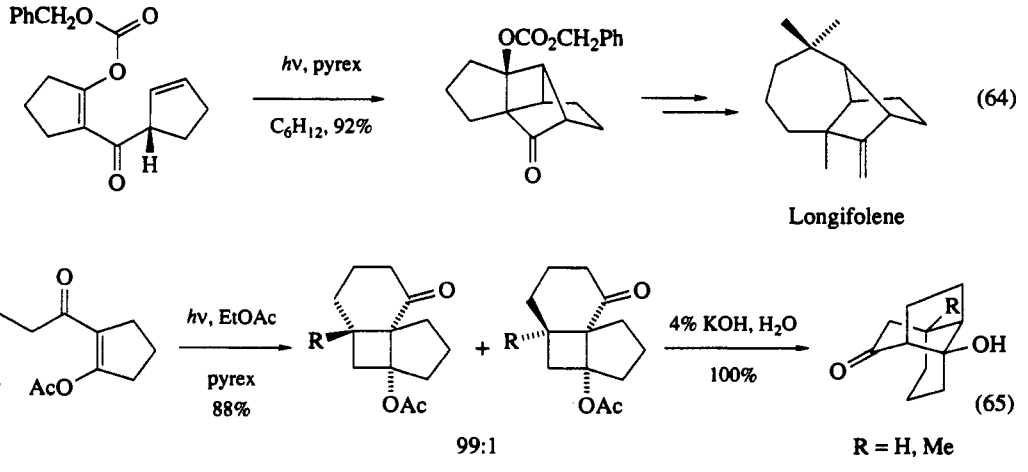
Wolff and Agosta have taken advantage of a similar result in the photocycloaddition of 1,5-dienes in an efficient approach to substituted fenestranes.[69,70] The unsubstituted system (**30**) yielded a mixture of photoadducts (equation 61) while enone (**31**), containing a methyl group on the internal carbon of the double bond, gave excellent yields of a single regioisomer (**32**) which was transformed to the [4.4.4.5]fenestrane (**33**) (equation 62). The photocycloadditions of 1,5-hexadienes have been carefully studied by Wolff and Agosta, who note important structural features for the reversal of regiochemistry in these systems.[56,69–72] Alkyl substitution at C-5 and incorporation of the enone double bond into a ring, particularly a five-membered ring, appear to effect a change in the mechanism for the cyclization. The simple systems such as (**34**) (equation 63; also equation 44) appear to cyclize initially from C-1 to C-5, in accord with the 'rule of five', and as substitution is added at C-5 the rate of cyclization is retarded. This is very similar to the steric effect observed in the cyclization of 5-substituted 5-hexenyl radicals, which show a depressed rate for the formation of the cyclopentylmethyl radical and an increase in the rate of formation of the cyclohexyl radical. Incorporation of the conjugated double bond into a ring reduces the twisting of the excited triplet and can severely alter the geometry for the cyclization. When both effects are combined, as in enone (**31**), the result is exclusive 1,6-cyclization.

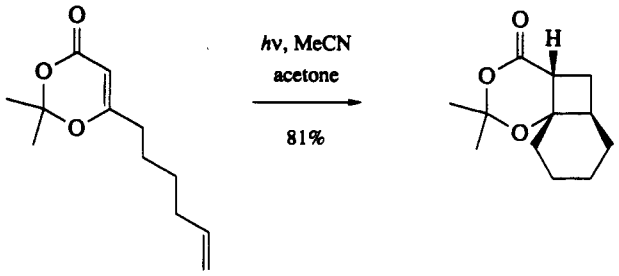


2.3.4.2 Stereoselectivity

Some of the most important recent advances in the use of [2 + 2] photocycloadditions in synthesis have been in the control of stereochemistry in complex polycyclic systems. The geometric constraints involved in the cyclizations to the photoadducts often result in extremely stereoselective cycloadditions. Additionally, preexisting stereogenic centers in the photocycloaddition substrate can be utilized to induce relative stereochemistry in the cycloadduct. The resident stereogenic center of the diene can be on the tethering chain, on the ring containing the excited state partner or on a ring containing the ground-state alkene.

First of all, the stereochemistry about the cyclobutane in the photoadducts is *cis* in almost all cases (equations 64–68).[66,73–77] There are rare exceptions, but these usually result from systems where the cycloalkenone is larger than six members or when the tethering chain can easily accommodate the *trans* cyclobutane (equations 69–72).[78–81] The most noteworthy exception is the recent example reported by Winkler in which dioxolenone (**35**) produced exclusively the *trans* cycloadduct (**36**) which was readily converted to the smallest known inside-outside bicycloalkanone (**37**).[82] This photoproduct presumably arises from initial cyclization in the chair-like conformation (**38**) (equation 73). Similarly, (**39**) has been converted to the carbon skeleton of the naturally occurring inside-outside bicyclic compound ingenol (equation 74).[83]





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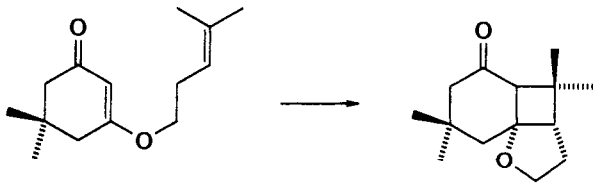

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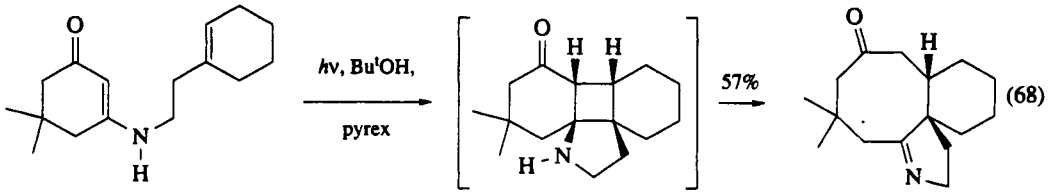

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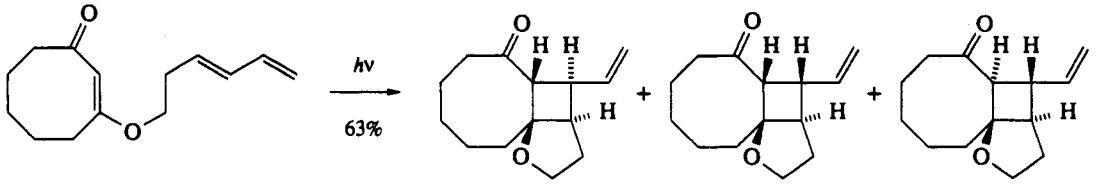
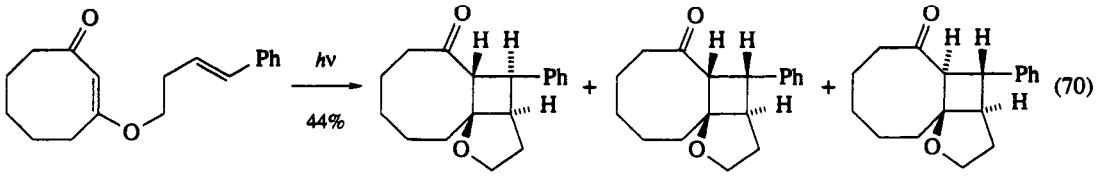


33 : 40 : 27 (69)



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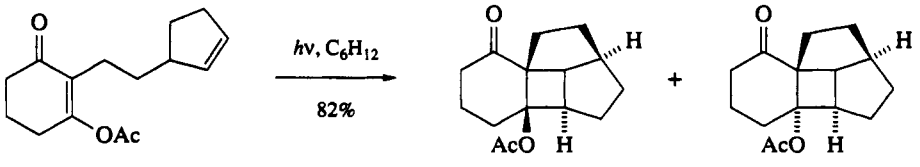

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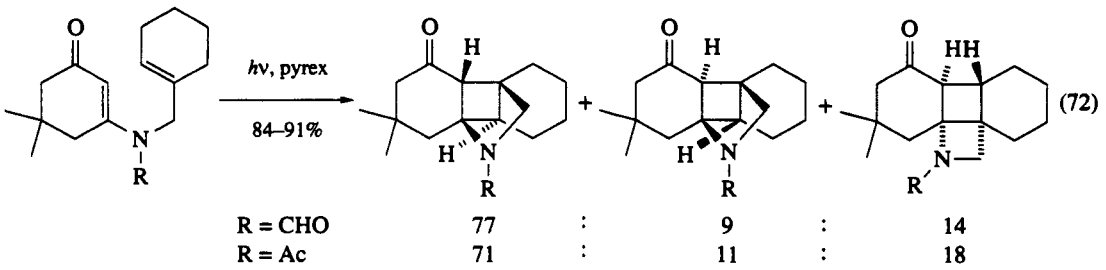

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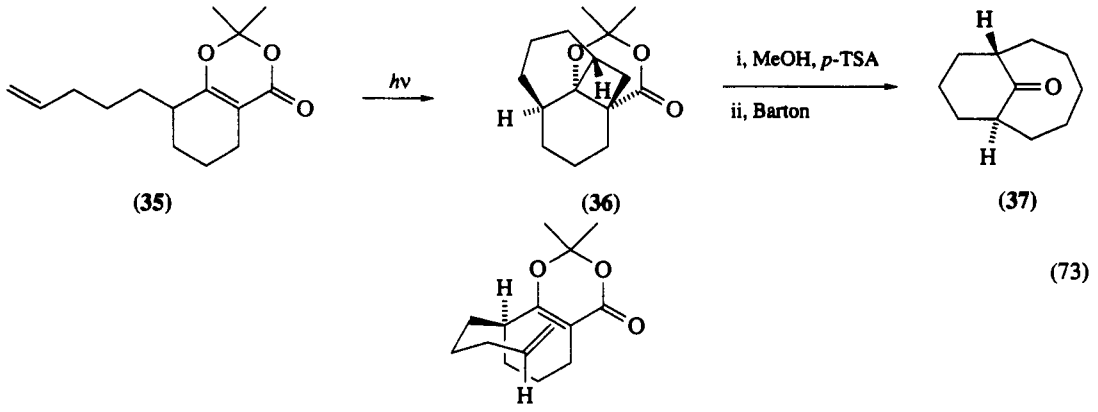
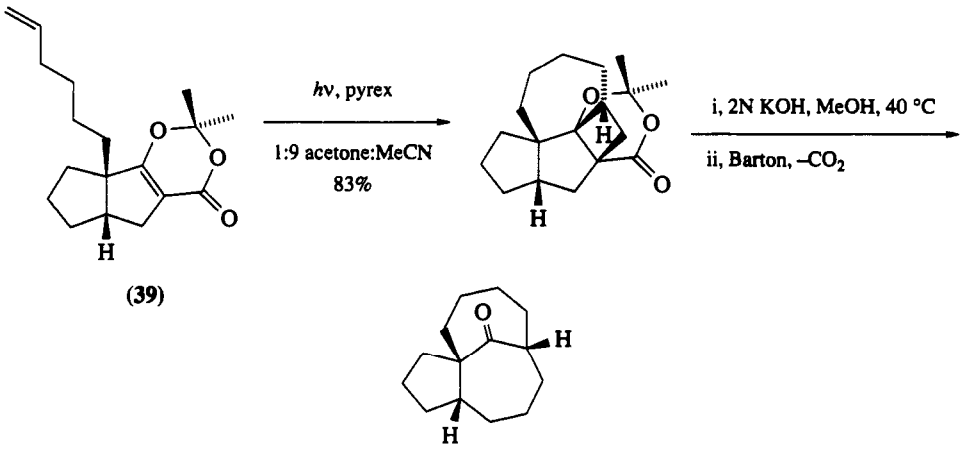


(35) (36) (37)

(73)

(38)

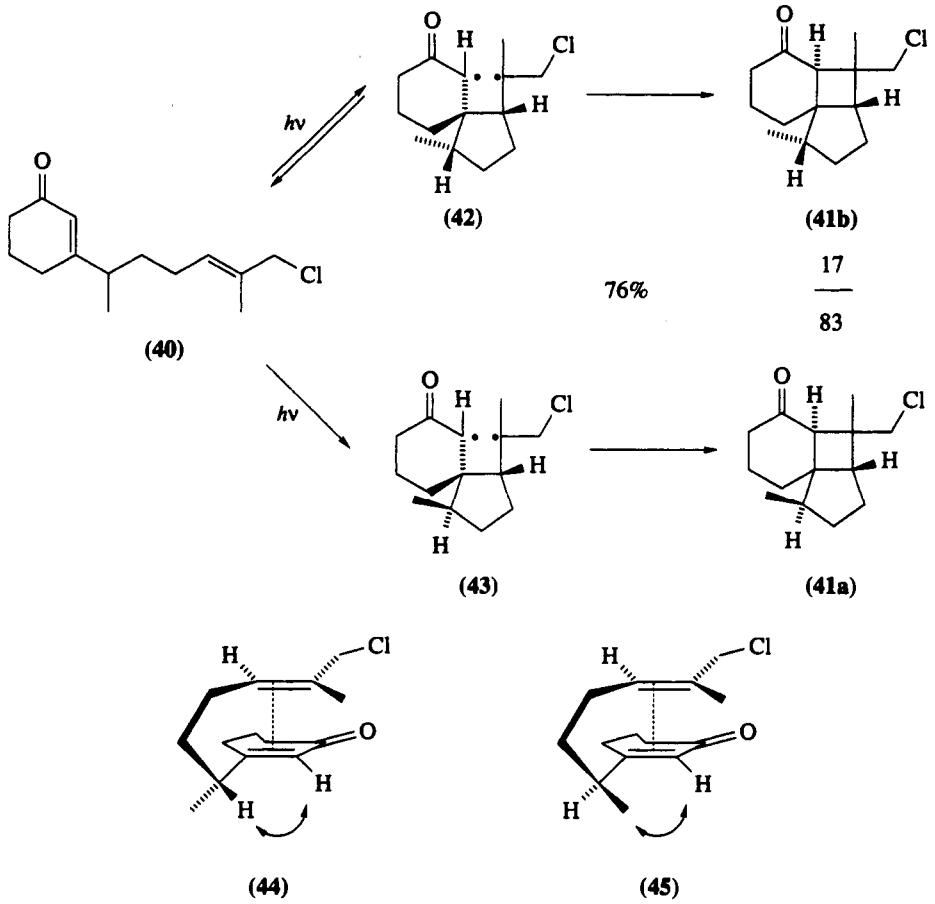


(74)

(39)

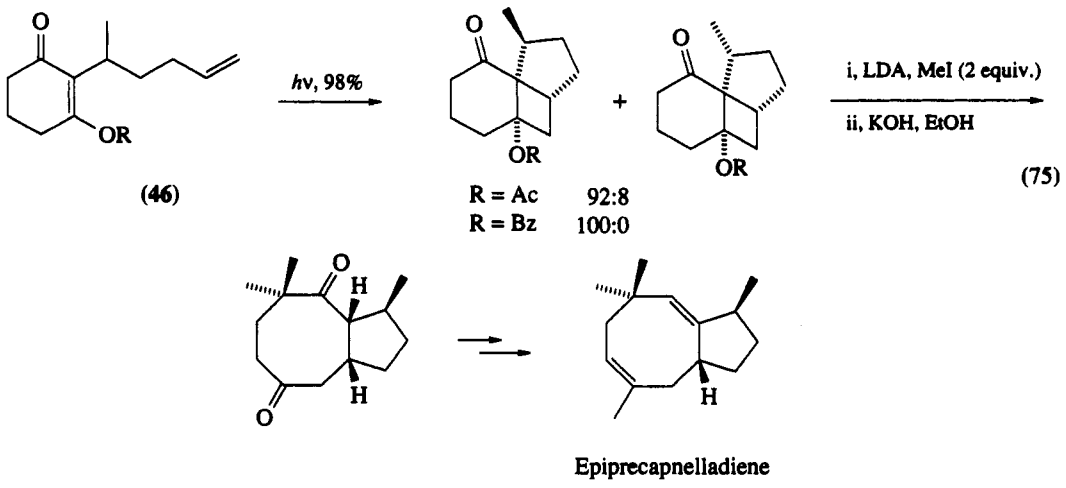
Stereochemical induction by a stereocenter on the tethering chain has been used effectively in the total synthesis of several natural products. In a synthesis of acoradiene, Oppolzer irradiated cyclohexenone (**40**) and obtained a 5:1 mixture of the β:α methyl diastereomers (**41**) in 76% yield together with some starting diene which had partially isomerized at the isolated alkene (Scheme 2).[84] The stereoselectivity was attributed to radical reversion of the 1,4-diradical (**42**) leading to the minor product due to a steric interaction between the secondary methyl group and the carbonyl α-hydrogen during the final cyclobutane closure. The resulting product ratio was presumed, therefore, to be a result of the thermodynamic preference for the major product. An alternative explanation is that the major product arises from a kinetic preference for the formation of the 1,4-diradical (**43**) because of the difference in energy of the two diastereomeric exciplexes (**44**) and (**45**). There is an $A_{1,3}$ interaction between the secondary methyl and the α-vinyl hydrogen in exciplex (**45**) while the equivalent interaction in (**44**) is between two hydrogens. Becker has recently presented evidence that there is no radical reversion in some closely related systems.[85]

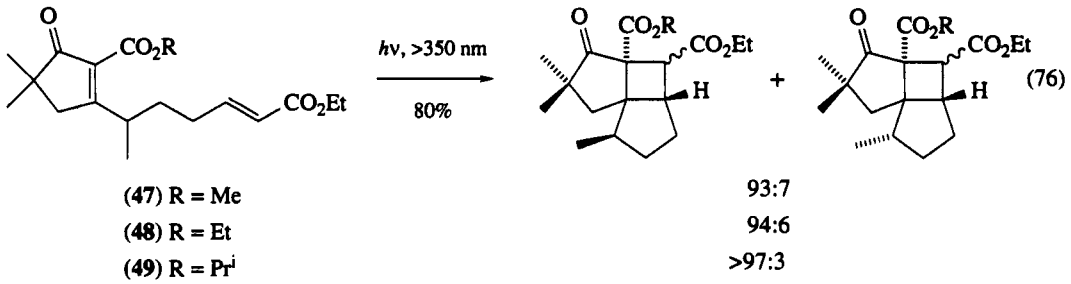
Which of these two pathways is operative is unclear at this time, but it is clear that the vinyl substituent on the cycloalkenone plays an important role in the selectivity. Pattenden, in a synthesis of epipre-

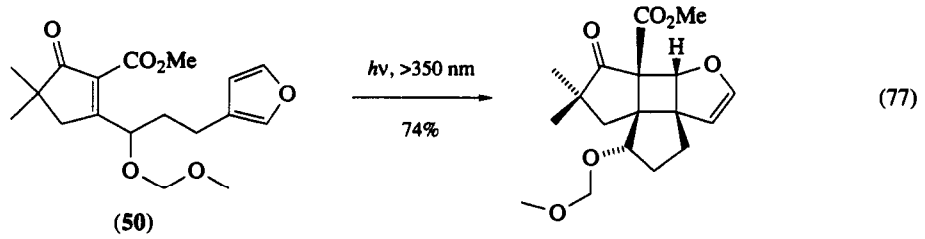


Scheme 2

capnelladiene,[86] carried out the photocycloaddition of enol acetate (**46**) and obtained a 92:8 mixture of diastereomers (equation 75). However, when the corresponding enol benzoate was utilized a single diastereomer was produced, presumably due to the increased steric interaction between the methyl group and the vinyl substituent. Similarly, Crimmins noted a sequential increase in stereoselectivity in the photocycloaddition of esters (**47**)–(**49**) from 93:7 with the methyl ester to >97:3 with the isopropyl ester (equation 76).[87] A similar case (**50**) gave a single cycloadduct in high yield (equation 77).[88]

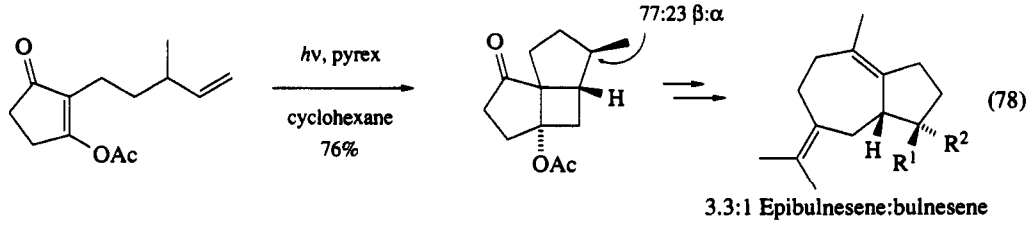


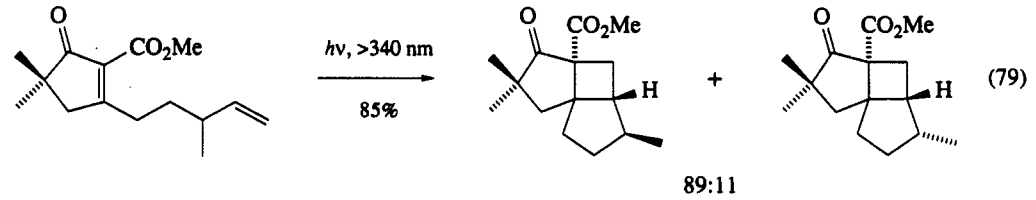


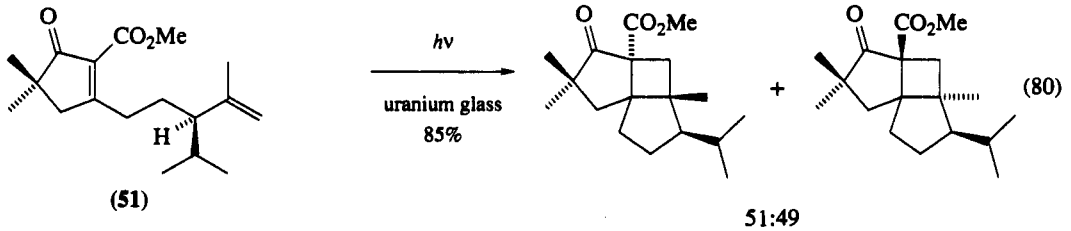


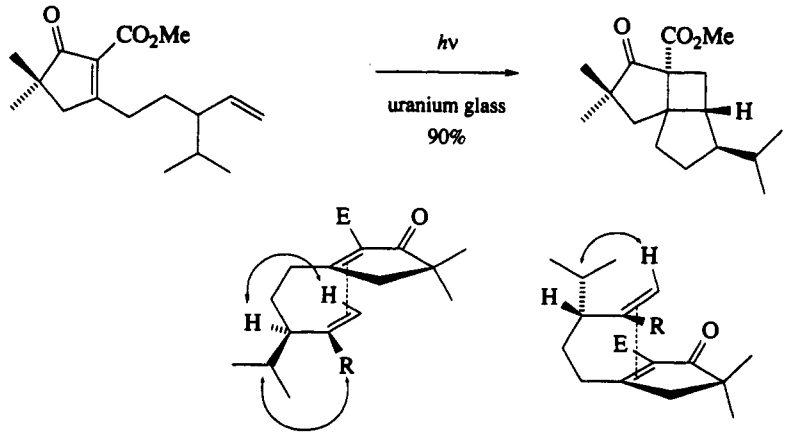
When the substituent is placed adjacent to the ground-state alkene in these systems, similar levels of stereoselectivity are observed as seen in equations (78)–(81).[89–91] Interestingly, diene (**51**), with a methyl group on the alkenic carbon adjacent to the isopropyl, is nonstereoselective while the system lacking the methyl group proceeds with complete stereoselectivity.[91] Apparently the $A_{1,2}$ strain between the methyl and the isopropyl groups in exciplex (**52**) counterbalances the $A_{1,3}$ strain between the hydrogen and isopropyl group in exciplex (**53**).

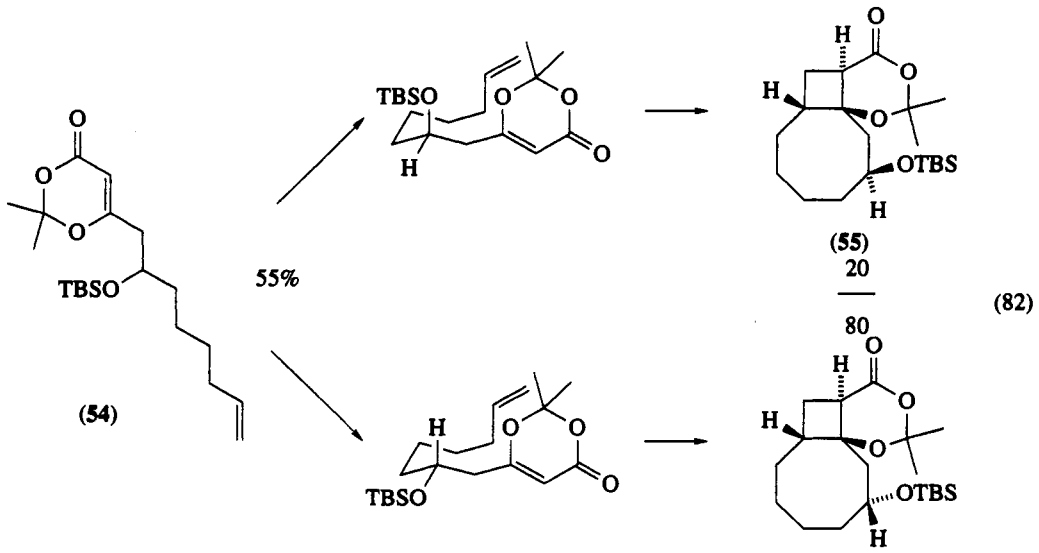
Modest asymmetric induction was seen in the cycloaddition of dioxolenone (**54**) to produce the eight membered photoadducts (**55**) and (**56**) (equation 82). The major product can be seen to arise from an exciplex in chair-like conformation with the silyloxy group in a pseudoequatorial position, while the minor isomer would require the silyloxy substituent to occupy a pseudoaxial site and would create a steric interaction between the OTBS and the ring oxygen.[56] Similar explanations can be put forth for the examples in equation (83).[92]

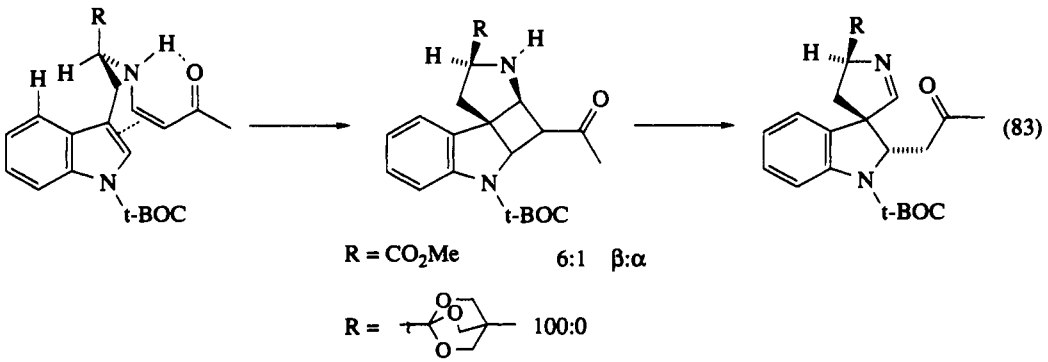








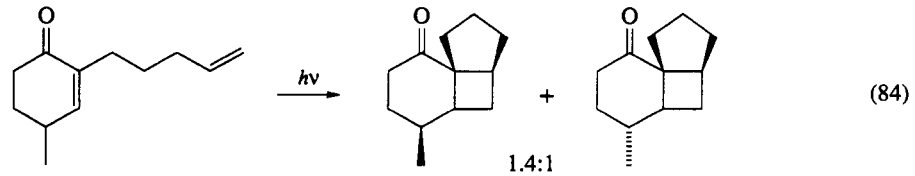




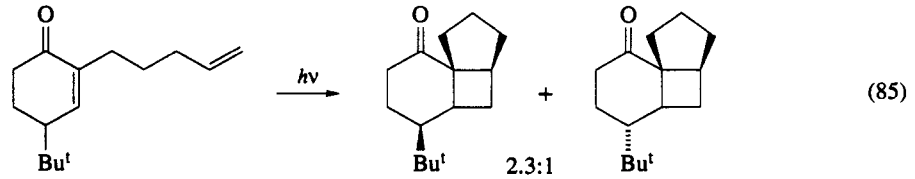
Becker has carried out a careful study of the effects of positioning a preexisting stereogenic center at the 4-position of cyclohexenones with the tethering chain attached at the 2-position.[93] Substitution at the 4-position generally influenced the alkene to approach the enone from the face opposite the alkyl group (equation 84) and increasing the steric bulk of the C-4 substituent resulted in a modest increase in stereoselectivity (equation 85). The selectivity increased from 2.3:1 to 2.7:1 when a methyl group was placed on the internal carbon of the alkene (equation 86), but the improvement is most notable when either one

(equation 87) or two methyl groups (equation 88) are added to the terminal carbon of the ground-state alkene. These results can be explained by comparing the energies of the diastereomeric exciplexes or by invoking a radical reversion explanation (Scheme 3). However, Becker has presented evidence in very closely related systems (equation 89) that no radical reversion is operative since the quantum yields are quite high and no alkene isomerization could be detected in recovered starting material.[85] In a similar case, Pirrung irradiated (**57**) to produce a single cycloadduct (**58**) which was converted to isocomene in two steps (equation 90).[94,95]

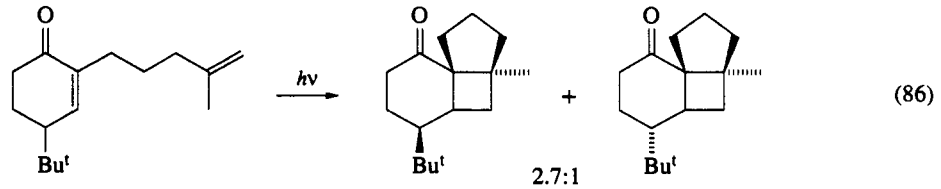
Several additional examples of stereochemical control in [2 + 2] photocycloadditions which include systems containing preexisting stereogenic centers on the ground-state alkene are shown in equations (91)–(97).[75,76,96–103] The stereoselectivity in these systems is typically controlled by the nonbonded inter-



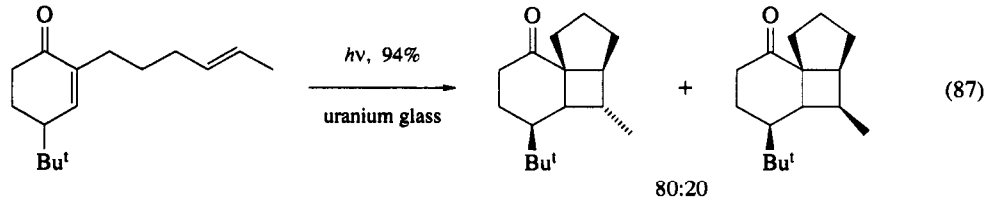
(84)



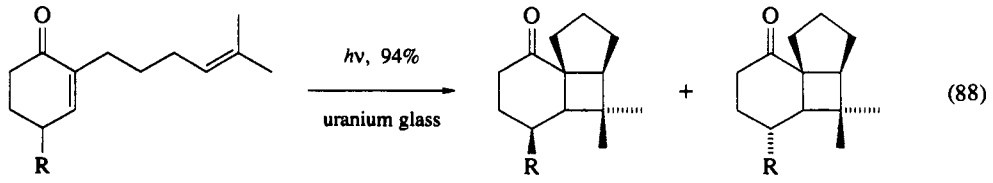
(85)



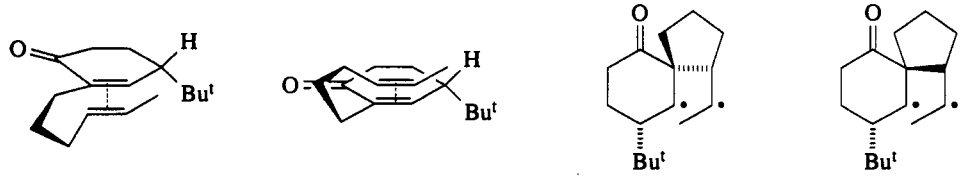
(86)



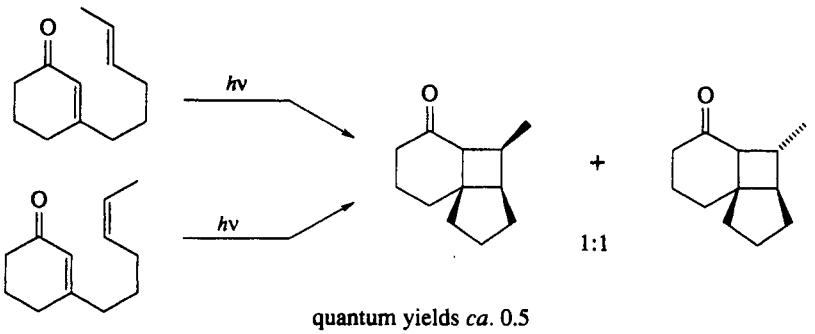
(87)



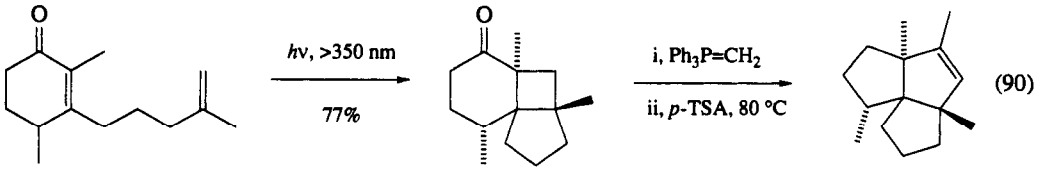
(88)



Scheme 3



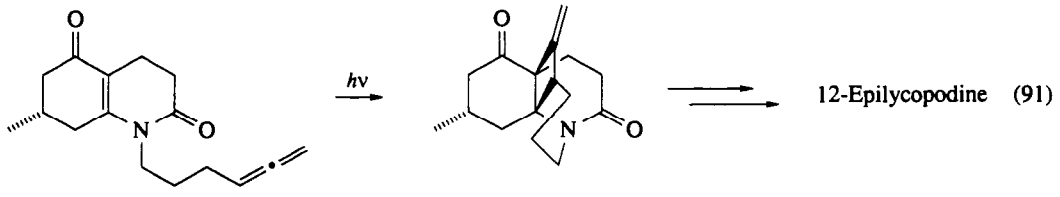
quantum yields *ca.* 0.5 (89)



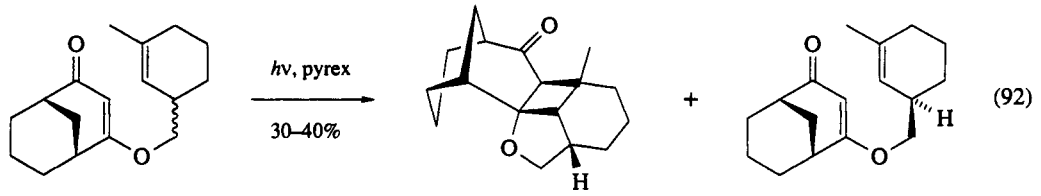
(57) (58) Isocomene (5 steps, 48%) (90)

actions between the two alkene portions and the tethering chain, as in the previously discussed cases. Of particular note is the diquinane enone (**59**), which produced only recovered starting material upon irradiation in hexane at 25 °C, but underwent smooth cycloaddition to (**60**) when irradiated at 110 °C in chlorobenzene at 350 nm (equation 96).[101,102] There is a severe nonbonded interaction between the angular and vinyl methyls in the transition state for initial cyclization in this system. The success of the higher temperature may be a result of accessing the reactive conformation by overcoming this steric interaction, or it is possible that there is a thermal barrier between two excited states of different reactivities. The photoadduct (**60**) has been elaborated to the naturally occurring fenestrane laurenene.

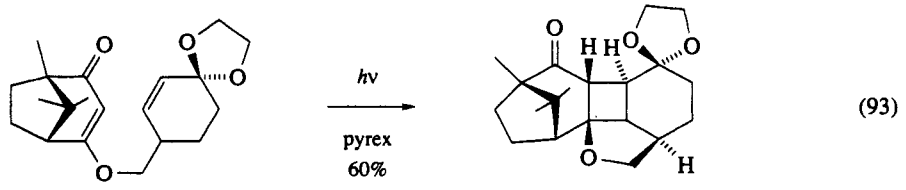
Also of interest are cyclohexenones with the tether attached at the 4-position, which have not been as widely applied as the 2- and 3-substituted cycloalkenones. Croft and Jeffries irradiated the diastereomeric enones (**61**) and obtained two cycloaddition products and two products from intramolecular hydrogen atom abstraction (equation 98).[104] All the products contained a *trans* decalin, however. This re-



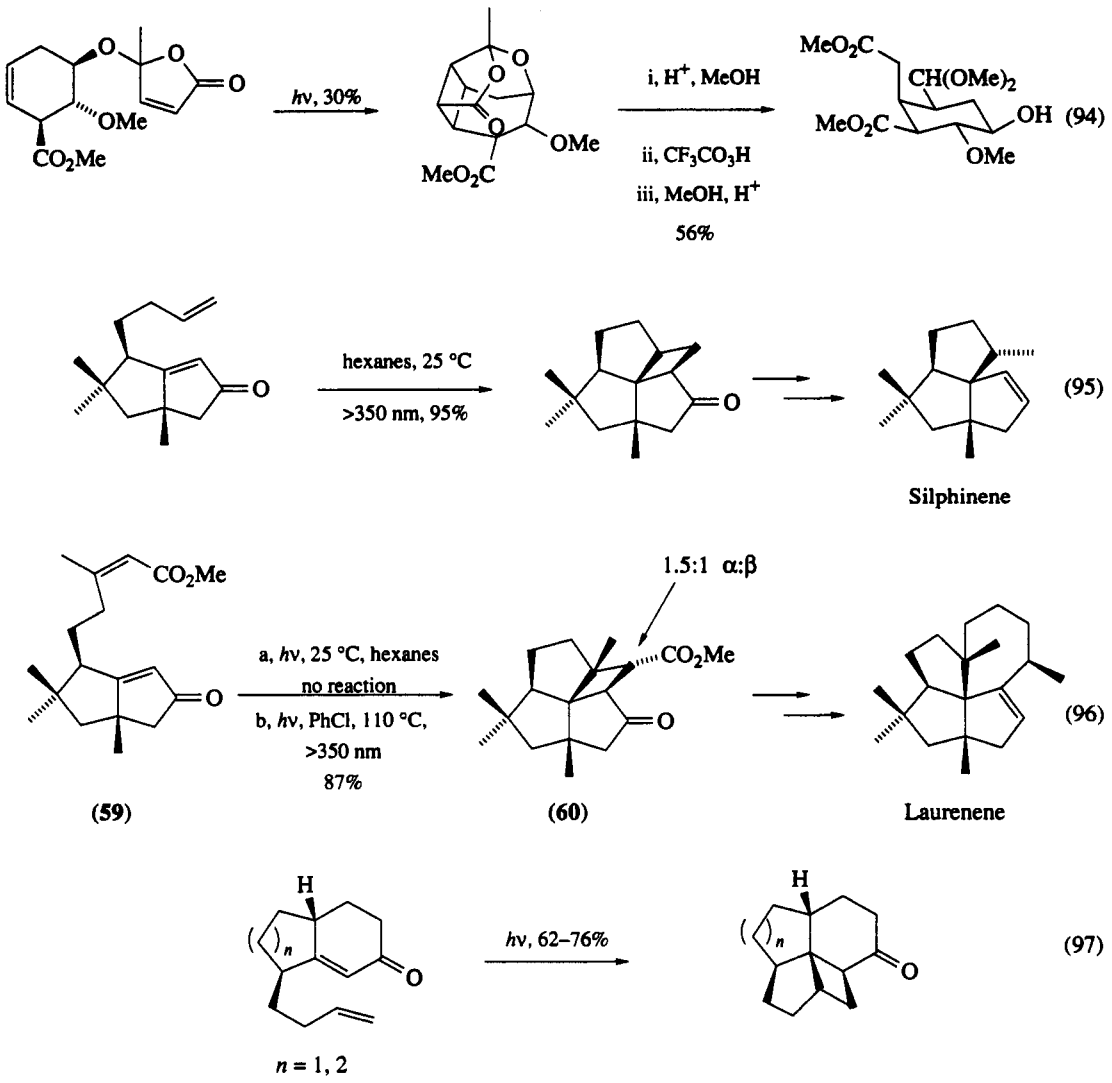
(91)



(92)



(93)

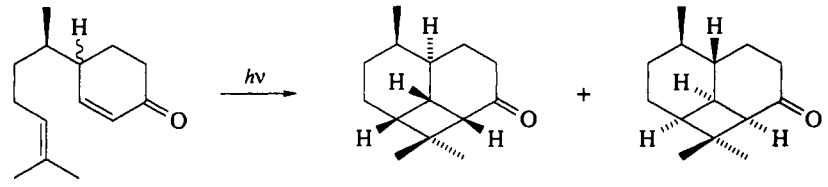


sult can be rationalized by assuming the excited triplet enone is twisted, with the tether occupying a pseudoequatorial site on the cycloalkenone as in (**62**). Smith[105] also saw predominantly *trans* products in the cycloaddition of (**63**) (equation 99), but obtained some *cis* product (**64**) probably due to the reduced degrees of freedom in the alkyne which would destabilize the transition state for the initial formation of the *trans* decalin. Both photoadducts were converted to hibiscone C. Dauben[43,106,107] has studied a variety of allenes attached to cyclohexenones and cyclopentenones at the 4-position. These all produce predominantly or exclusively the *cis* decalin products, in contrast to the cases above. This result (equation 100) in combination with some anomalous results (equations 101, 102) have prompted Dauben to suggest that intramolecular [2 + 2] photocycloadditions involving allenes as the ground-state partner (with the allene tethered at the 3- or 4-position) are likely proceeding through initial cyclization at C-2 of the enone rather than C-3.[43] This could explain the different stereochemical result with these systems. If allenes in general proceed through a different mechanistic pathway, this might also explain some inconsistencies in the intermolecular photocycloadditions with allenes.

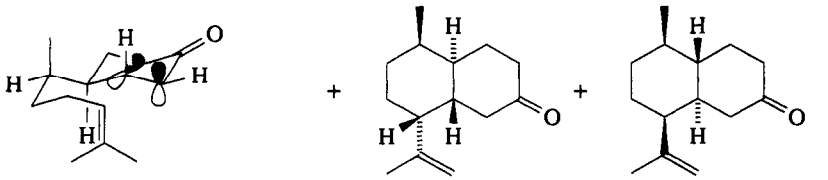
2.3.5 UNACTIVATED ALKENES

Synthetic applications of [2 + 2] photocycloadditions of unactivated alkenes have been limited due to the low regioselectivity and stereoselectivity observed in this process. However, Wender recently reported an intramolecular example of a diene–diene photochemical [2 + 2] which provides rapid access to *cis*-fused 5–8 ring systems and subsequently linearly fused triquinanes.[108] Sensitized irradiation of (**65**)

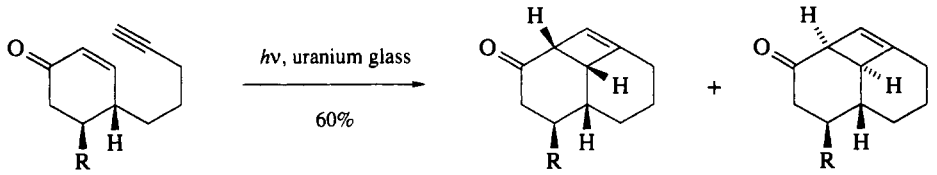
produced the *cis*-fused 5–4 product. This product is a result of the initial formation of a five-membered ring from the more stable conformer (**65**). The *cis* diradical (**66**) presumably closes rapidly to product while the *trans* diradical (**67**) cannot form the cyclobutane because of the inherent strain in the product and thus reverts back to the diene. Thermolysis of the product (**68**) produced the cyclooctadiene (**69**) which was converted to coriolin (Scheme 4).



(61) 1:1:1:1 (98)

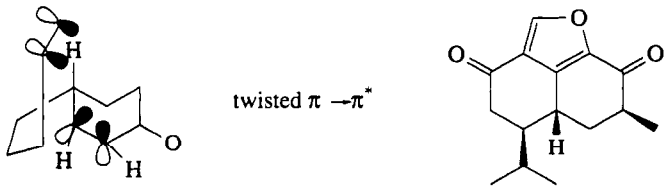


(62)

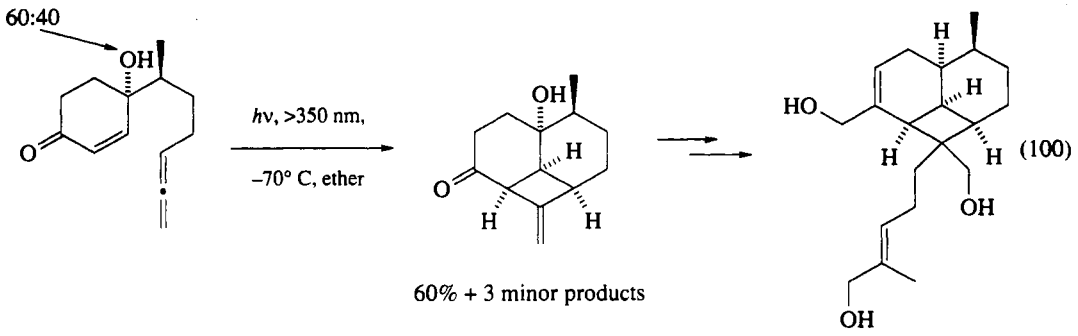


(63) (64) (99)

R = H 1:2
R = Pr^i 1:1.5

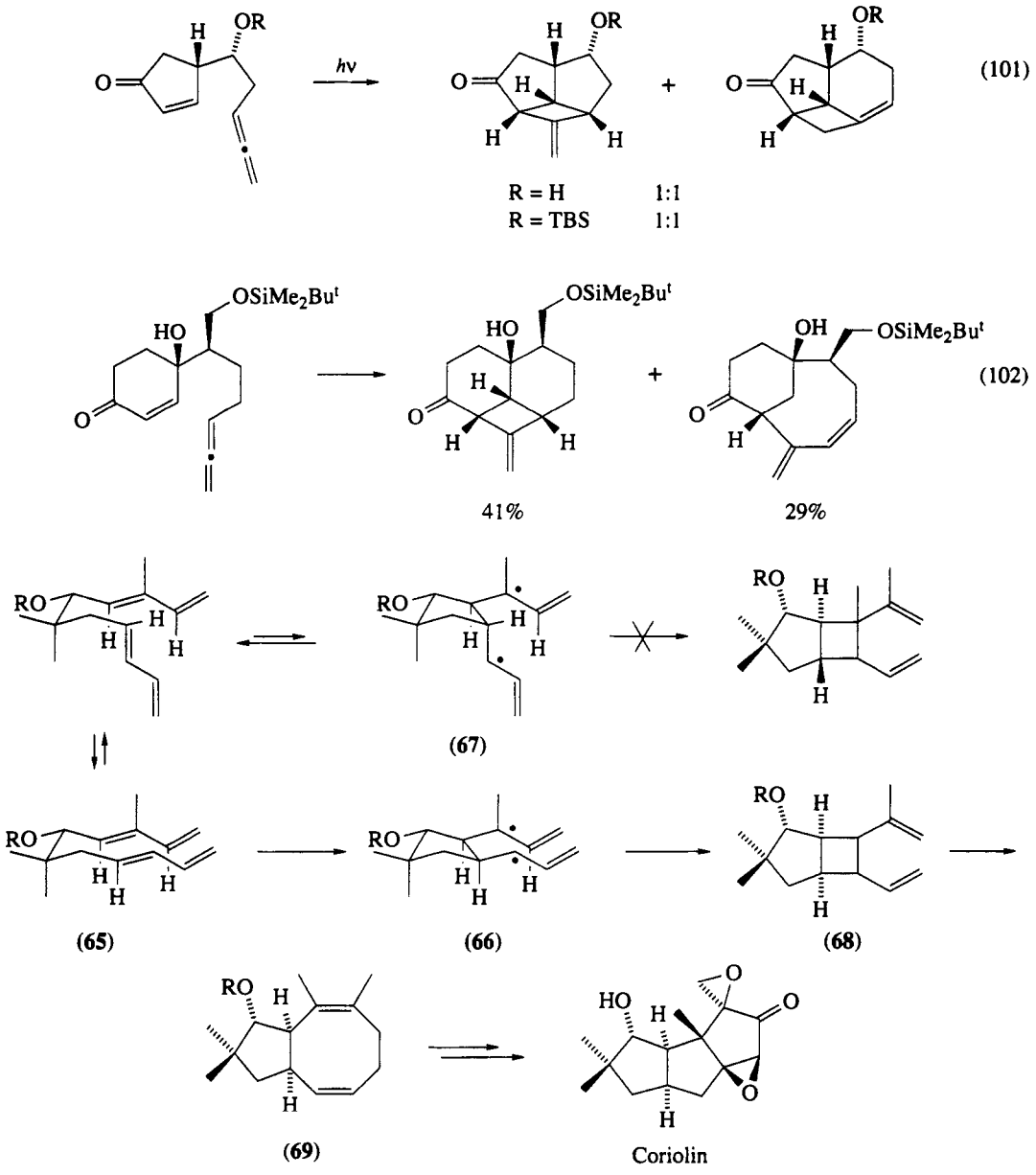


Hibiscone C



60% + 3 minor products (100)

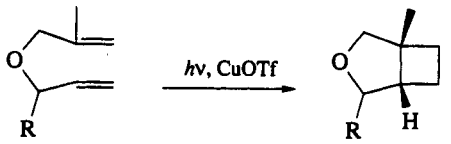
Trihydroxydecipiadiene



Scheme 4

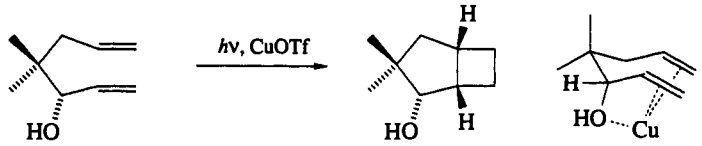
2.3.6 COPPER CATALYZED [2 + 2] PHOTOCYCLOADDITIONS

Salomon has recently investigated the copper(I) triflate catalyzed photocycloadditions of allylic alcohols and allylic ethers in an effort to improve the selectivity in photocycloadditions of unactivated alkenes (equations 103–105,108).[109] One particularly interesting case is illustrated in equation (104), where the more sterically hindered product is produced as a result of the photocycloaddition of a rigidly held tridentate copper complex. McMurry has also utilized a copper(I) catalyzed [2 + 2] photocycloaddition in the synthesis of β-panisene (equation 106).[110] Interestingly, the noncatalyzed cycloaddition shown in equation (107), which might also produce a precursor for β-panisene, was unsuccessful.

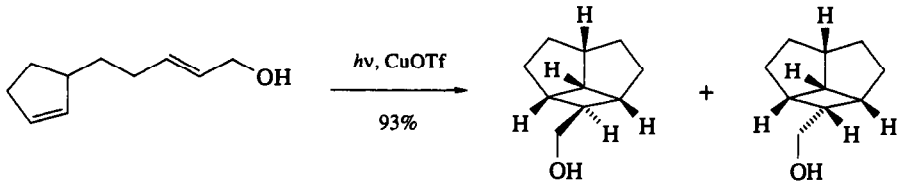


(103)

R = H, 41%
R = Bu^n, 83%

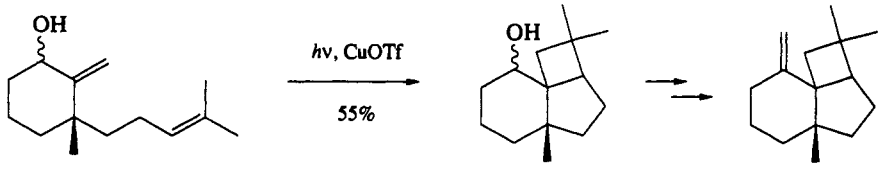


(104)



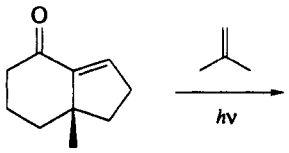
(105)

64:36

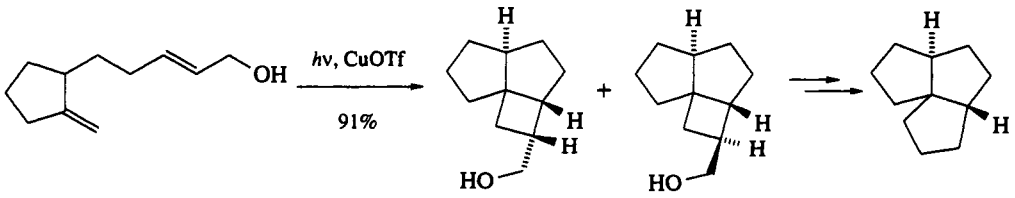


(106)

β-Panisene



(107)



(108)

75:25

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2.4
The Paterno–Büchi Reaction

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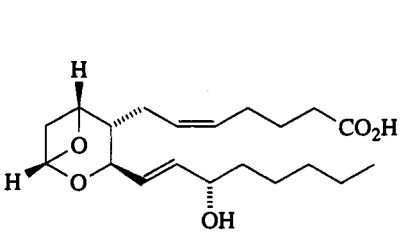
2.4.1 INTRODUCTION

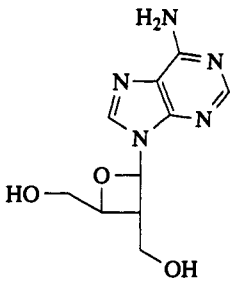
In the 80 years since the original report[1] of a photochemical addition to form an oxetane, the Paterno–Büchi reaction[2] has become increasingly familiar to chemists engaged in the synthesis of complex molecules. Existing reviews[3–6] have summarized mechanistic considerations and defined the scope and limitations of the photocycloaddition reactions. In confluence with the widespread advances in synthetic methods and asymmetric synthesis, the Paterno–Büchi reaction has prospered and led to significant developments in the area of organic synthesis.

The chemical and biological relevance of oxetane-containing materials is illustrated (*vide infra*) by compounds such as thromboxane A_2 (**1**),[7] oxetanocin (**2**)[8] and the unique amino acid antibiotic oxetin (**3**).[9] The elusive thromboxane A_2 molecule, for example, is unstable owing to its strain from the acetal linkage of the four-membered ring oxetane unit. While there are many useful methods for oxetane formation, including ring expansion,[10] ring contraction[11,17] and alkylation,[12] oxetane synthesis from the 'quenching' of photochemically excited carbonyl compounds and alkenes is perhaps the most direct and flexible. In addition, both the thermal[13] and Lewis acid catalyzed[14] [2 + 2] cycloadditions of electron-rich alkenes with carbonyl compounds are known and generally occur with regioselectivity complementary to that of the photochemical process. For example, the photochemical reaction of biacetyl with ketene diethyl acetal provides solely the 3-alkoxyoxetane (**4**), whereas the thermal reaction gives the more labile 2-alkoxyoxetane (**5**).[14,15]

This photochemical umpolung is useful from the perspective of chemoselectivity in synthetic transformations. In addition, oxetane-containing products, prepared regioselectively, can be valuable synthetic intermediates. Both oxetane and vinyloxetane derivatives react with nucleophiles in intermolecular and intramolecular condensations and with transition metals[18] and carbenoids.[19] A second feature of oxetane-containing photoproducts, which has important implications, is that they can act as vehicles for subsequent manipulations and stereocontrolled synthesis. For example, the oxetane photoproduct (**6**)



(1)



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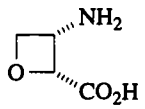

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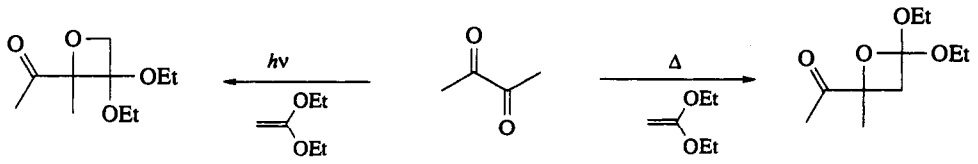
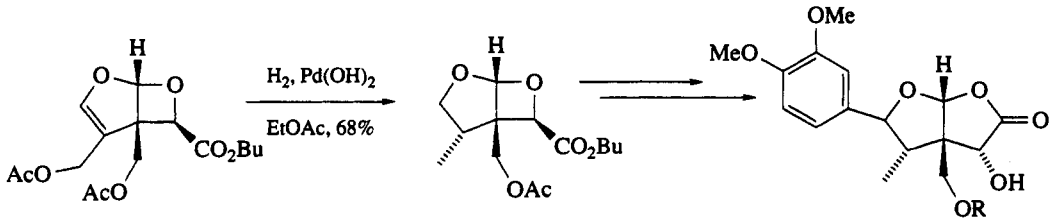


(4) (5)

undergoes consecutive hydrogenolysis and hydrogenation to form stereospecifically the tetrahydrofuran compound (7),[20] a precursor to hybrid platelet activating factor (PAF) antagonist ligands.[21]



(6) (7)

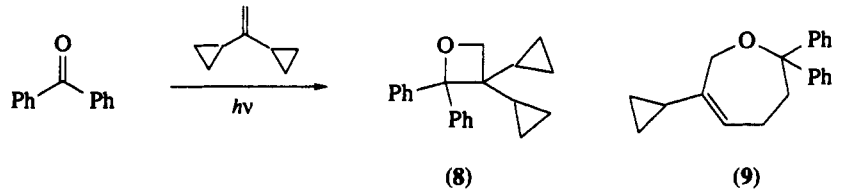
The chemo-, regio- and stereo-selectivity observed in the Paterno–Büchi photocycloaddition make the reaction a valuable synthetic method as its numerous applications to targets in synthesis attest. This review will summarize the important mechanistic and synthetic advances. Knowledge of these precedents will likely initiate further scrutiny and applications of the reaction to the synthesis of architecturally complex targets.

2.4.2 MECHANISTIC CCONSIDERATIONS

The Paterno–Büchi reaction has been studied mechanistically ever since Paterno and Chieffi[1] first reported that the photoreaction of ketones and alkenes produced, unexpectedly, the corresponding oxetane. Indeed, a recent surge of studies of the photoreaction mechanism has stimulated numerous applications in organic synthesis.

Early mechanistic studies by Arnold[3] supported the Schlenk mechanism, in which a putative 1,4-diradical intermediate resulted from the addition of the n,π^* triplet state of benzophenone to *cis*- and *trans*-2-butene. The preoxetane diradical led to the same mixture of *cis* and *trans* oxetanes (1:6), suggesting the existence of a 'most stable' diradical species in which rotation occurred prior to oxetane ring closure. Further support for the existence of diradical intermediates came from work by Nishida,[21] in which irradiation of benzophenone with 1,1-dicyclopropylethylene gave 81% of product (**8**) at room temperature, but 65% of the tetrahydroxepin (**9**) at 160 °C. The thermal stability of oxetane (**8**) at 160 °C suggests the cyclopropyl–carbinyl rearrangement of an intermediate diradical. Subsequently, Caldwell[22] refined the Schlenk mechanism to include an initial charge transfer, generating an exciplex intermediate. In the reaction of benzophenone with both deuterated and nondeuterated *cis*- and *trans*-2 butene, a negligible product isotope effect of 1.03 ± 0.01 was obtained. This observation is contrary to the prediction of a small

inverse isotopic effect as a result of the rehybridization from sp^2 to sp^3 at the labeled site in oxetane formation. A π-bonded charge transfer complex that aligns the orbital of the carbonyl symmetrically with respect to the alkene double bond was formulated (Figure 1) to account for the observed isotope effects. Additionally, product isotope effects for the *cis–trans* photoisomerization of 3-methyl[2-^{2}H]-2-pentene (1.003 ± 0.007 for the *trans* isomer) indicate that the preference for intermediate diradical (**10**) *versus* (**11**) is negligible. Therefore the 'most stable diradical' hypothesis[23] is apparently not applicable in certain cases, and other factors such as charge distribution and polarizability can be significant.



(8) (9)

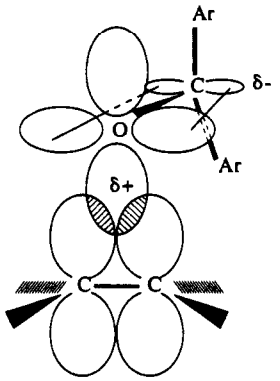


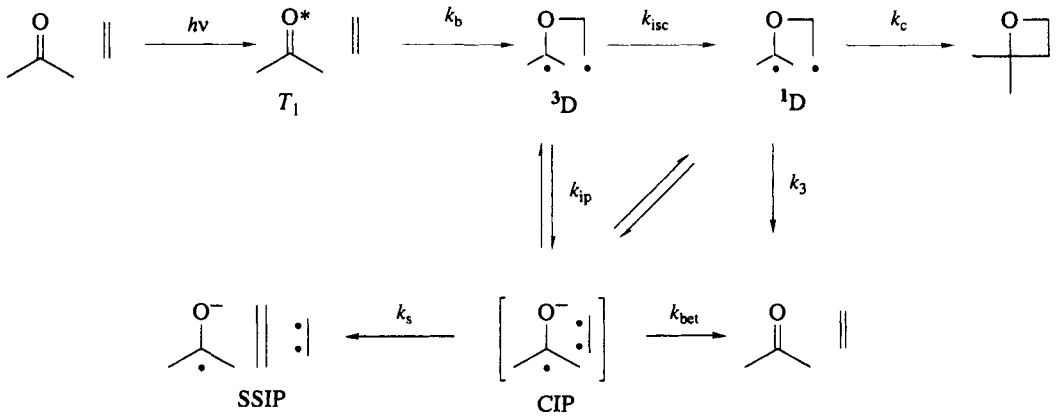
Figure 1

(10) (11)

Further support for the prior generation of electron transfer complexes has come from recent investigations by Turro.[24] It was found through fluorescence and phosphorescence quenching studies of enol ethers with both singlet and triplet ketones that charge transfer occurred to the extent of 10 or 15%; in the case of electron-rich alkenes, donation of charge from the alkene *p*-orbitals to the ketone *n*-orbital produced an 'invisible' exciplex. This mechanism successfully accounted for the low regioselectivity observed in oxetane formation from enol ethers, since the 'best diradical' model would suggest higher regioselectivity. However, the involvement of triplet exciplexes in [2 + 2] photocycloadditions of cyclic enone π,π^* triplets to alkenes has been recently found to be inconsistent with kinetic data.[25] The greater rate of quenching of enone triplets by electron-poor alkenes was seemingly inconsistent with polar exciplex formation, but the implication of the formation of triplet exciplex precursors in oxetane formation to the 'fundamentally different case of photoannulation' was found to be inappropriate.

The nature of the intermediates in the Paterno–Büchi reaction has been inferred largely from indirect measurements. However, recently the reaction course has been monitored through spectroscopic methods. The first observation of a 1,4-diradical intermediate was claimed by Hayashi,[26] who used a nanosecond laser-photolysis technique to monitor the time dependence of the intermediate 1,4-diradical absorption produced by the irradiation of benzophenone and *cis*-3-methyl-2-pentene. Experiments involving methyl viologen dication quenching indicate that a transient absorbing at 530 nm had a lifetime of 6–25 μs. Scaiano[27] has recently pointed out that the spectrum reported by Hayashi is indentical with the UV band of the ketyl radical of benzophenone (λ_{max} = 332 nm) and that the lifetime of the putative diradical is implausibly long. These conclusions have received further support from recent work by Cald-

well.[28] A study of the transient spectroscopy of benzophenone in the presence of both tetramethylethylene and ethyl vinyl ether found UV absorptions (λ_{max} = 330 nm) with lifetimes of 1.5–4 ns. Similar results have been obtained in recent studies by Peters.[29] In an effort to determine the pathway for formation of the 1,4-diradical, a picosecond dynamics study monitoring the quenching of the triplet state of benzophenone with 1,4-dioxene was undertaken. The transient triplet spectrum is quenched with a half-life of 175 ± 25 ps to form a new species, λ_{max} = 535 nm, which is assigned as the 1,4-diradical. As the diradical decays, intersystem crossing of the triplet to the singlet occurs concomitant with oxetane ring closure. In addition, a new species appears (λ_{max} = 690 nm in MeCN) whose absorbance corresponds to that of the radical anion of benzophenone. It has been postulated that this species arises from heterolysis of the 1,4-diradical to generate a radical anion and an alkene radical cation. To determine whether exciplexes are formed prior to diradical formation, the photolysis of 4-phenylbenzophenone in 1,4-dioxene was examined and a transient absorption (λ_{max} = 520 nm) was found to persist at least 250 ns following irradiation. Since both benzophenone and 4-phenylbenzophenone undergo similar rates of electron transfer with DABCO,[30] a polar transition state best describes any pre-diradical intermediate. Scheme 1 summarizes a mechanism for the Paterno–Büchi reaction which accommodates the available data.



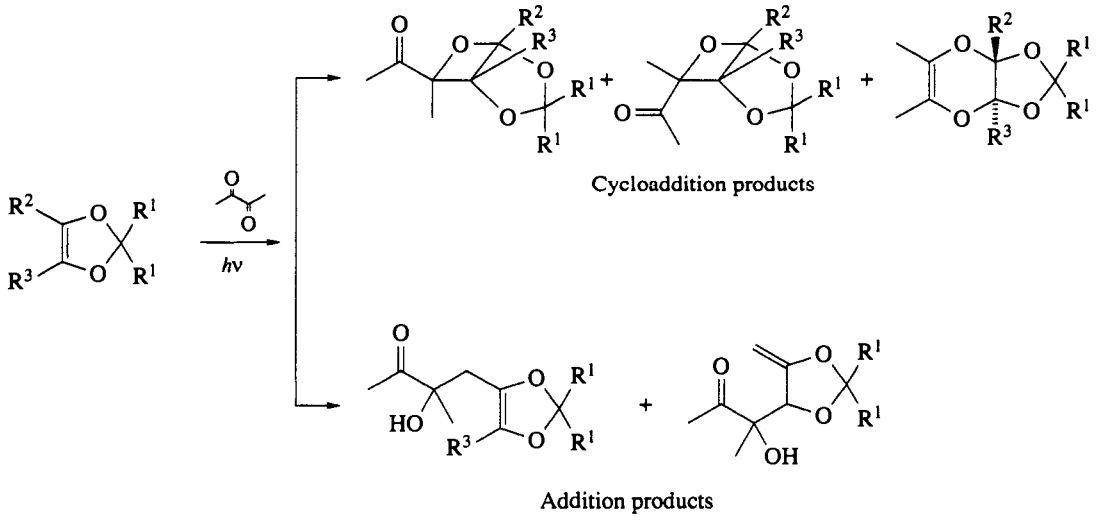
Scheme 1

Recent investigations of the solution photochemistry of biacetyl lend further support to the polar exciplex hypothesis. Luminescence quenching studies reveal the donor–acceptor nature of biacetyl triplet quenching and stereochemical scrambling in the product oxetane and recovered alkene.[31] An extension of the basic exciplex mechanism was recently reported by Mattay and coworkers.[32] ESR measurements of the reaction of biacetyl with electron-rich 1,3-dioxoles with *in situ* irradiation led to the observation of both the biacetyl radical anion and the dioxene radical cation. This 'ionic photo-association' process contrasts with Peters[29] observation of a diradical transient that was postulated to exist in equilibrium with a contact ion pair. Scheme 2 shows some typical photoproducts which result from photolysis of 1,3-dioxoles in the presence of biacetyl. Oxetane-containing products are obtained in all cases, and dioxoles containing allylic hydrogens readily form addition products. In the case of the parent unsubstituted 1,3-dioxole, one-third of the product mixture results from 1,4-addition. Calculated exciplex lifetimes (0.2–0.5 ns) and nonvariance of this lifetime with the alkene quencher led to extension of the exciplex mechanism to include electron transfer as shown in Scheme 3. Insofar as the ESR measurement supports both the radical anion and cation structures, clear differentiation between an exciplex with charge transfer and a contact ion pair may not be possible. However, the theory is a powerful tool for predicting photoreaction chemoselectivity. In the previously described photochemical addition of biacetyl and 1,1-diethoxyethylene, spin densities obtained from ESR measurements indicate that the 1,1-diethoxyethylene radical cation contains 80% of the spin density at the β-carbon (Scheme 4). This explains the regioselective joining observed with biacetyl to form exclusively the 3-alkoxyoxetane, a useful photochemical 'umpolung' of the reactivity of biacetyl.[14,32]

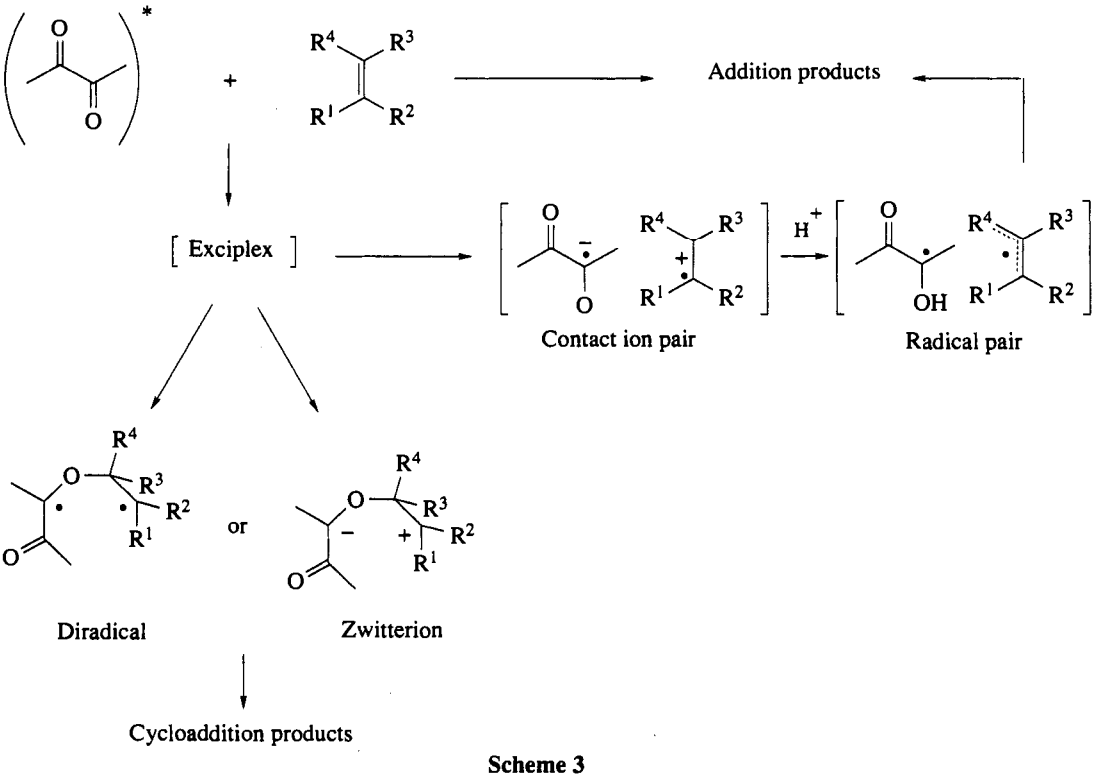
To probe further the nature and reactivity of the transient species produced in the Paterno–Büchi reaction, trapping experiments have been recently performed. Putative diradical intermediates have been trapped with many reagents, including molecular oxygen[33] and sulfur dioxide.[33,34] A mechanistic study of trioxane formation from quinones has implicated both quinone–alkene CT exciplexes and preoxetane diradicals as intermediates. For example, in the laser photolysis of tetramethylallene and benzoquinone, irradiation under a high pressure of oxygen gave oxetane (**15**), which arises from the less-stable vinyl diradical (**14**), and the 1,2,4-trioxane (**13**) which results from oxygen trapping of the longer-lived allyl

diradical (**12**). However, in the analogous reaction with *t*-butylethylene it was found that the oxetane ratio (**17**):(**16**) was relatively insensitive to the oxygen pressure. Increased pressure should increase the ratio (**17**):(**16**) by trapping out the more stable preoxetane diradical leading to (**16**). These results may require that another intermediate precedes the preoxetane diradical intermediate and dominates in the trapping process.

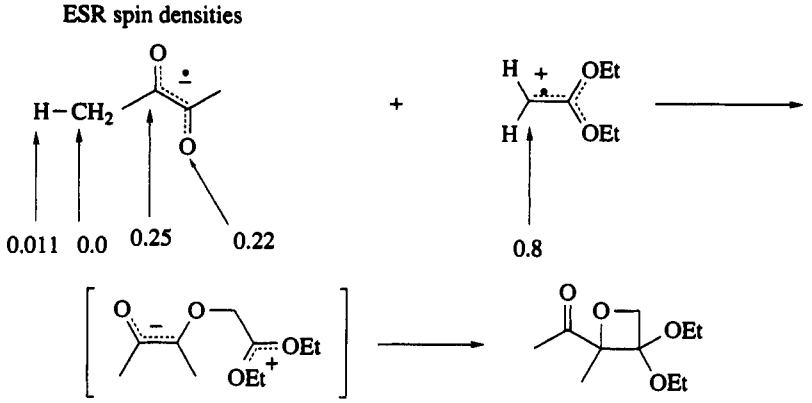
Adam and coworkers have recently trapped laser-generated Paterno–Büchi intermediates on a preparative scale in the synthesis of synthetically and medicinally useful peroxides.[35,36] Artemisinin, or qinghaosu (**18**), is a potent antimalarial drug of low toxicity and is effective against chloroquine-resistant malaria.[37] The necessity of the peroxy group for the biological action of the drug has been established. Dioxygen trapping of diradical intermediates in the Paterno–Büchi reaction affords 1,2,4-trioxanes. For



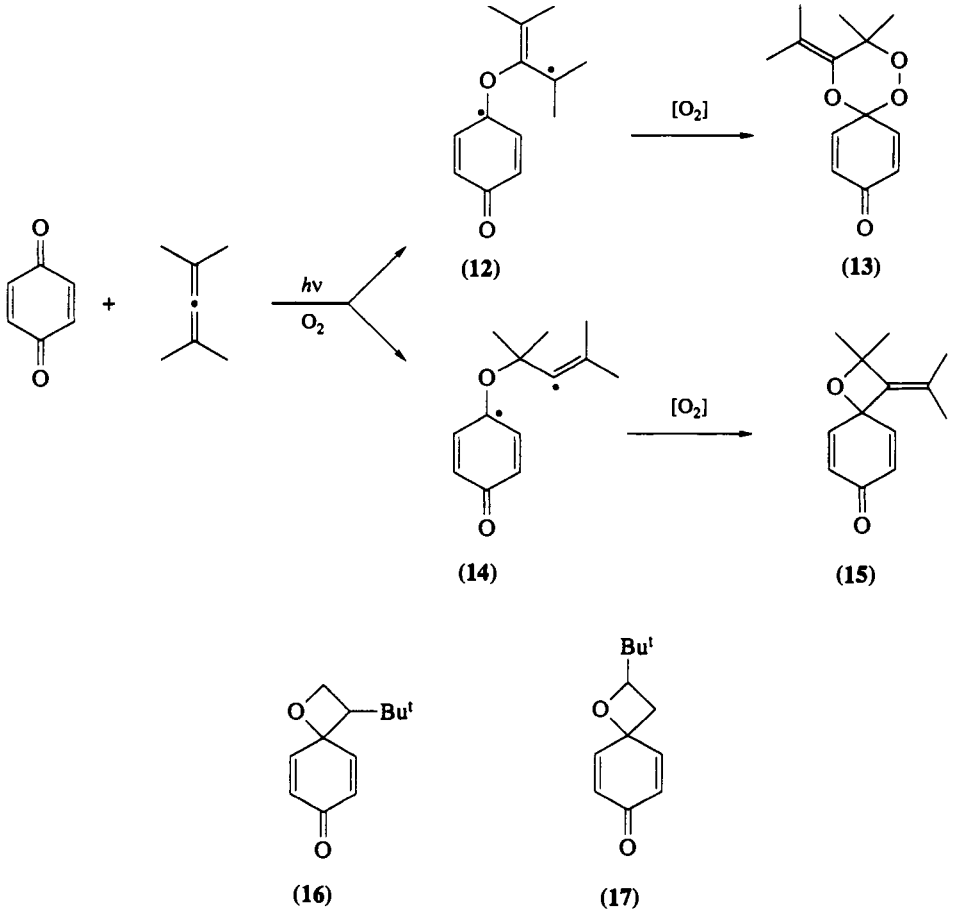
Scheme 2



Scheme 3

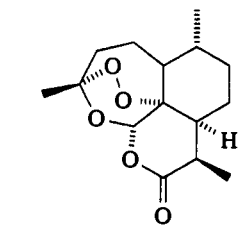


Scheme 4



example, the previously described triplet of the preoxetane diradical derived from benzophenone and 1,4-dioxene (lifetime approximately 1.5 ns)[29] can be trapped by molecular oxygen (10 atm) to form the *cis*-fused 1,2,4-trioxane (**19**) in 7% isolated yield. Similarly, argon ion laser irradiation of dioxene and benzoquinone provided the trioxane (**20**) in 20% isolated yield. In a more recent study, qinghaosu-like 1,2,4-trioxanes have been synthesized.[36] Visible laser irradiation of 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**21**) with benzoquinone gave *trans*-(**22**), *cis*-(**22**) and *cis*-(**23**) in a 29:9:18 ratio, as well as small amounts of regioisomeric oxetane products. However, under the same conditions, phenanthraquinone (**24**) yielded only oxetane-containing photoproducts. The differences in trapping reactivity were attributed to either the existence of zwitterionic intermediates or short lifetimes for triplet diradical intermediates. The construction of novel lactone trioxanes of the qinghaosu class has demonstrated the utility

of trapping, and yields spiro-annulated lactone trioxanes as potentially active artemisinin analogues. The Paterno–Büchi reaction thus offers an alternative to other available methods for 1,2,4-trioxane synthesis.[36,38,39] In addition, the recently reported conversion of 1,2,4-trioxanes to *syn*-1,2-diols[39] and electrophile-induced rearrangements of trioxane systems[40] bode well for continued interest in the preparative trapping of transient intermediates and illustrates how the study of reaction mechanism has produced new and useful synthetic methods.



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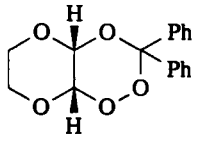

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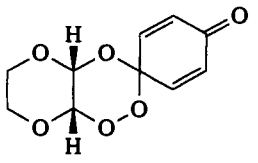

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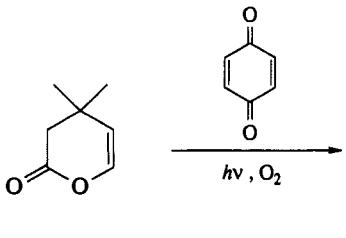

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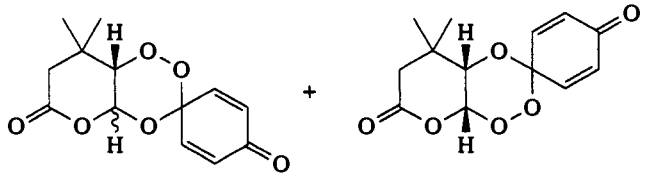

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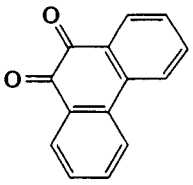


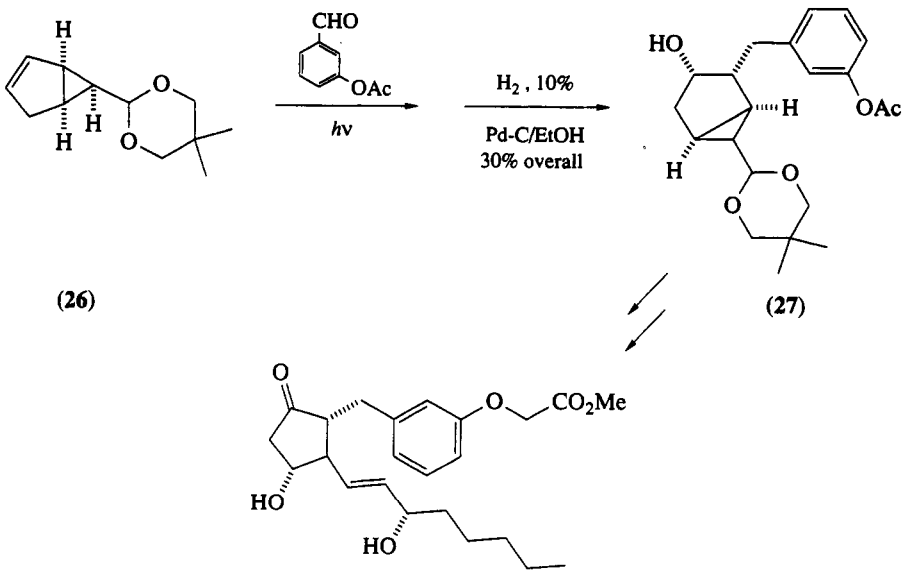
(24)

2.4.3 PHOTOCHEMICAL SYNTHESIS USING ALKENYL AND ALKYNYL ADDENDS

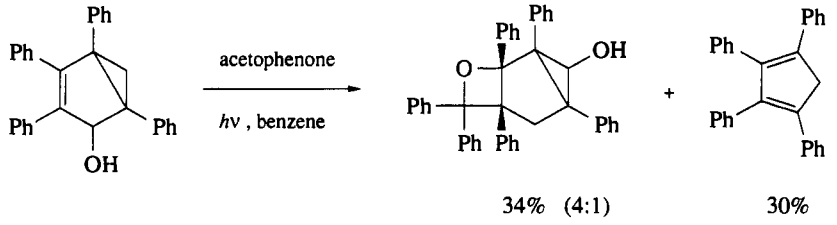
The synthesis of oxetanes from alkenic precursors has been demonstrated and the range and scope of Paterno–Büchi photocycloadditions are broad. In general, both the reaction regioselectivity and stereoselectivity can often be predicted by considering the reaction mechanism (Section 2.4.2); for example, the directing effects of alkene substituents are readily understood. Synthetic applications are numerous owing to the rapid stereocontrolled assembly of multifunctional targets.

A photochemical approach towards prostaglandin analogs relied on stereoselective use of the Paterno–Büchi reaction.[40] The analog (**25**), which possesses the natural prostaglandin configuration, was shown to be a potent inhibitor of ADP-induced platelet aggregation *in vitro*.[41] Irradiation of a benzene solution of (**26**) and *m*-acetoxybenzaldehyde, followed by benzylic hydrogenolysis of the oxetane ring, gave (**27**) in 30% overall yield from (**26**). Further analysis of the product mixture revealed the formation of 10–20% of a regioisomeric oxetane. However, the predominant formation of (**27**) in the reaction possibly reflects the ability of the cyclopropyl group to stabilize an incipient radical.

A similar application of a vinylcyclopropane in a stereoselective photoreaction has been reported by Dürr and coworkers.[42] Scheme 5 shows the addition of a bicyclo[3.1.0]hexenol derivative and acetophenone, which afforded the strained 7-oxatricyclo[4.2.0.0]octane and a comparable amount of tetraphenylcyclopentadiene. Since the vinylcyclopropane is known to undergo photochemical isomerization and photofragmentation to the cyclopentadiene, it is conceivable that these reactions precede photocycloaddition. If this is the case, the major oxetane (4:1 selectivity) arises from addition of the alkoxy radical to



produce a cyclopropyl–carbinyl radical. The photoreaction thus demonstrates the trapping of a photofragmentation intermediate and the formation of a strained oxetane structure.

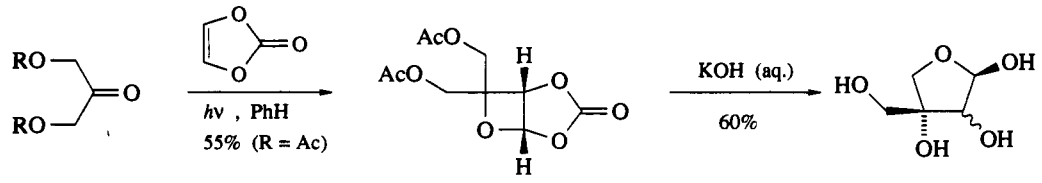


Scheme 5

Araki has made use of the Paterno–Büchi reaction in the synthesis of *C*-glycosyl compounds and branched-chain sugars. For example, irradiation of a benzene solution of 1,3-diacetoxyacetone (**28**) and vinylene carbonate gave the oxetane photoproduct (**31**) in 55% yield. This adduct was subsequently hydrolyzed to (±)-apiose (**32**) in 60% yield.[43] Photocycloaddition of (**28**) with (*Z*)-vinylene diacetate gave mixtures of *cis*- and *trans*-photoproducts (46% and 49% yield, respectively). An independent control experiment established that the excited ketone promotes equilibration of the alkene. The higher overall yield of open-chain ethylenediol derivatives compared with vinylene carbonate in the photocycloaddition was attributed to the photolability of (**31**). A limitation of the cycloaddition process was uncovered with the use of carbonyl compounds (**29**) and (**30**); competitive Norrish type II photoprocesses formed alternative oxetane products (**33**) and (**34**). A similar problem has been noted for benzyl glyoxalate as a carbonyl addend in Paterno–Büchi photoadditions.[44] In a related series of experiments, the more easily prepared silyl enol ethers[45] reacted with (**28**) to form the 3-siloxyoxetane (**35**).[4,45] The 2-alkoxyoxetane was not isolable, but careful derivatization of the crude reaction mixture revealed that it was a significant side-product (22% *vs.* 46%). This is consistent with the modest regiochemistry in the Paterno–Büchi reaction of enol ethers and the lability of 2-alkoxyoxetane observed by Schroeter and coworkers.[16]

A similar approach to branched-chain aldonolactone sugars has been recently reported by Mattay.[46] Lithium aluminum hydride reduction of photoproduct (**36**) afforded the desired alcohol which rearranged under acidic conditions to the deoxygenated apiose derivative (**38**). This process is notable since such reductions usually proceed with cleavage of the oxetane moiety. Also noteworthy are the rapid assemblage of highly oxygenated functionality and the ease of the synthetic procedure.

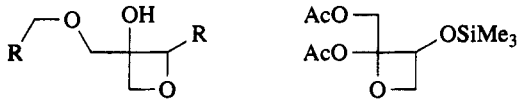
Carbohydrate templates have provided interesting applications of the Paterno–Büchi reaction. In a series of papers, Araki has demonstrated the feasibility of oxetane formation from glucals.[47,48] Photocy-



(28) R = Ac
(29) R = Bn
(30) R = Me

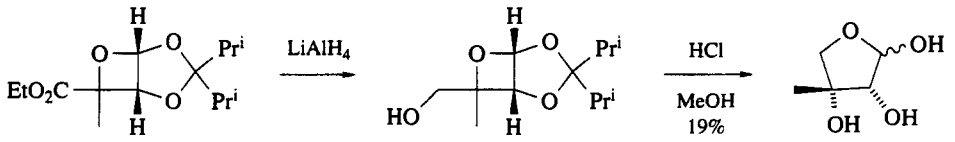
(31)

(32)



(33) R = H
(34) R = Ph

(35)

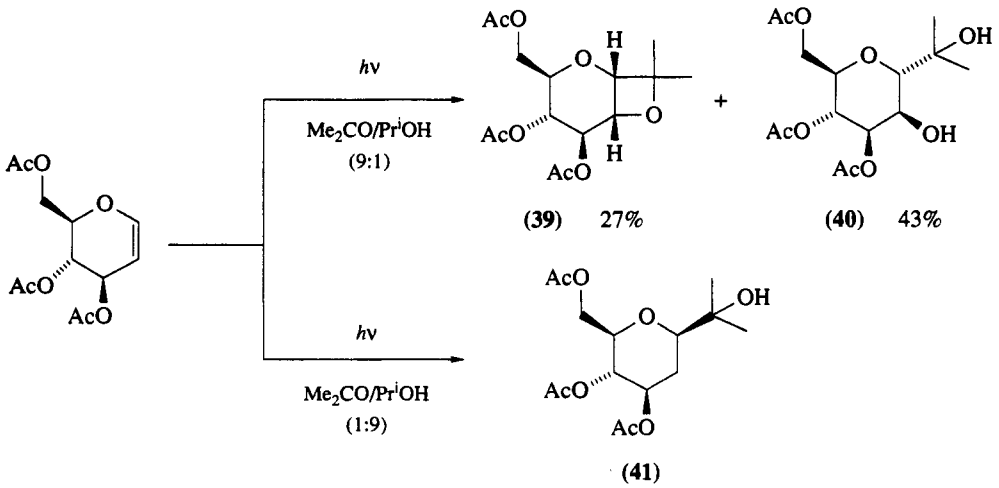


(36)

(37)

(38)

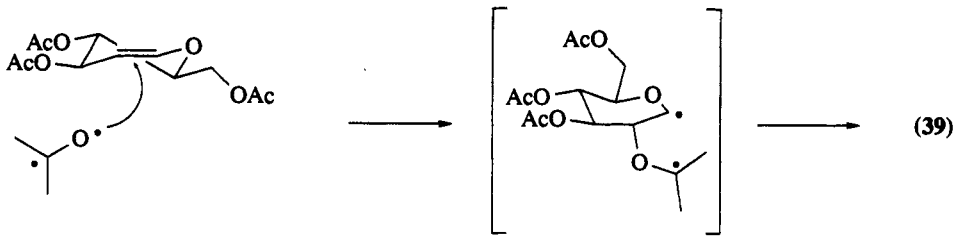
cloaddition of acetone to 3,4,6-tri-*O*-acetyl-D-glucal was found to exhibit a remarkable solvent effect, providing oxetane (**39**) when acetone was employed as solvent in addition to varying amounts of ring-opened product (**40**) depending on the chromatographic conditions.[49] *C*-Glycoside (**41**) was the major product when the photolysis was performed in isopropanol. The general mode of oxetane formation was believed to occur as shown in Scheme 6. Since the carbonyl oxygen in the n,π^* triplet state is electron deficient,[50] attack occurs at the β-carbon of the glucal to form an anomerically stabilized glucopyranosyl radical.[51] Stereochemical control is thus exerted by the adjacent β-acetoxy group. Additionally, an electronic effect may be operative, in which the axial β C—O bond[52] is aligned synplanar to the singly occupied *p*-orbital, providing for SOMO(*p*)–LUMO(σ*) stabilization.[51] The high orientational selectivity is in accord with the results of Carless[53] in which cyclic enol ethers give rise to 3-alkoxyoxetanes predominantly. This is contrary to the case of acyclic enol ethers where only modest regioselectivity is observed.[16,54] Oxetane formation did not occur in benzene, thus illustrating the need for hydrogen donating solvents such as isopropanol. Acetone-sensitized formation of glycoside (**41**) from isopropanol can be explained by addition of an electron-donating radical to the less electron-rich glycal carbon in an equatorial fashion.



(39) 27%

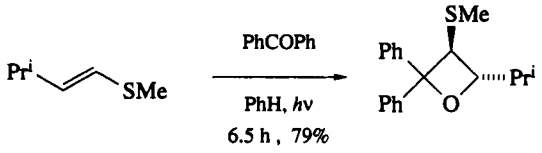
(40) 43%

(41)



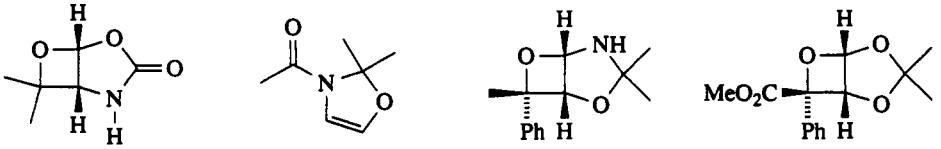
Scheme 6

A recent effort to improve the modest regioselectivity observed in photochemical additions to enol ethers was recently reported by Smith and coworkers.[55] Vinyl sulfide (**42**) was prepared using a standard Horners–Emmons alkenation reaction and irradiated with benzophenone in degassed benzene. A high selectivity for *trans*-4-alkyl-3-methylthiooxetanes (**43**) was observed, as shown by analysis of the product using X-ray diffractometry. In addition, reaction times were reduced approximately eight-fold relative to similar enol ether substrates, which indicates possible radical stabilizing and electronic effects.



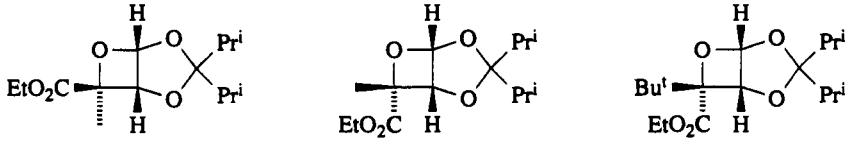
(**42**) (**43**) *trans*

The photochemistry of more complex and highly substituted alkenic partners has been studied. In 1978, Hartmann and coworkers reported the photocycloaddition of 4-oxazolin-2-one with acetone, used as a photosensitizer in the reaction of 4-oxazolin-2-one with alkenyl and alkynyl partners, to form oxetane (**44**).[56] Recently, Scharf has described the photochemistry of 3-acetyl-2,3-dihydro-2,2-dimethyloxazole (**45**).[57] Irradiation of (**45**) in the presence of acetophenone produced the oxetane (**46**) with the phenyl group *endo* (17%), in addition to 21% of a ring-opened derivative. The stereoselectivity is in agreement with the high *exo* carboxyl selectivity observed in the photocycloaddition of methyl phenylglyoxylate with 2,2-dimethyl-1,3-dioxole to produce oxetane (**47**).



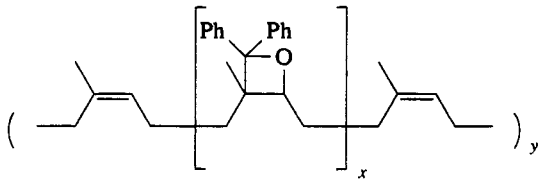
(**44**) (**45**) (**46**) (**47**)

In a related study, 2,2-diisopropyl-1,3-dioxole was found to undergo cycloaddition with ethyl pyruvate to form a 4:1 mixture of regioisomeric oxetanes (**48**) and (**49**).[14] However, the strongly accepting diethyl mesoxalate fails to undergo photocycloaddition, whereas cyclopentene forms oxetane photoproducts with this carbonyl compound. Mattay has demonstrated[14,46] that 2,2-diisopropyl-1,3-dioxole can be irradiated with trimethylpyruvic acid ethyl ester to form a single (unassigned) stereoisomer of oxetane (**50**). It would be interesting to determine the stereochemistry of this transformation since this information is relevant to the issue of the relative importance of steric and electronic effects in the photocycloaddition reaction.[58]

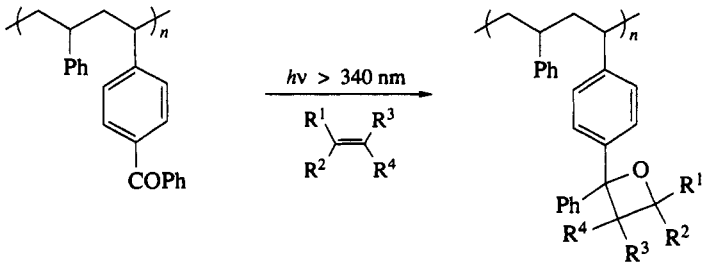


(**48**) (**49**) (**50**)

A recent application of the Paterno–Büchi reaction involved the synthesis of novel polymeric structures. Guillet and coworkers have described the photolysis of benzophenone and *cis*-1,4-polyisoprene (natural rubber) that forms a copolymer (**51**) of isopropene and isomeric isoprene–diphenyloxetane adducts.[59] NMR analysis indicates incorporation of about 25 mol % oxetane rings, giving a stiffer polymer with a higher glass transition, the result of inclusion of motionally restricting ring structures and bulky phenyl groups in the polymer chain. Another type of 'photopolymerization' that uses alternatively the photoexcited group as the polymerization template involves the solid-phase photocycloaddition of alkenes to poly(vinylbenzophenone) (Scheme 7).[60] In addition, polyfunctional alkenes such as squalene have been utilized in photocrosslinking of poly(vinylbenzophenone). Further studies of polymeric systems offer much potential, especially in areas of polymer modification and in the development of novel macromolecular materials.



(51)

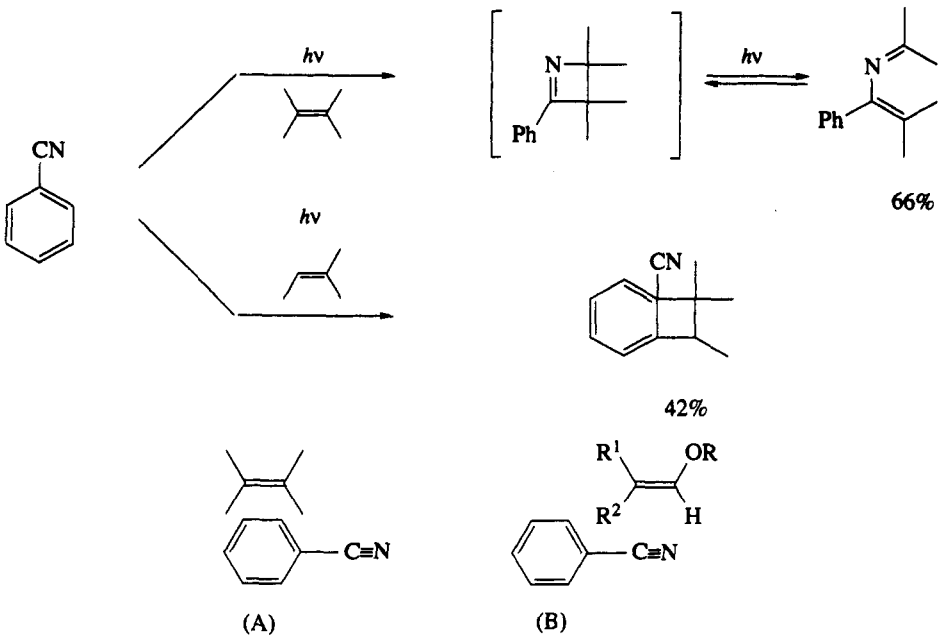


Scheme 7

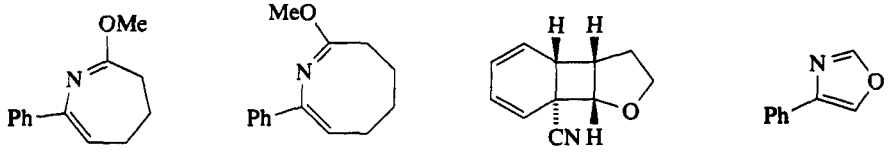
While most of the previously described photochemical reactions of alkenes have centered on aldehyde and ketone partners, there have been recent reports on the behavior of nitriles and carboxylic acid derivatives. Cantrell has reported the photochemical cycloadditions of benzonitrile to alkenes.[61] A dramatic dependence of alkene structure on the chemoselectivity of benzonitrile addition was noted. For example, Scheme 8 shows that 2,3-dimethyl-2-butene reacts under photolytic conditions to give mainly the azabutadiene product (66%) plus 8% of the thermally stable azetine valence isomer, suggesting that the azabutadiene isomer results from a photochemical ring opening. Photolysis of 2-methyl-2-butene with benzonitrile, on the other hand, gave as a major product the 1-cyanobicyclo[4.2.0]octadiene derivative. While the reasons for this divergent photochemical behavior are not clear, it has been proposed that singlet exciplexes or charge transfer complexes of benzonitrile with alkenes are generated with various geometries. Thus electron-poor alkenes locate themselves over the high electron density of the benzene ring (A), whereas electron-rich alkenes such as enol ethers will form an exciplex oriented over the electron-poor cyano group (B).

In a recent study, Mattay and coworkers[62] have studied the photoreactions of benzonitrile with cyclic enol ethers. Both methoxycyclohexene and methoxycyclopentene show a preference for type II cycloaddition, giving the azabutadiene derivatives (**52**) and (**53**), respectively. The regioselectivity of the process, although in disagreement with the assignment reported by Cantrell,[61] was proven by hydrolysis of (**53**) to the methyl 7-phenyl-7-oxoheptanoate derivative. In addition, irradiation of benzonitrile and dihydrofuran produced a 20% yield of the type I *ortho* adduct (**54**), while photoreaction of 1,3-dioxole produced 4-phenyloxazole (**55**), presumably by hydrolysis of an incipient azabutadiene derivative. The formation of 2-azabutadiene derivatives is of considerable interest in both the construction of medium-membered ring nitrogen-containing heterocycles and in the synthesis of 5,6-dihydro-2*H*-1,3-oxazine[63] and pyridine[64] structures.

The photochemical reactions of arenecarboxylic acid esters with alkenes has received recent attention by Cantrell.[65,66] For example, irradiation of 2,3-dimethyl-2-butene and methyl benzoate gave a mixture of alkoxyoxetane (**56**), carbonyl–alkene metathesis[4] product (**57**) and ketone (**58**), resulting from alkoxy radical allylic hydrogen abstraction and radical recombination. Such alkoxyoxetane photoproducts are

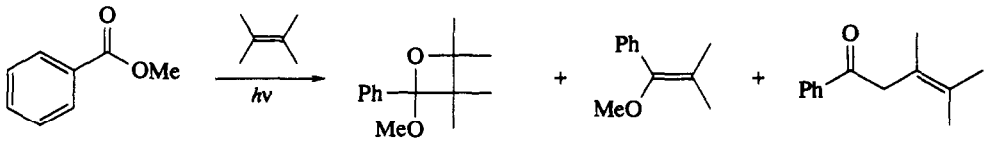


Scheme 8

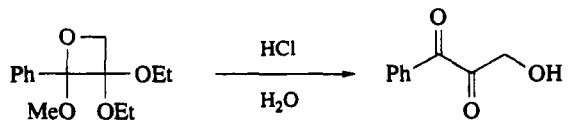


(52) (53) (54) (55)

useful synthons, as shown by the acid-catalyzed hydrolysis of acetal (**59**) to the diketone (**60**), a useful precursor to the tricarbonyl functional unit.[67]

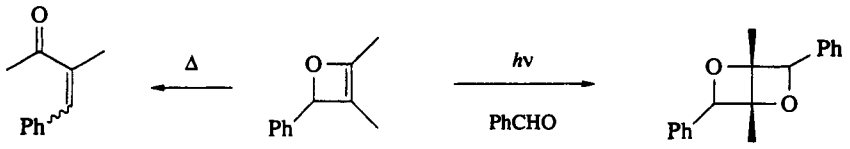


(56) 52% (57) 7% (58) 9%



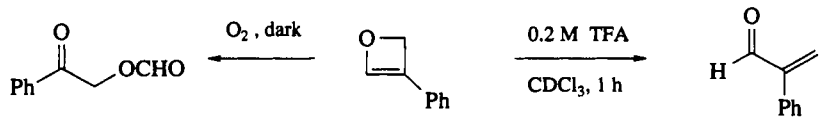
(59) (60)

Numerous papers have been published describing the photochemical production of enones from carbonyl compounds and alkynes.[68] The first detection of an oxetene intermediate involved low-temperature (–78 °C) photolysis of 2-butyne and benzaldehyde to form the photoproduct (**61**), which was observed by NMR. The oxetene undergoes further photoreaction with benzaldehyde to form the novel fused oxetane (**62**). Recently, Friedrich has reported further studies on the reactivity of oxetenes and developed alternative syntheses of the parent compound and 3-phenyloxete (**64**).[69] The parent oxetene is found to have a thermal half-life of approximately 8 h in solution at room temperature. The phenyl-substituted derivative (**64**) underwent slow ring-opening under acidic conditions to form 2-phenylpropenal and air oxidation to yield a formate derivative, probably *via* a radical process.



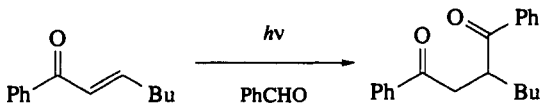
(63) (61) (62)

(Z):*(E)* = 2 : 1 at 20 °C (photostationary state)
(E) only at −78 °C



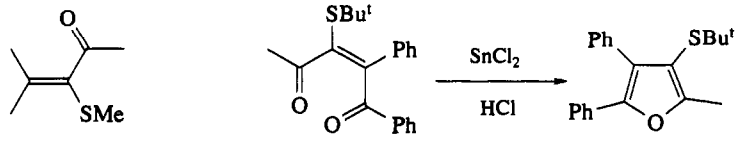
(64)

A related photochemical process in which an oxetene intermediate may not be involved is the photolysis of benzaldehyde and 1-hexyne,[70] yielding as major products (**65**) and (**66**). Since no ring-opening products derived from regioisomeric oxetanes could be observed, it was proposed that benzoyl radicals were adding to the alkyne from the unsubstituted terminus. Further photoreaction of (**65**) to (**66**) was observed upon prolonged irradiation. This result is in contrast to the original report by Büchi,[71] in which irradiation of benzaldehyde and 5-decyne produced 6-benzylidene-5-decanone (13%), presumably from electrocyclic oxetene ring opening.



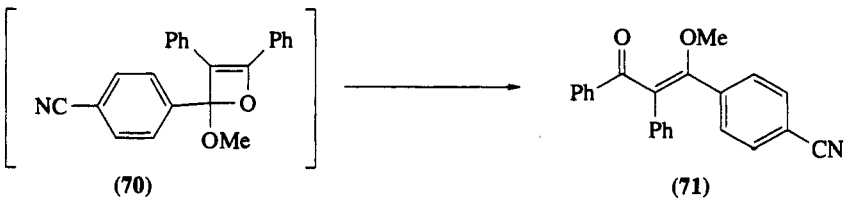
(65) (66)

Bos and coworkers have developed several applications of alkyne–ketone photoadditions to organic synthesis.[72] Irradiation of a solution of acetone and 1-methylthio-1-propyne gives as a major product the cycloadduct (**67**); this results from selective oxetane formation due to radical stabilization by the methylthio group, followed by electrocyclic ring opening. Similarly, photoreaction of benzil and 1-*t*-butylthio-1-propyne gave the adduct (**68**) in 45% yield, which was transformed in 90% yield to the furan (**69**).



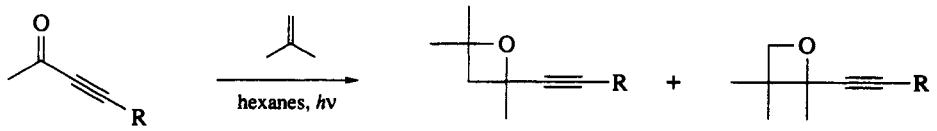
(67) (68) (69)

Photoaddition of carboxylate esters to diphenylacetylene has also been reported.[73] For example, irradiation of methyl *p*-cyanobenzoate and diphenylacetylene gave in 86% overall yield the enol ether (**71**), presumably a result of carbonyl n,π^* triplet addition to the alkyne to form the unstable oxetene, which rapidly ring opens. This complements the utility of aromatic esters in the Paterno–Büchi reaction with alkenes as discussed by Cantrell.[65,66]



(70) (71)

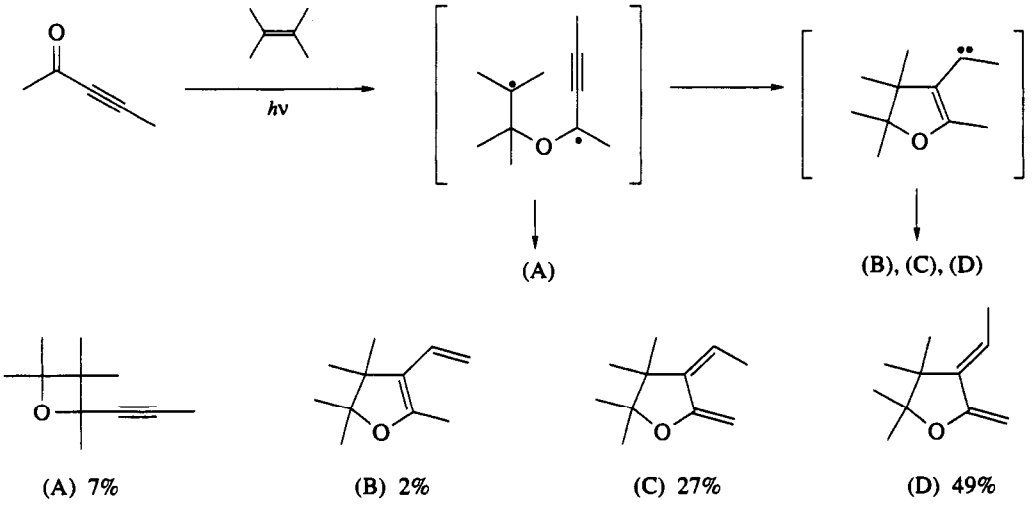
Preliminary investigations describing the photoadditions of ynones to alkenes[74] have determined that these species may react through n,π^* excitation to produce alkynic oxetanes. Irradiation of 3-butyn-2-one with isobutene gave a 46% isolated yield of (**72**) and (**74**) (14:86). 3-Octyn-2-one analogously provided a 50% isolated yield of (**73**) and (**75**) (15:85), a regioselectivity predicted on the basis of the 'best' diradical intermediate.



(**72**) R = H
(**73**) R = Bu

(**74**) R = H
(**75**) R = Bu

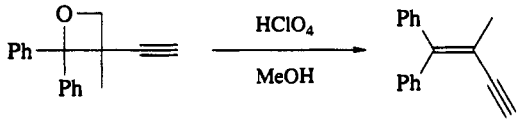
In a related series of experiments, Agosta[75] and coworkers have discovered alternative pathways for 1,4-diradicals generated from addition of photoexcited ynones to alkenes. For example, in the photolysis of 3-pentyn-2-one with tetramethylethylene, products arising from both [3 + 2] and [2 + 2] cycloaddition have been noted (Scheme 9). It is proposed that oxetane formation proceeds from the short-lived first excited singlet state of the alkynone, since addition of triplet quenchers to the reaction has no effect on oxetane formation. On the other hand, the [3 + 2] mode of cyclization is quenched by triplet scavengers such as naphthalene, which suggests the existence of a longer-lived quenchable state that can add to tetramethylethylene to form a carbenoid. The intermediacy of the carbene has been implicated by deuterium and alcohol-trapping experiments; however, attempts to observe this species *via* laser flash photolysis and ESR were unsuccessful.[76]



(A) 7% (B) 2% (C) 27% (D) 49%

Scheme 9

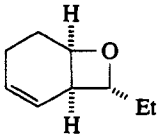
An example in which the chemoselective photoaddition of carbonyl compounds to a conjugated enyne becomes an important issue has been reported by Carless.[77] A solution of 2-methylbut-1-en-3-yne and benzophenone was irradiated to form in 58% yield the oxetane (**76**), which was converted under acid catalysis to conjugated enyne (**77**). Surely the synthetic utility of such a process, as well as further applications of alkynyl–carbonyl photocycloadditions, will be forthcoming.



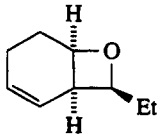
(**76**) (**77**)

2.4.4 PATERNO–BÜCHI REACTION OF DIENYL AND ALLENYL SYSTEMS

The use of dienes such as piperylene in the quenching of triplet states of carbonyl compounds is well known.[78] However, in many photochemical studies, attempts to quench the carbonyl T_1 state are often complicated by the formation of oxetane photoproducts.[79] Since the photosensitized dimerization of diene triplets is well known,[80] synthetic applications utilizing dienes in the Paterno–Büchi photocycloaddition are rather limited. However, the diene addend not only allows for rapid assemblage of functionality but remains a continuing challenge in terms of experimental efficiency and generality.

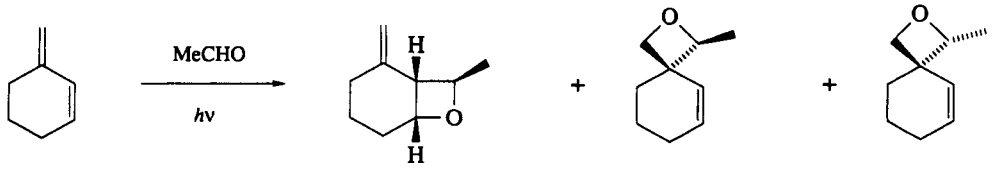


(78)



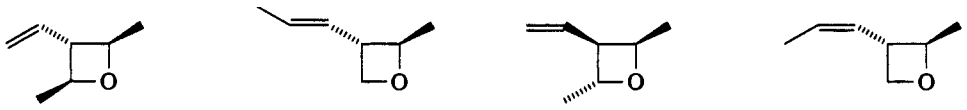
(79)

Perhaps the earliest use of a conjugated diene system was the photoaddition of propionaldehyde to cyclohexa-1,3-diene, first reported by Kubota and coworkers.[81] Oxetanes (**78**) and (**79**) were obtained in a 4:1 ratio, presumably through attack of excited singlet propionaldehyde on the diene,[82] whereas diene dimers are thought to originate *via* attack of triplet diene on another ground-state diene molecule. The use of Pyrex filters in these experiments suggests that propanal is excited to its n,π^* singlet state. The case of endocyclic *versus* exocyclic alkene selectivity has been considered by Duthaler and coworkers.[83] Irradiation of diene (**80**) and acetaldehyde gave a 45.5:11:43.5 mixture of isomeric oxetanes (**81**), (**82**) and (**83**), which indicates low site-selectivity in oxetane formation but preferential *endo* stereoselectivity for spirooxetane (**83**).



(80) (81) (82) (83)

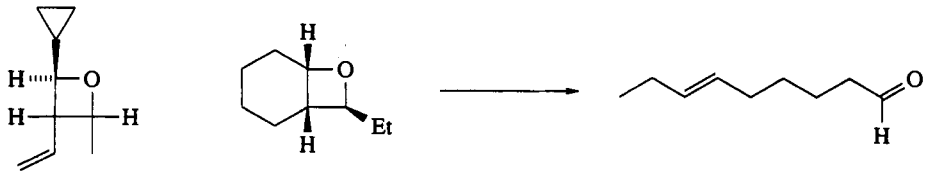
Likewise, photocycloaddition of acetaldehyde to (*E*)-penta-1,3-diene gave oxetanes (**84**) and (**85**) as major products (51%, 25%), indicating that attack at the more substituted double bond is preferred with high orientational selectivity.[84] The formation of (**86**) and (**87**) from (*Z*)-penta-1,3-diene (48%, 27%) implicates a singlet intermediate because of the observed retention of stereochemistry.[79,85]



(84) (85) (86) (87)

Further evidence for singlet 1,4-diradical intermediates has been obtained in the case of photocycloaddition of cyclopropanecarbaldehyde with (*E*)-penta-1,3-diene, in which the formation of the cyclopropyloxetane (**88**) dominated. This is in contrast to the case of aromatic carbonyl compounds and cyclopropylethylene in which the formation of considerable amounts of ring-opened products and oxepins, formed by cyclopropylcarbinyl–allylcarbinyl rearrangement, implicates the intermediacy of a triplet 1,4-diradical.[23]

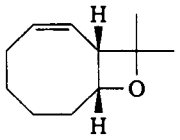
Jones and coworkers have utilized a carbonyl–alkene metathesis sequence in the synthesis of insect pheromones.[86] Oxetane (**89**) was synthesized efficiently from adduct (**78**) by hydrogenation (PtO_2, EtOH) since direct irradiation of cyclohexene and propionaldehyde gave photoreduction products, possibly owing to the greater availability of allylic hydrogens. Pyrolysis of (**89**) (270 °C) or treatment with $\{Rh(CO)_2Cl\}_2$ in benzene gave *trans*-non-6-enal (**90**; 89%). $LiAlH_4$ reduction of (**90**) provided *trans*-non-6-en-1-ol, a sex attractant of the Mediterranean fruit fly. Similar thermal[87] or catalyzed[88] cyclorever-



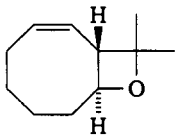
(88) (89) (90)

sions were noted previously to be both stereoselective and favor the formation of metathesis products instead of regenerated carbonyl–alkene pairs.

Several applications of the Paterno–Büchi reaction in medium-membered ring functionalizations have been documented. Sakurai and coworkers[89] have reported the photoaddition of acetone to 1,3-cyclooctadiene to produce a 4:1 mixture of *cis* and *trans* oxetanes (**91**) and (**92**). Interestingly, acetone adds stereorandomly to cyclooctene to give a 1:1 mixture of *cis* and *trans* oxetanes. These results have been interpreted in terms of a mechanism in which diradicals are generated from ketone triplets. Jones and coworkers[90] have recently uncovered a critical dependence of the photoaddition stereoselectivity on the concentration of the alkene component. Irradiation of butanal and cyclooctene in acetonitrile resulted in a 65:17:18 mixture of adducts (**93**), (**94**) and (**95**). A different (2.8:47.5:49.7) mixture results when irradition was performed in neat alkene. At low concentrations of alkene a more stereorandom triplet path may be operative. At higher alkene concentrations, addition of aldehyde singlets leads predominantly to *cis* isomers, most likely by formation of a singlet exciplex in which the n,π^* electrophilic carbonyl attacks the alkene in an 'edge-on' arrangement.[91]



(91)



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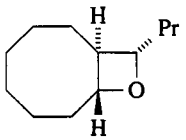

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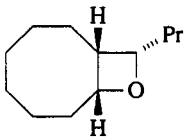
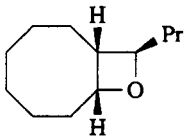
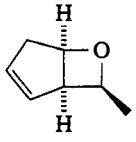


(94)



(95)

A recent synthesis of the tricyclic secoiridoid (±)-sarracenin (**98**) relied on the Paterno–Büchi addition of acetaldehyde and cyclopentadiene as the initial step.[92] Irradiation of cyclopentadiene and acetaldehyde provided a 5:1 mixture of bicyclic oxetanes (**97**) and (**96**) in 5–10% yield. Treatment of the crude photolysate with CSA and methanol followed by tosylation of the crude product gave (**99**), which represents the toluenesulfonate ester derived from the major oxetane (**97**).[93] The tosylate was displaced by the anion prepared from dimethyl β-styrenylmalonate to afford the substituted malonate (**100**) in 84% yield (Scheme 10). Attempts to effect ring opening of the oxetane mixture were unsuccessful.[17] Decarboxylation and demethylation gave the alcohol (**102**) which was subjected to ozonolysis and reductive work-up to afford (±)-sarracenin in 60% yield. The oxetane-based synthesis is noteworthy due to its brevity and use of a biosynthetically postulated trialdehyde equivalent.



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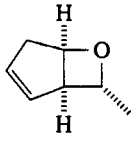

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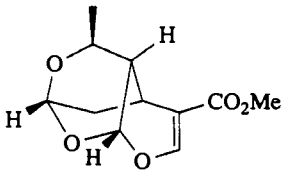

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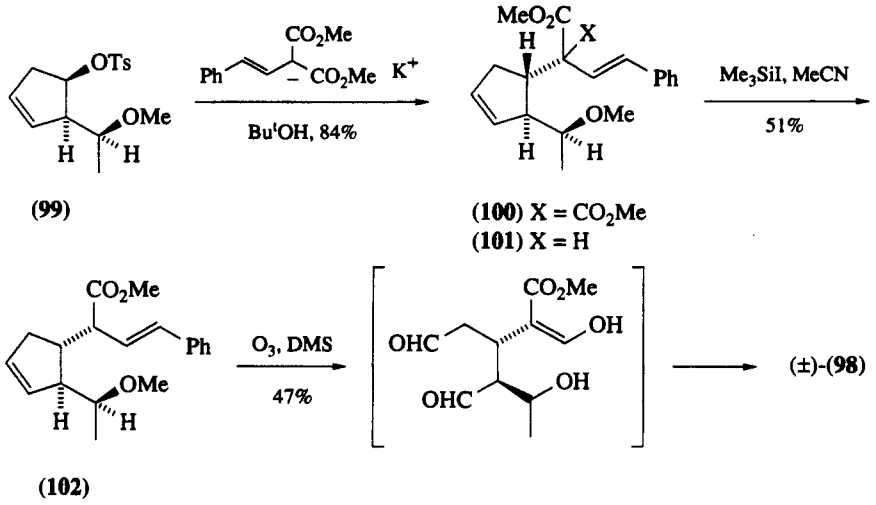
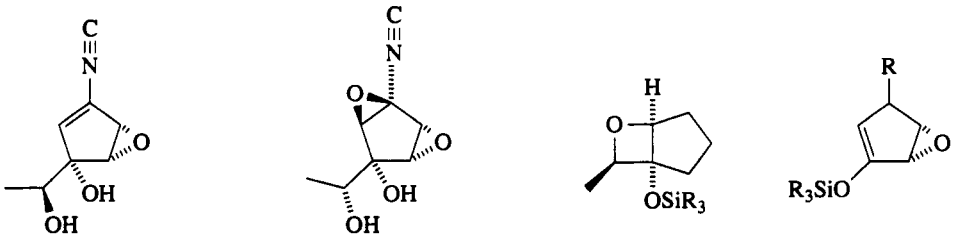


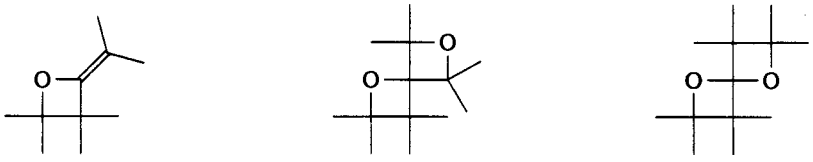
Scheme 10

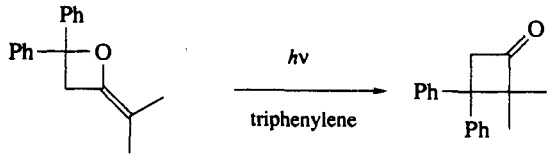
In studies directed towards the synthesis of the fungal isonitrile antibiotic isonitrin B (**103**),[94] a cyclopentanoid metabolite related to trichoviridine (**104**),[95] various trialkylsilyl enol ethers were irradiated with propionaldehyde to produce equimolar amounts of stereoisomeric bicyclic oxetanes (**105**).[96] The corresponding silyl dienol ethers, however, gave little oxetane product owing to preferential diene photopolymerization. The use of vinyl epoxide derivatives such as (**106**), however, offers a possible access to the epoxycyclopentanoid system with simultaneous control of the face selectivity of the photoaddition by the epoxide moiety.



Even more rare are photocycloadditions involving carbonyl compounds to allenes.[5] Arnold[97] has found that acetone and tetramethylallene can be irradiated to form a mixture of 2-alkylideneoxetane and 1,5- and 1,6-dioxaspiro[3,3]heptane products (**107**:**108**:**109** = 8:51:27), all resulting from initial attack of the carbonyl n,π^* state on the central carbon linkage. Hammond[98] subsequently reported a study in which alkylideneoxetane derivatives (**111**) were photoisomerized to cyclobutanes (**110**).

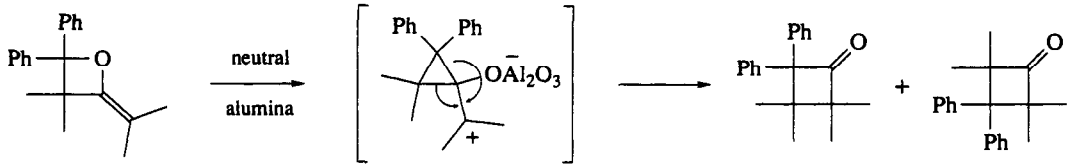
Similarly, it was found that (**111**) rearranged to a 78:22 mixture of cyclobutanes (**112a**) and (**112b**), presumably through a cyclopropylcarbinyl cation.[99] Extension of the alkene photocycloaddition to ketenimines has been reported by Singer and coworkers.[100] Iminooxetane (**113**) was formed by irradiation of an acetone/dimethyl-*N*-phenylketenimine mixture and was found to possess a 21.8 kcal mol^{-1} barrier to *syn–anti* imine exchange determined from variable-temperature NMR experiments. An effort to use the allene–carbonyl photocyclization in a photopolymerization reaction has been described by Andrews and





(111) (110)

Feast.[101] Dibenzoylbenzene derivative (**114**) was irradiated with tetramethylallene for 3.5 minutes in benzene to produce a polymeric structure in which there were 90% oxetane structures incorporated along the backbone. This process constitutes an example of step-growth photopolymerization *via* the triplet state of an aromatic carbonyl moiety. The products are thermally unstable and readily degraded by acids, but are quite soluble in organic solvents and may possess useful properties as new materials.



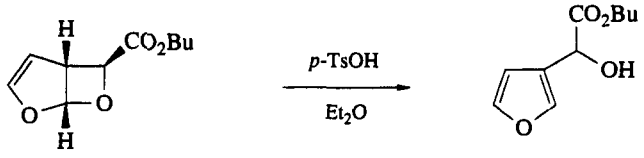
(111) (112a) (112b)

(113) (114)

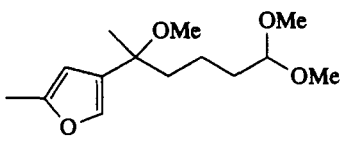
2.4.5 THE FURAN–CARBONYL PHOTOCYCLOADDITION

The Paterno–Büchi photocycloaddition reaction[4,5] of various carbonyl compounds to furans was initially investigated by Sakurai[102] in 1965 and was found to afford only the head-to-head photoproducts with high *exo* relative face selectivity. An NMR study by Whipple and Evanega[103] later confirmed the *exo* mode of cycloaddition. Since the time of the original report the photoreaction has been systematically studied by several groups and the 2,7-dioxabicyclo[3.2.0]hept-3-ene ring system has been exploited in several facets of synthesis.

A recent synthesis of 3-substituted furan derivatives illustrates an important application of the furan–carbonyl photocycloaddition.[104] Zamojski has reported the rearomatization of oxetane (**115**) in the presence of *p*-toluenesulfonic acid to 3-furylmethanol derivative (**116**). Synthesis of (**117**), itself a substrate for the intramolecular photocycloaddition reaction (Section 2.4.6), involved a similar rearomatization process ($PPTS/CH_2Cl_2$) and capitalized upon the chemoselectivity observed in the ketone–furan photocycloaddition.[105] Similarly, a synthesis of perillaketone (**118**) by Kawanisi[106] involved irradiation of a carbonyl compound and furan. A complication in the rearomatization is that acid also catalyzes the reversion of the photoadduct to starting materials; to circumvent this problem the photoreaction was run in the presence of acid, so that rearomatization would occur *in situ* and the products of competitive reversion would promptly recombine.



(±)-(115) (±)-(116)



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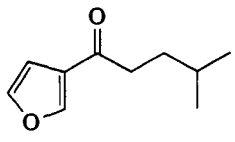

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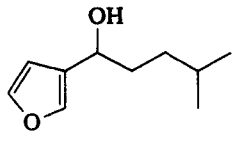

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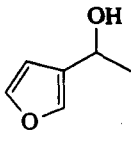
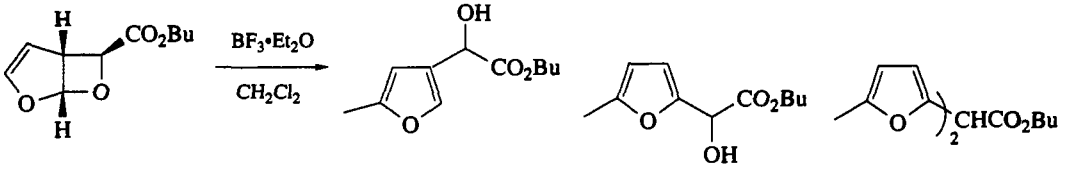


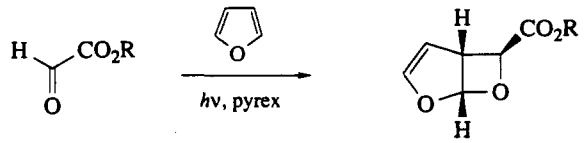
(120)

Irradiation of furan with 4-methylpentanal in the presence of methanesulfonic acid gave 3-substituted furans (**119**) and (**120**), the latter formed by Norrish type II cleavage of the starting aldehyde to acetaldehyde and subsequent photocycloaddition and rearomatization. Oxidation of (**119**) with Collins reagent gave the desired perillaketone (**118**).[104] Isomerization of furan–carbonyl photoproducts with Lewis acids, on the other hand, is a more complicated process.[107] Jarosz and Zamojski have found that treatment of bicyclic oxetane (**121**) with $BF_3{\cdot}Et_2O$ gave a 16:36:48 mixture of substituted furans (**122**), (**123**) and (**124**), the latter two compounds arising from Lewis acid catalyzed reversion to and subsequent reaction of 2-methylfuran and butyl glyoxylate.

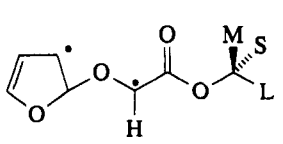


(121) (122) (123) (124)

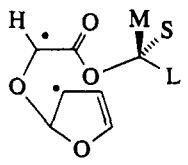
An effort to use the methods of asymmetric synthesis to obtain substituted 3-furylmethanol derivatives in optically active form has been reported by Zamojski.[108] Irradiation of (*R*)-(–)-menthyl glyoxylate and furan gave the *exo* photoproduct (*R*)-(–)-menthyl 2,7-dioxabicyclo[3.2.0]hept-3-ene-6-carboxylate (**125**), which was determined by degradation and comparison with (–)-dimenthyl maleate to have the (*S*)-configuration at C-6. Similarly, irradiation of 8-phenylmenthyl glyoxylate gave oxetane of 15% *ee*.[109] An explanation for the low enantioselectivity has been advanced[108] and is summarized in Scheme 11. Photocycloaddition between furan and alkyl glyoxylates probably occurs in both *exo* and *endo* fashions; however, in the *endo* diradical intermediate (B) a 180° rotation around the C—O bond must occur before oxetane closure occurs. In addition, the *s-trans* (C) and *s-cis* (D) conformations of the glyoxylate system



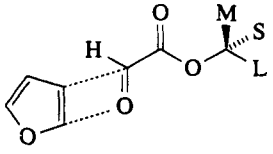
R = (*R*)-(–)-menthyl (**125**) 7.3% *ee*



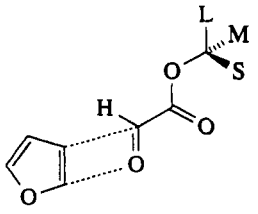
(A)



(B)



(C)



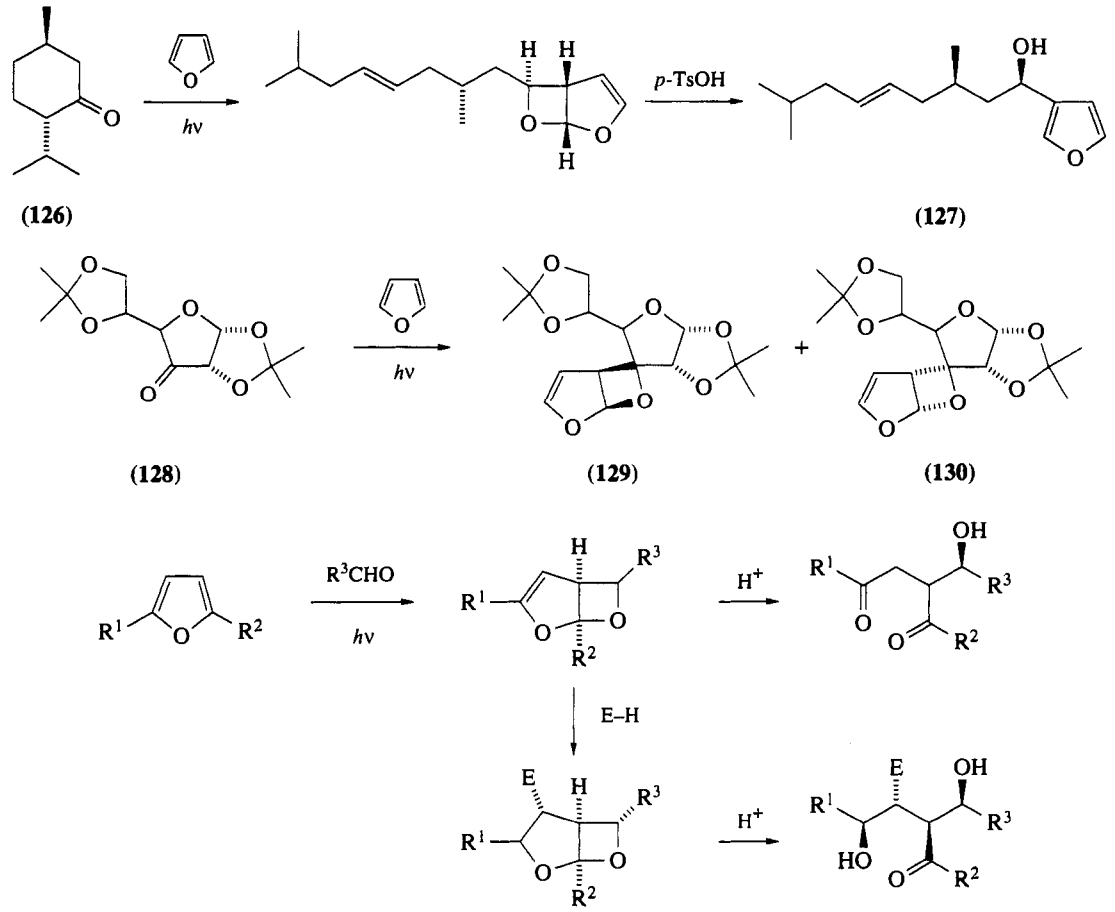
(D)

Scheme 11

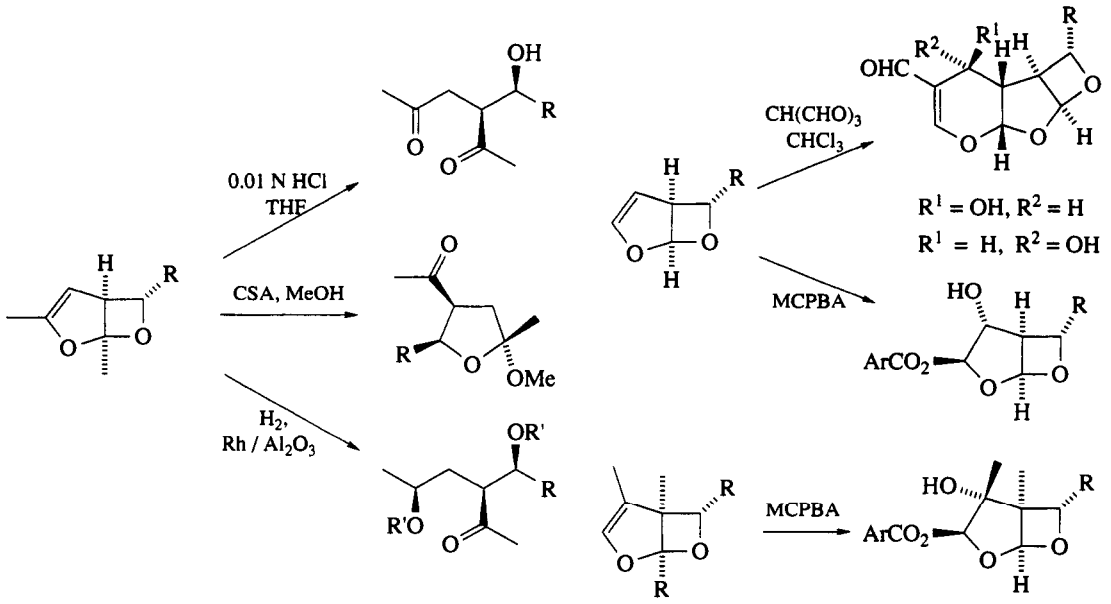
should lead to opposite enantiomers of the bicyclic oxetane if the glyoxylate enters in an *exo* fashion. Although the use of chelation to produce entirely *s-cis* conformers of chiral glyoxylate derivatives may hold promise for asymmetric synthesis in the Paterno–Büchi reaction, the high 'non-chelation' selectivity achieved with chiral phenylmenthyl glyoxylates may suggest alternative explanations for asymmetric induction (Section 2.4.7).

The use of conformationally rigid carbonyl compounds in an attempt to enhance the asymmetric induction in the photocycloaddition has been reported by Zamojski.[110] Irradiation of (*R*)-(–)-menthone (**126**) and subsequent acid-catalyzed rearomatization gave a 2:1 mixture of diastereomeric 3-furyl alcohol derivatives (**127**) resulting from Norrish type I photoisomerization and subsequent Paterno–Büchi cyclization with furan. The major stereoisomer was assigned as in structure (**127**), indicating 1,3-asymmetric induction in accord with Cram's model.[111] The conformationally restricted hexofuranose (**128**) gave four diastereomeric adducts upon irradiation in the presence of furan. Photoproducts (**129**) and (**130**), which result from attack of the furan molecule from the less hindered β-face of (**128**), constituted approximately 75% of the product mixture. The authors suggest the importance of steric factors in this reaction and show how conformationally restricted systems may in certain cases be useful for obtaining asymmetric photoproducts.

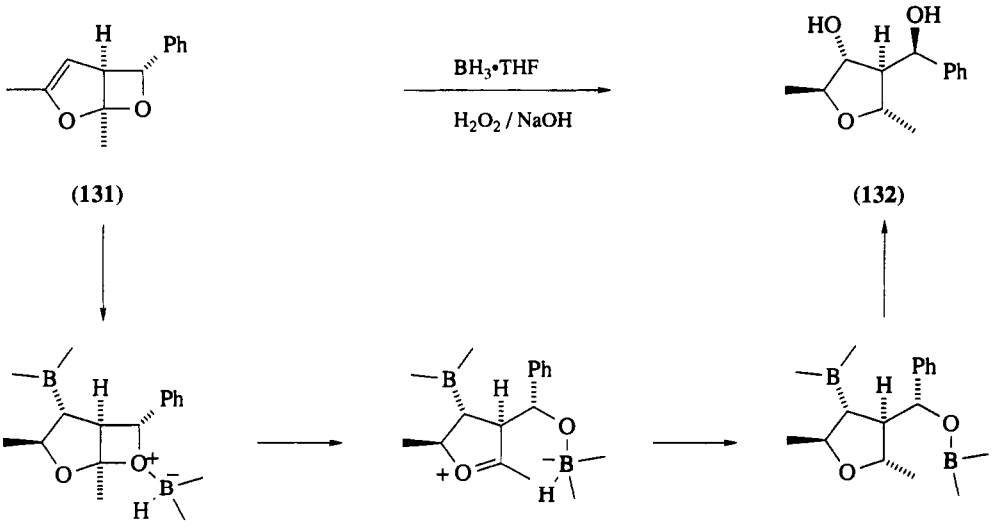
The relationship of the furan–carbonyl photocycloaddition to the aldol condensation[16] has been noted in studies by Schreiber and coworkers.[112,121] Scheme 12 shows that the furan is equivalent to a (*Z*)-enolate and that hydrolytic unmasking of the 'photoaldol' adducts affords *threo* aldols of 1,4-dicarbonyl compounds.[113] The cup-shaped *cis*-dioxabicyclo[3.2.0]heptene skeleton of the photoaldol lends control to a variety of reactions wherein electrophilic reagents add to the enol ether on its convex face (Scheme 13). Hydroboration–oxidation [BH_3·THF (inverse addition); H_2O_2/NaOH] of the photoaldol (**131**) (Scheme 14) gave the 1,3-diol (**132**) in 82% yield, resulting in total stereocontrol over five contiguous chiral centers in a two-step procedure. The stereochemistry of (**132**) was verified by single-crystal X-ray diffractometry of the corresponding bis(*p*-bromobenzoate) derivative (Figure 2).



Scheme 12



Scheme 13



Scheme 14

In addition to the functionalization protocols of Schemes 13 and 14, vinylic substitution reactions involving metalation and palladium-mediated carbon–carbon bond formation have been formulated,[114] which further broaden the variety of structural types available from the Paterno–Büchi reaction. For example, deprotection and stannylation of photoaldol (**133**), followed by refunctionalization of the α-enol ether position of vinylstannane (**134**), gave the substituted oxetane (**135**) in good overall yield. Similar functionalization of bicyclic oxetane (**136**) *via exo*-face dihydroxylation and acid-catalyzed reorganization of the acetal to the protected 3-deoxy-(±)-streptose (**137**) has been reported, which illustrates the synthetic utility of such processes in the synthesis of polyoxygenated materials.[115]

An application of the furan–carbonyl photocycloaddition to the synthesis of the antifungal metabolite (±)-avenaciolide (**146**)[116,121] involved as the first step the photocycloaddition of nonanal to furan on a multigram scale (Scheme 15). Hydrogenation and hydrolysis of the resulting bicyclic oxetane (**138**) gave a butyrolactol derivative (**139**) which was reacted with vinylmagnesium bromide to give a 5:1 mixture of stereoisomeric allyl alcohols (**140**). The two proximal, secondary hydroxy groups were engaged as an acetonide that upon oxidation (PCC, NaOAc) provided aldehyde derivative (**141**). Ozonolysis of (**141**) in MeOH and reductive work-up produced dialdehyde (**142**) that was epimerized *via* 'ancillary stereocontrol' to the equatorial isomer (**143**).[117] Acidification of the dialdehyde acetonide in the same pot de-

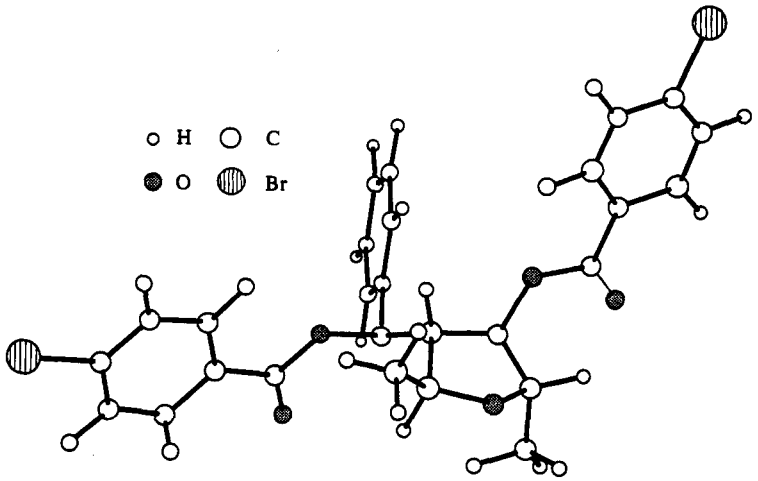
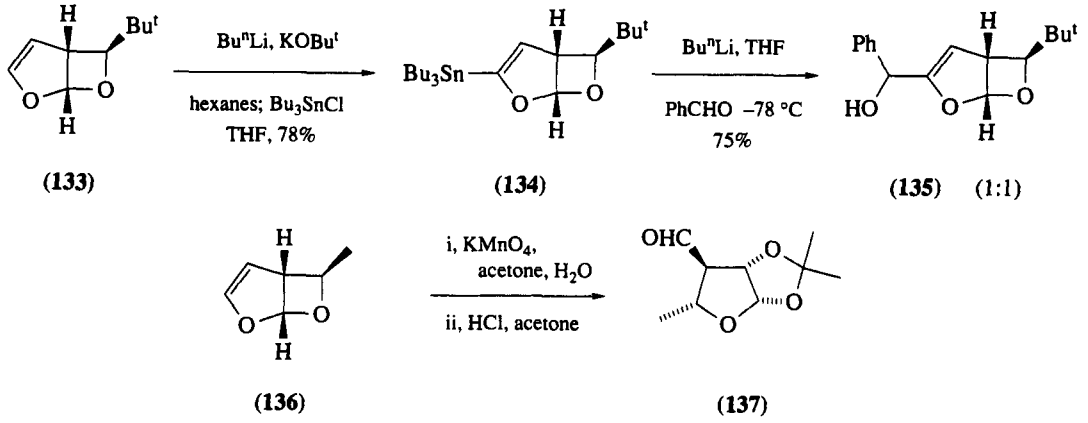


Figure 2



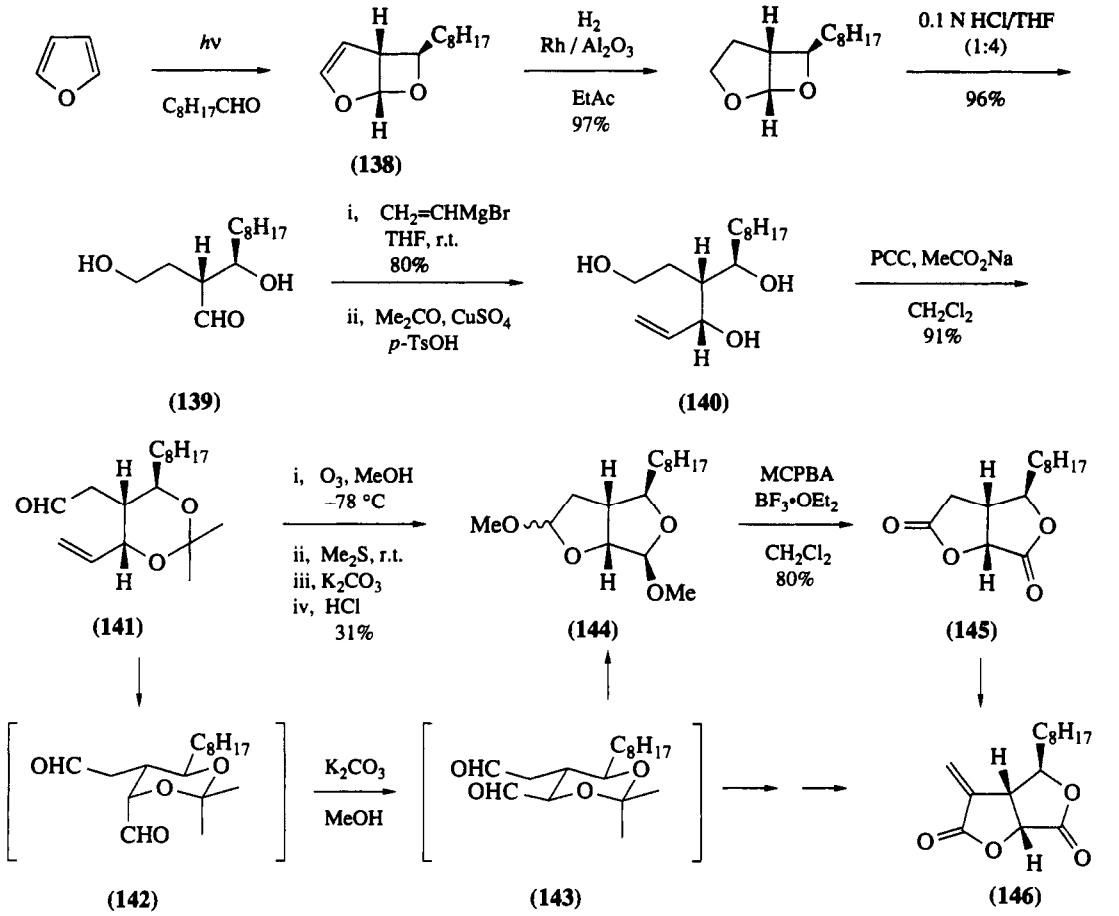
(133) (134) (135) (1:1)

(136) (137)

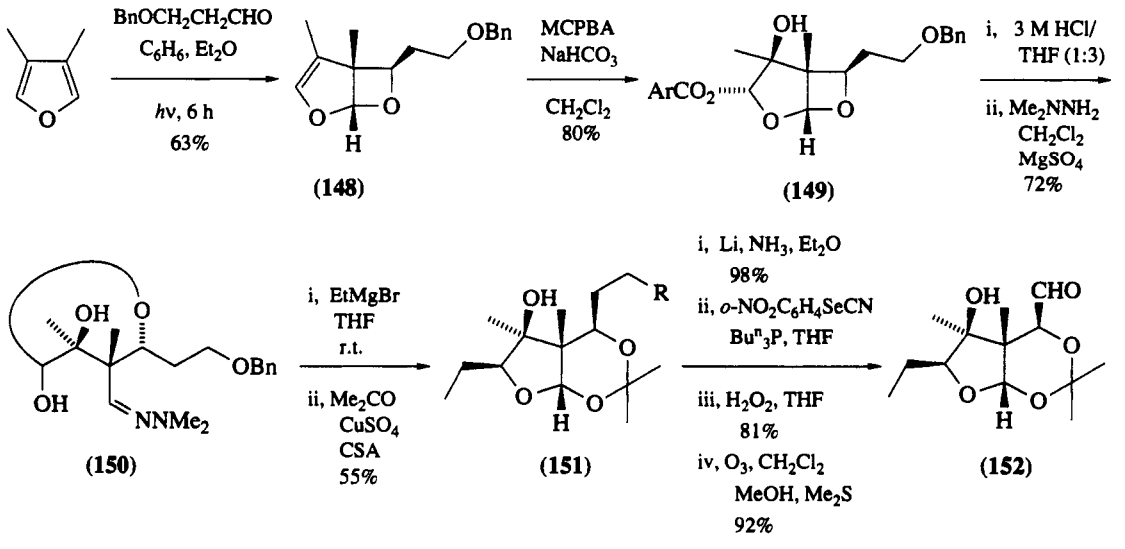
livered the bis-methoxy lactol (**144**), which was oxidized using Grieco's procedure[118] to the bis-lactone (**145**) in 80% yield. Methylenation of (**145**) gave (±)-avenaciolide (**146**) in 10 steps.

A recent application of the furan–carbonyl photocycloaddition involved the synthesis of the mycotoxin asteltoxin (**147**).[119–121] Scheme 16 shows the synthetic procedure that began with the photoaddition of 3,4-dimethylfuran and β-benzyloxypropanal to furnish photoaldol (**148**), which was epoxidized with MCPBA to afford the functionalized product (**149**) in 50% overall yield. Hydrolysis (THF, 3N HCl) provided the monocyclic hemiacetal which was protected as its hydrazone (**150**). Chelation-controlled addition of ethylmagnesium bromide to the latent α-hydroxy aldehyde (**150**) and acetonide formation produced compound (**151**), which was transformed through routine operations to aldehyde (**152**). Chelation-controlled addition of the lithium salt of pentadienyl sulfoxide (**153**) followed by double 2,3-sigmatropic rearrangement provided (**154**) as a 3:1 mixture of isomers (Scheme 17). Acid-catalyzed cyclization of (**154**) (CSA/CH_2Cl_2) gave the bicyclic acetal (**155**), which was transformed in several steps to (±)-asteltoxin (**147**).[120]

The furan–carbonyl photocycloaddition reaction has also been used in the determination of the absolute stereostructure of asteltoxin.[122] The photocycloaddition of D-glyceraldehyde acetonide and 3,4-dimethylfuran gave a 1.2:1.0 mixture of photoproducts (**156**) and (**157**) each obtained in about 54% enantiomeric excess, reflecting the lability of the aldehyde towards racemization under the reaction conditions. The relative configurations of (**156**) and (**157**) were proven by converting the major photoproduct (**156**) ($MCPBA/CH_2Cl_2$ followed by hydrolysis) to the bis-tetrahydrofuran (**159**) (Scheme 18). The *cis* relationship of hydroxyl and acetoxymethyl substituents at C-5 and C-6 was proved by comparison of the coupling constant ($J_{5,6} = 2.2$ Hz) with related compounds prepared in the racemic synthesis.[120] Treatment of (**158**) under previously described conditions gave bis-tetrahydrofuran (**160**); comparison of opti-



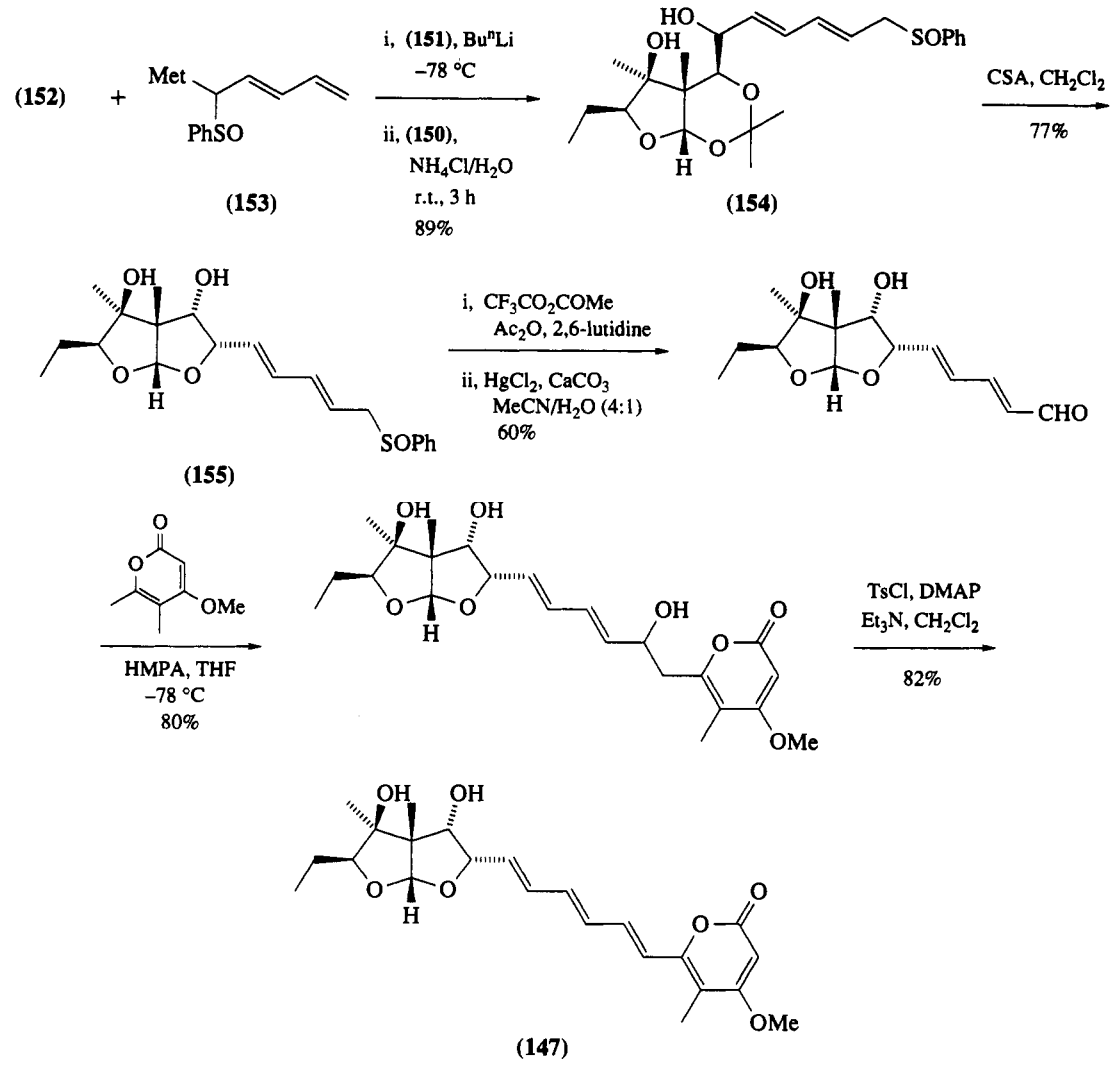
Scheme 15



Scheme 16

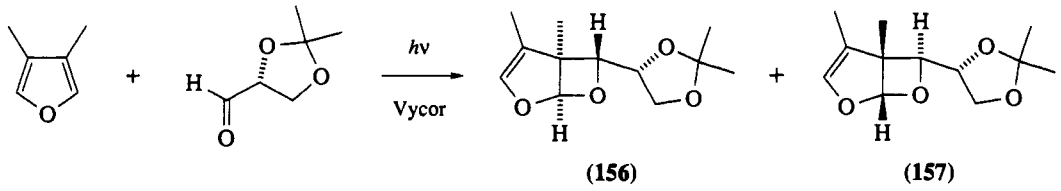
cal rotation values with an identical sample prepared by degradation of asteltoxin demonstrated that the absolute configuration of asteltoxin is as drawn in structure (**161**).

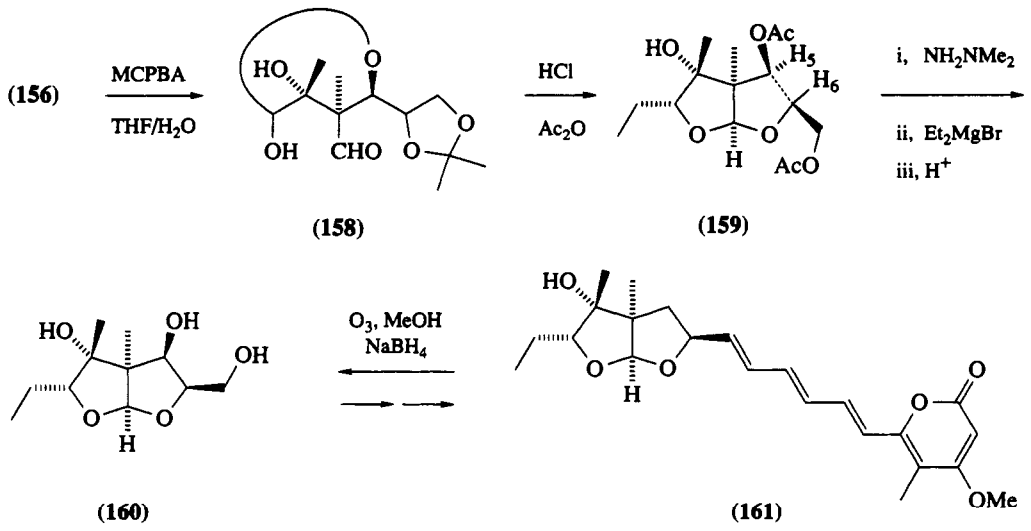
In synthetic studies directed toward the synthesis of the antileukemic cembranolide isolobophytolide (**162**),[123] the photocycloaddition of 2,5-bis(hydroxymethyl)furan and β-*t*-butyldimethylsiloxybutanal



Scheme 17

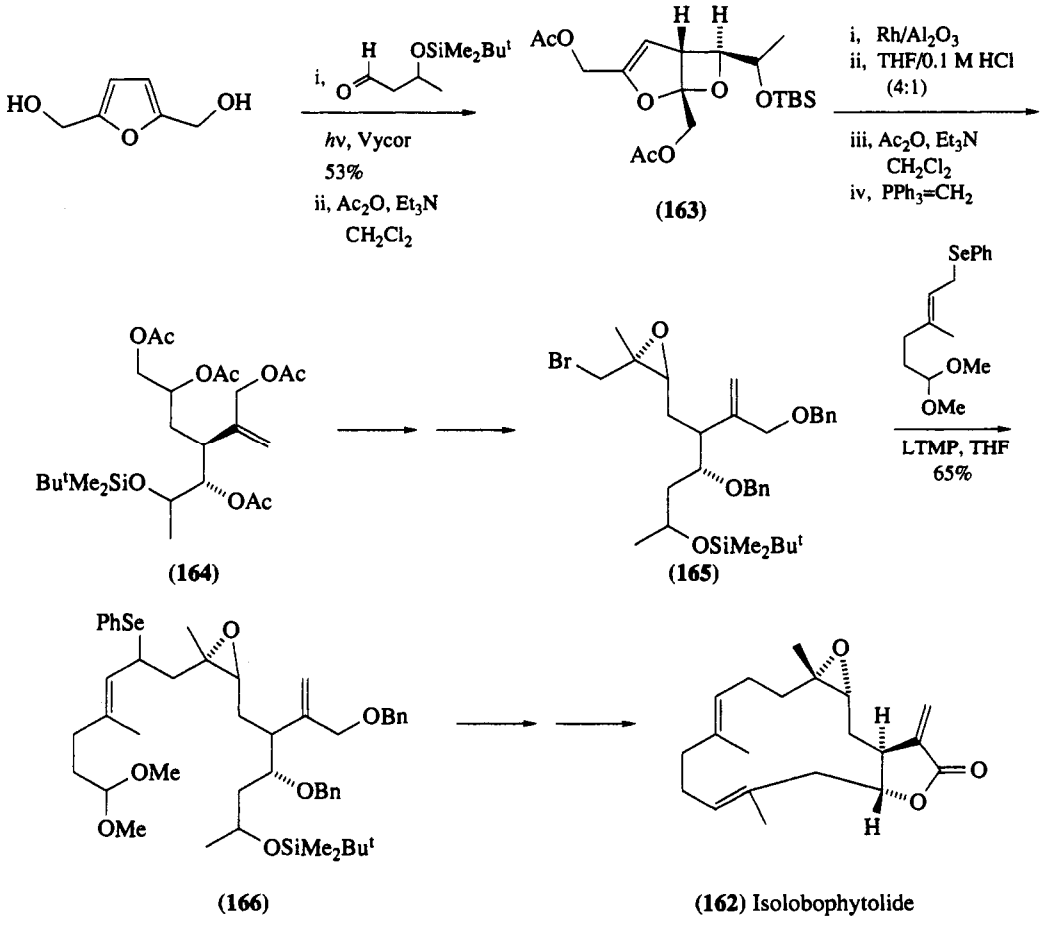
proceeded smoothly (53%) in tetrahydrofuran on multigram scale and provided, after acetylation, the photoaldol product (**163**) (Scheme 19).[105,124] The reaction proceeds with normal *exo* selectivity but results in a mixture of diastereomers by virtue of the lack of facial selectivity in the addition of chiral aldehydes. Hydrogenation of the enol ether from the convex face using Rh/Al_2O_3 minimized competing hydrogenolysis of the allylic acetate, a process that was problematic when palladium- and platinum-based catalysts were used. Subsequent hydrolysis of the photoproduct, acetylation and Wittig methylenation afforded the acyclic derivative (**164**), which contains three of the four stereocenters present in isolobophytolide. A series of protecting group interconversions and routine transformations parlayed (**164**) into epoxy bromide (**165**), which was alkylated with an allylic selenide anion to afford epoxy selenide (**166**). The seco derivative (**166**) contains all the carbons and stereocenters present in the natural





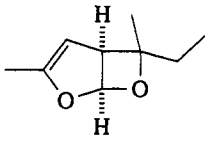
Scheme 18

product. Unfortunately, conditions to effect the ring closure that will be required in order to complete the cembranolide synthesis have not yet been discovered.

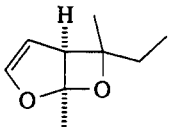


Scheme 19

One limitation encountered in synthetic studies of this reaction is the lack of chemoselectivity in the addition of aldehydes to unsymmetrically substituted furans. For example, the photochemical addition of benzaldehyde to 2-methylfuran provides a 1:3:1 mixture of oxetanes resulting from the *exo* addition of aldehyde to the more and less substituted alkenes, respectively. Ketone photocycloadditions are more selective. For instance, irradiation of 2-butanone and furan forms a 7:1 mixture of regioisomeric oxetanes (**167**) and (**168**) (1:1 mixture of epimers).



(**167**)



(**168**)

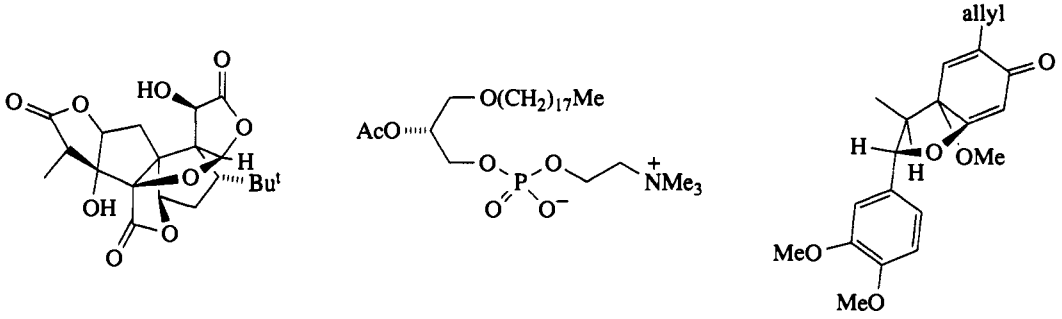
A recent use of silyl- and stannyl-substituted furans[125] in the photocycloaddition reaction has resulted in the short synthesis of a ginkgolide B–kadsurenone hybrid, potential antagonists of the platelet activating factor (PAF) (Scheme 20). Photoaddition of 2-tributylstannylfuran and *n*-butyl glyoxylate resulted in the formation of a single photoproduct (**169**). A Stille coupling[126] of bromoveratrole [$Pd(PPh_3)_4$/THF] produced the arylated dihydrofuran (**170**), which was hydrolyzed[112] to an unstable keto-aldehyde. Chemoselective reduction of this species using conditions described by Luche[127] resulted in the formation of a mixture of lactol isomers (**171**). Treatment of this mixture with Otera's distannoxane transesterification catalyst (toluene, 50 °C)[128] afforded a separable mixture of bicyclic compounds (**172**) and (**173**). These studies illustrate the use of a main group metal both to direct the site of addition and to participate in a transition metal catalyzed coupling reaction. In this fashion, the inherent lack of chemoselectivity of photochemically excited aldehydes in their addition to unsymmetrical furans can be overcome.

The stereoselective synthesis of unsaturated oxetanes has recently been achieved by Feigenbaum and coworkers.[129] Previous studies have indicated that photochemical *cis–trans* isomerization of enals is rapid and results in the formation of equivalent amounts of stereoisomeric alkene adducts.[105,116] For example, irradiation of *trans*-crotonaldehyde and 2,6-dimethylfuran produced a 1:1 mixture of alkenic isomers (**174**) and (**175**) in 64% yield. Irradiation of 4-trimethylsilylbutyn-2-one and furan[129] provided with 5:1 stereoselectivity the bicyclic oxetane (**176**) in which the methyl group occupies the *exo* position, presumably because of the small steric requirement of the triple bond. Desilyation of the protected alkyne produced an alkynic oxetane which was hydrogenated under Lindlar conditions to bicyclic vinyloxetane (**177**); attempts to use the unprotected butyn-2-one gave low isolated yields of oxetane because of extensive polymerization. The stereochemical outcome thus broadens previous alkynyloxetane syntheses[75,78] and makes possible the preparation of new oxetane structures that may be synthetically useful.

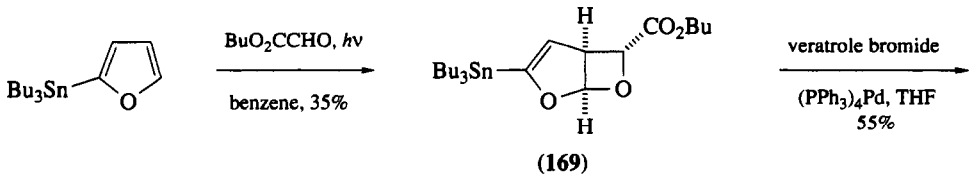
Recent work by Cantrell[130] extends the range of possible carbonyl addends in the furan–carbonyl photocycloaddition to include arenecarboxylic acid esters. For example, irradiation through Vycor of methyl benzoate and excess furan gave a mixture of alkoxyoxetane (**178**) and enol formate (**179**). Prolonged irradiation led to the predominant formation of product (**179**), most likely through a photo-induced [2 + 2] cycloreversion process. In the reaction of 2,5-dimethylfuran with methyl benzoate, an (*E*/*Z*) mixture of product (**181**) amounted to 44% of the product mixture, indicating possible intervention of a photochemically allowed suprafacial 1,7-sigmatropic rearrangement of (**180**).

Andrews and Feast[131] have described a further application of the Paterno–Büchi reaction in which furans are used in step-growth polymerization. Irradiation of *m*-dibenzoylbenzene and furan produced the monomeric 2:1 adduct (**182**), which was polymerized further with *m*-dibenzoylbenzene to produce polymers containing isomeric oxetane units. The step-growth polymerization in this case was limited by low monomer solubility, slow oxetane formation, and hydrogen abstraction processes that led to crosslinking.

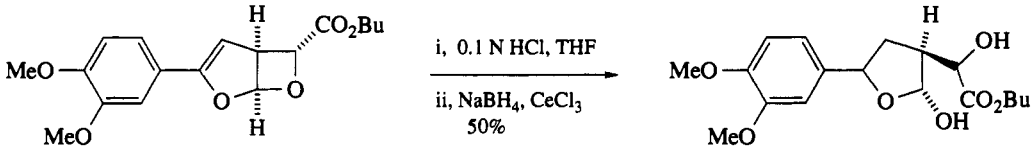
In addition to furan, other heterocycles have been examined.[105] Thiophene undergoes efficient photocycloaddition with benzaldehyde to afford a single *exo* photoproduct (**183**) in 60% yield. As reported by Jones and coworkers,[132] the photolysis of *N*-methylpyrrole in the presence of aldehydes or ketones yields the corresponding 3-hydroxyalkyl derivative (**184**), even when the reaction mixture is free from any trace of acid. In order to use the pyrrole nucleus for stereoselective alkaloid synthesis (*cf.* caesalpinine, **185**)[133] in the fashion developed with the furan nucleus, pyrrole substituents that stabilize the presumed intermediate bicyclic oxetane must be discovered.



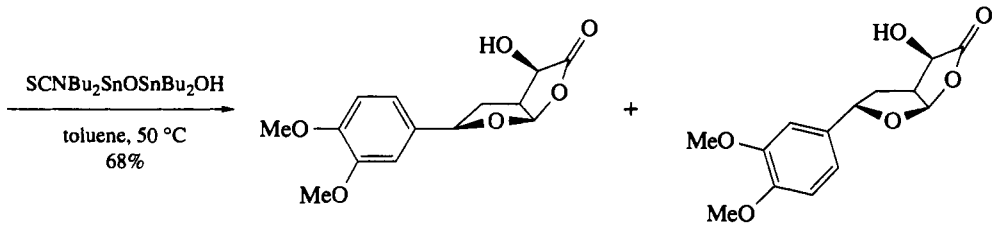
Ginkgolide B | Platelet activating factor | Kadsurenone



(169)

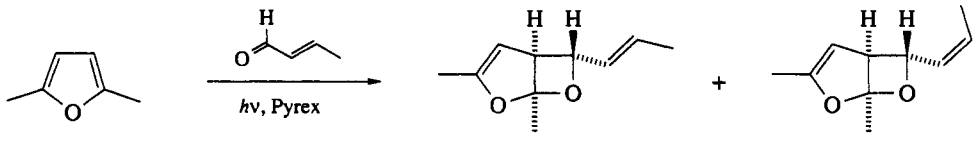


(170) | (171)

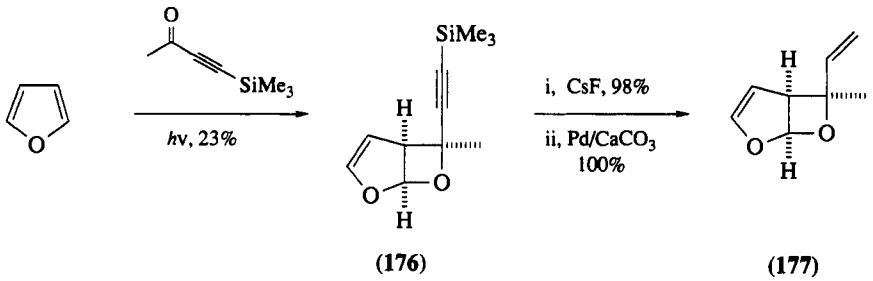


(172) | (173)

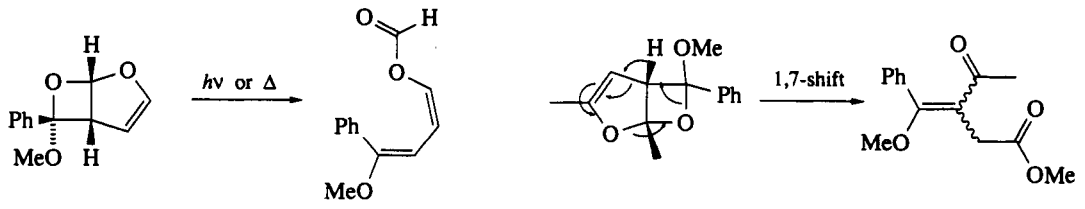
Scheme 20



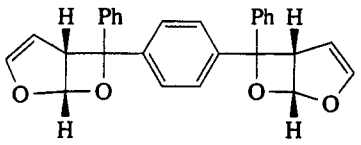
(174) | (175)



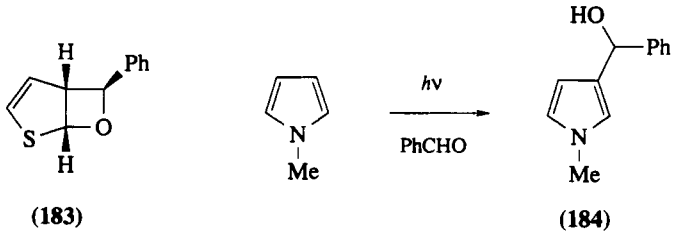
(176) | (177)



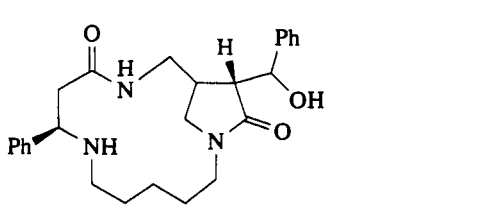
(178) (179) (180) (181)



(182)



(183) (184)



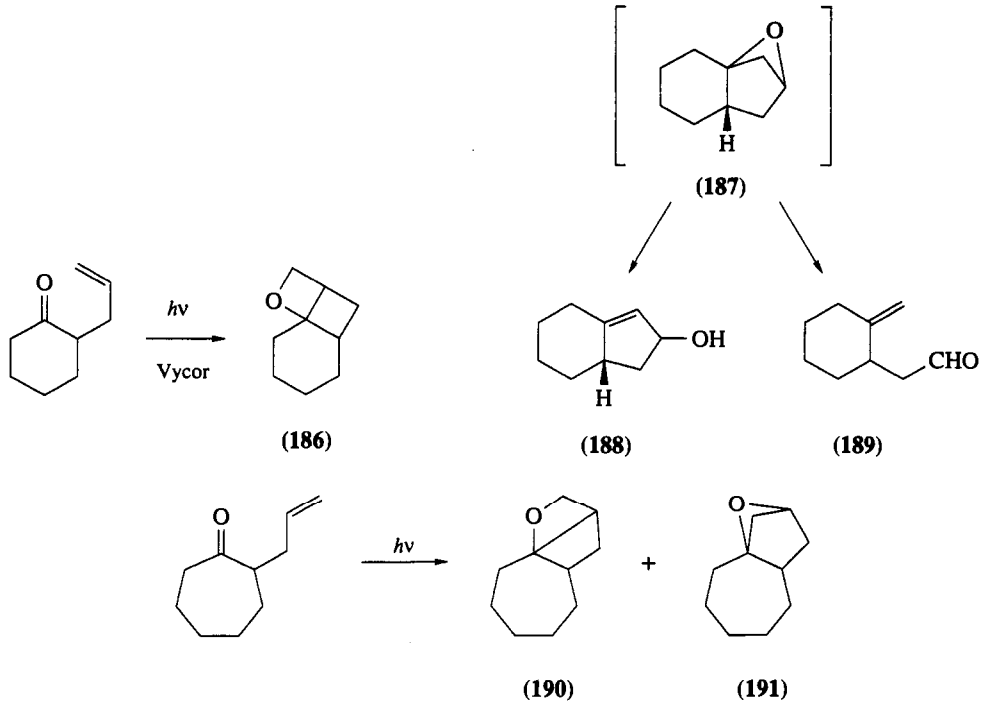
(185) Caesalpinine

2.4.6 THE INTRAMOLECULAR PATERNO–BÜCHI PHOTOCYCLOADDITION

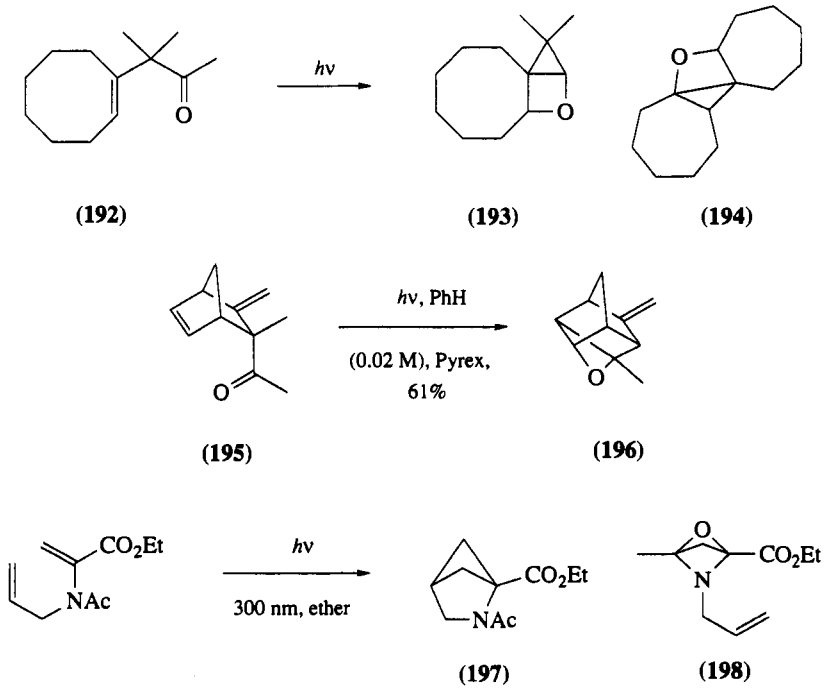
The intramolecular attack of an excited carbonyl on an alkene can occur to provide oxetane products, even in cases when the corresponding intermolecular reaction is unsuccessful. Thus the intramolecular reaction surely benefits from favorable entropic considerations. Jones[4] and Carless[5] have summarized the scope and utility of intramolecular Paterno–Büchi photocycloadditions. There is general agreement that successful implementation of an intramolecular reaction requires that the Norrish type II photoreactions[134] and other hydrogen abstraction processes be overcome. In addition, the intramolecular reaction provides access to polyoxygenated ring systems that can exhibit remarkable properties because of their strain.

Early reports by Kossanyi and coworkers[135] illustrate the variety of strained products that can be obtained from intramolecular photoreactions. For example, irradiation of 2-allylcyclohexanone gave a mixture of (**186**; 32%), (**188**; 22%) and (**189**; 14%), the latter two arising presumably from decomposition of the strained tricyclic oxetane (**187**). In a related azulene synthesis,[136] Kossanyi obtained high yields of oxetanes (**190**) and (**191**), the latter comprising 80% of the reaction mixture. When thermolyzed, compound (**191**) formed a mixture of isomeric dihydroazulene compounds that could be dehydrogenated (Pd/Al_2O_3) to form azulenes.

Engel has reported[137] the synthesis of the strained oxetane (**193**) from the β,γ-unsaturated ketone (**192**), the reaction being facilitated by the high π-electron density of the alkene and a flexible tether, which allows the alkene π- and oxygen *n*-orbitals to become coplanar. A similar oxetane product (**194**) has been made by Cookson and Rogers.[138] Smith and Dieter[139] have reported the chemoselective formation of oxetane (**196**) from ketoalkene precursor (**195**), in which geometrical constraint leads to selective

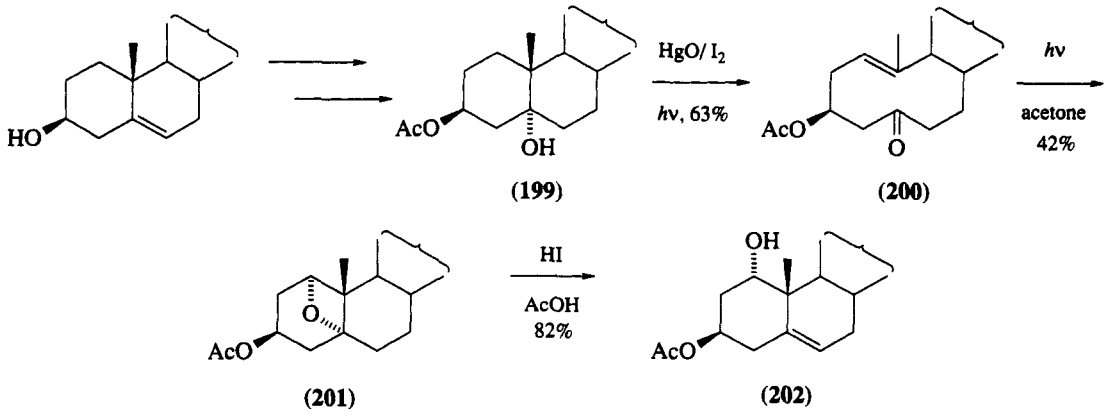


reaction at the remote γ,δ-alkenic site. The curious formation of oxetane (**198**) in the course of a synthesis of 2,4-methanoproline derivative (**197**)[140,141] further attests to the ability of the intramolecular Paterno–Büchi reaction to form oxetane rings more strained than could likely be formed in an intermolecular reaction.



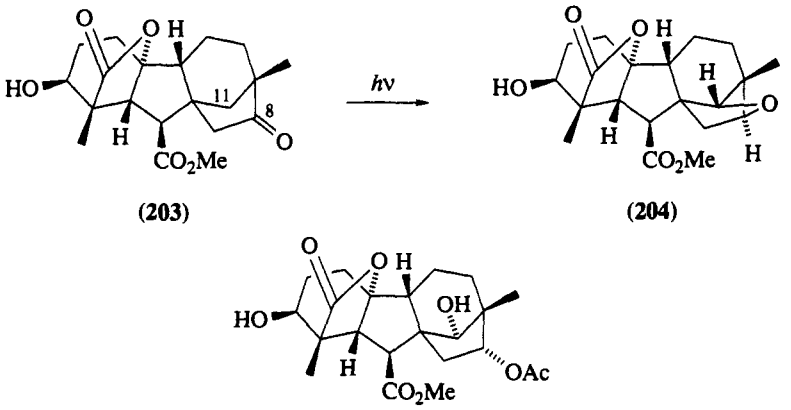
Several reports of transannular Paterno–Büchi photocyclizations have been documented.[142,143] Mihailovi has demonstrated that cholesterol can be hydroxylated indirectly but stereoselectively at C-1 through a Paterno–Büchi reaction, thus allowing access to vitamin D_3 analogues.[143] Scheme 21 illustrates the procedure in which the A–B ring fusion of alcohol (**199**) was first cleaved *via* photochemical hypoiodite

fragmentation to give ketone (**200**). This material was then irradiated in acetone to provide in 42% overall yield the oxetane (**201**), which was converted directly to 1α-hydroxycholesterol 3-acetate (**202**) by acid-catalyzed ring openings. The sequence is notable for its ability to functionalize cholesterol efficiently and with useful chemoselectivity. On a related terpenoid system, Adam and Sung[144] used Norrish type I photocleavage and subsequent photocycloaddition of gibberellin C derivative (**203**) to construct the strained oxetane (**204**). Acid-catalyzed ring opening of (**204**) delivers the C-11 hydroxylated gibberellin derivative (**205**), in which nucleophilic attack has occurred stereospecifically with inversion at C-8.



(199) (200) (201) (202)

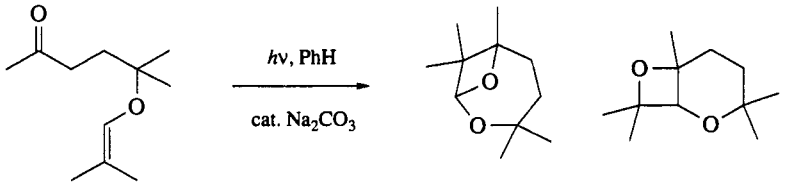
Scheme 21



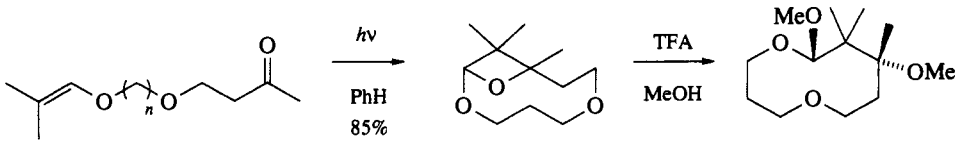
(203) (204) (205)

The intramolecular photocycloaddition has been used in the synthesis of medium and large ring compounds. Carless has described a photochemical route[145] to an analog of the thromboxane A_2 ring system.[146] Irradiation of vinyloxy ketone (**206**) in benzene gave 11% of (**207**) and 54% of the orientational isomer (**208**). Unlike thromboxane A_2,[7] the dioxaoctane (**207**) was stable towards methanol but reacted readily with nucleophiles under acidic conditions. The need for *gem*-disubstitution γ to the carbonyl group for a successful photoreaction was established by irradiation of the demethyl version (**206**), in which Norrish type II photoreactions dominated, illustrating a further limitation of the intramolecular process. In a similar manner, Carless[147] has synthesized the cyclic acetal (**211**) by irradiating seco derivative (**209**) to give the 2-alkoxyoxetane (**210**) which undergoes rapid reaction with MeOH/TFA. Photoaddition of shorter-chain ketone (**212**), on the other hand, gave a 1:1 mixture of oxetane products (**213**) and (**214**) in high yield. In these examples it is worth noting that there are no γ hydrogens, which precludes any Norrish type II photocleavage process. However, a related photochemical synthesis of tetrahydrofuranol and tetrahydrapyranol derivatives uses the Norrish type II photoreaction in the abstraction of δ and ε hydrogens to form useful oxygen heterocycles.[148]

The secochamigrane sesquiterpene laureacetal-C (**215**)[149] provides a fitting introduction to the synthetic applications available to the intramolecular furan–carbonyl photocycloaddition. Initial investigations by Schreiber and Hoveyda used 3-substituted furans as substrates, and many of these were available themselves through the intermolecular photoaldol reaction (Section 2.4.5).[105] For example, irradiation of

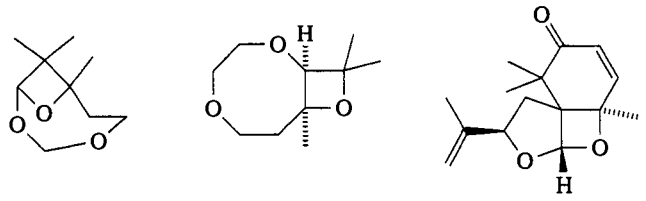


(206) (207) (208)



(209) $n = 3$
(212) $n = 2$

(210) (211)



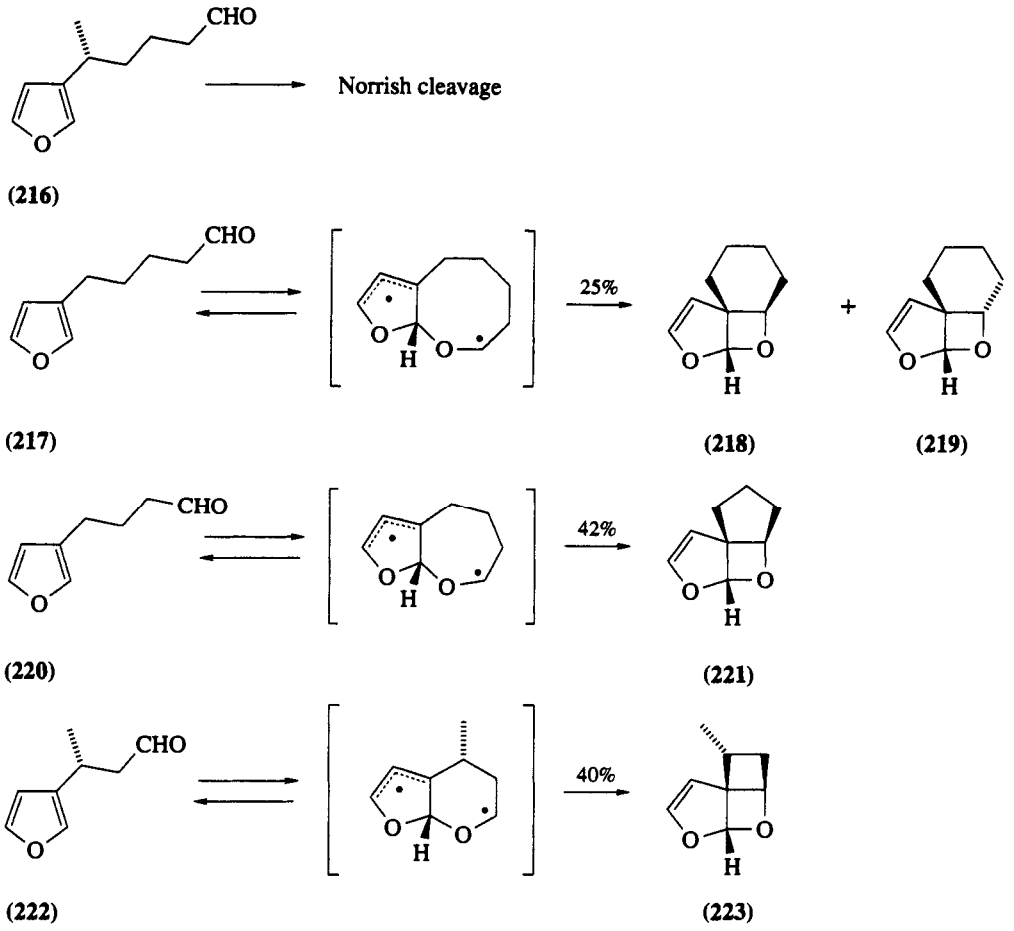
(213) (214) (215)

a 0.1 M solution of furyl aldehyde (**217**) in Pyrex gave as major products the oxetanes (**218**) and (**219**) in a 3:2 mixture (Scheme 22), with Norrish cleavage occurring to the extent of only about 10%. Aldehyde (**216**), on the other hand, gave solely Norrish type II cleavage, illustrating the dramatic effect of substitution. In a study of five-membered ring carbocycle formation, aldehyde (**220**) was irradiated and formed a single stereoisomeric photoadduct (**221**) in 42% yield (*ca.* 5% Norrish cleavage). By comparing the expected diradical intermediates (eight- *versus* seven-membered rings), the increased yield (**221**) relative to (**219/218**) can be understood. Even the highly strained product (**223**) could be obtained by irradiation of (**222**), presumably because of the ready formation of a six-membered ring intermediate diradical.

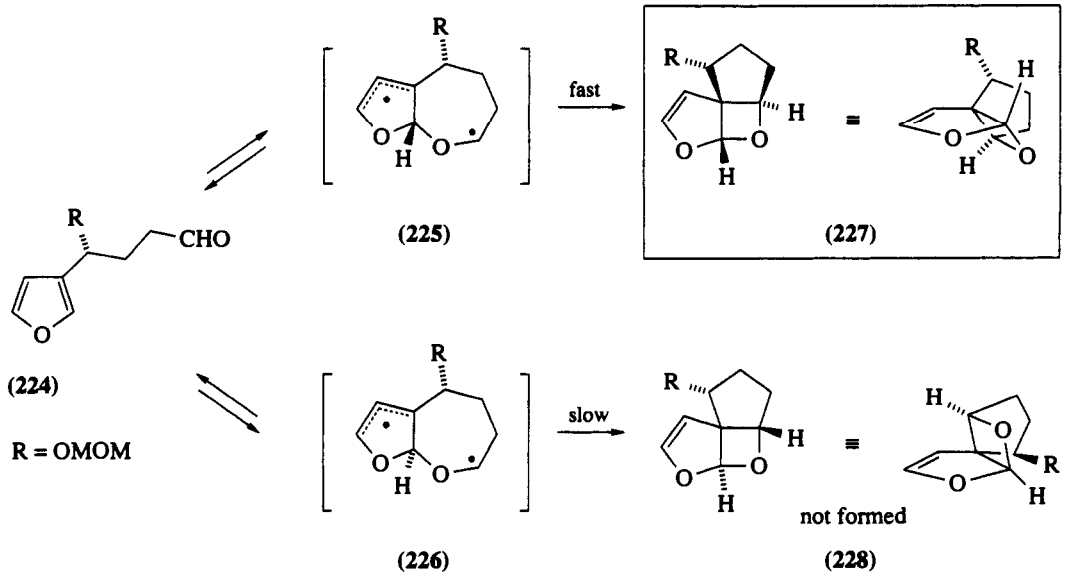
Synthesis of similarly strained β-lactam products has been reported by Aoyama and coworkers.[150] Asymmetric induction by an α-furyl stereocenter was demonstrated by irradiation of compound (**224**) in benzene to form photoproduct (**227**) as a single stereoisomer (Scheme 23). Molecular models indicate that the transition state leading to the alternative stereochemistry (**228**) would be destabilized by steric interaction between the MOM ether and ketal hydrogen,[151] which may explain the high degree of facial selectivity in the reaction. The suggestion was made that the initial carbon–oxygen bond formation is reversible.[105] Although diradicals (**225**) and (**226**) may be formed with little selectivity, the rate of coupling of diradical (**226**) is expected to be considerably slower than that of diradical (**225**).

In contrast to intermolecular photoaldols, which can be manipulated with facility, intramolecular cycloadducts undergo retro-[2 + 2] cycloaddition when subjected to hydrolytic conditions. In an alternative protocol, oxymercuration of (**229**) afforded α-mercurio ketone (**230**; 42%) which was acetylated under standard conditions to provide 1,4-diketone (**231**) quantitatively.[152] Similarly, epoxidation of (**229**) provided functionalized photoaldol (**232**), which was hydrolyzed and acetylated to form α-acetoxy derivative (**233**). Finally, hydrolysis of (**234**) (4:1 THF/0.1 N HCl) gave lactol (**235**) in nearly quantitative yield, illustrating the utility of the intramolecular furan carbonyl photocycloaddition in spirocycle formation.

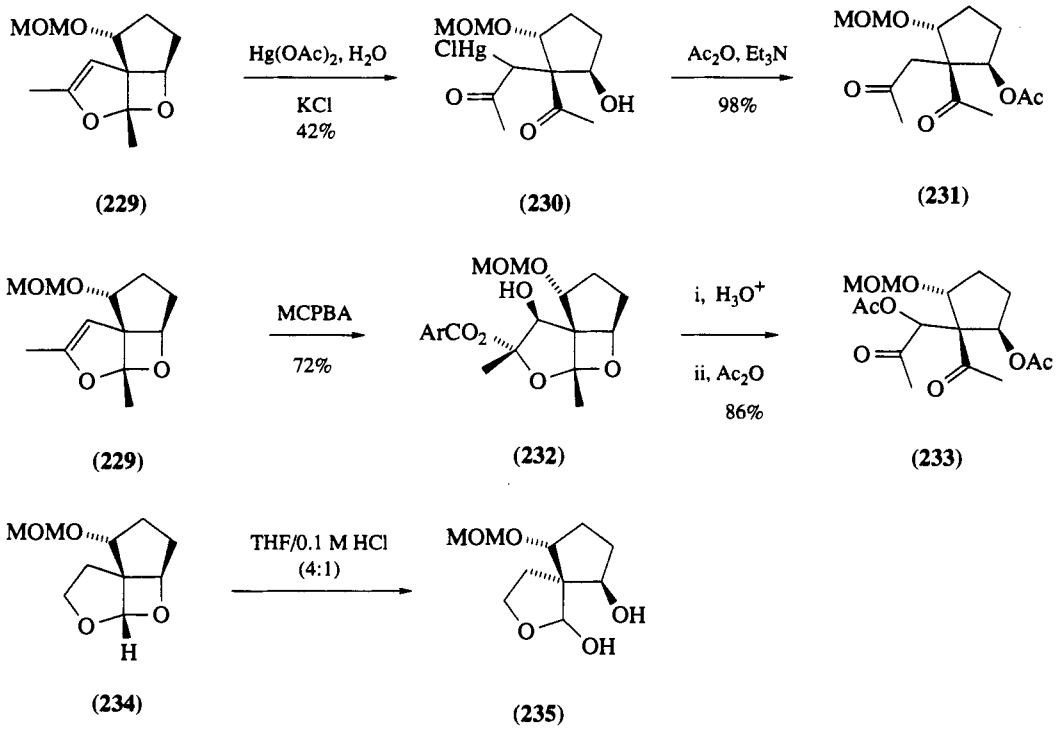
Intramolecular Paterno–Büchi reactions of imides with alkenes provide some interesting examples of oxetane formation and rearrangement.[153] Photolysis of cyclic imide (**236**) gave quantitatively oxetane (**237**) which, upon treatment with aqueous acid, underwent fragmentation to amide (**238**), illustrating a potentially useful medium-membered ring synthesis.[154] Mazzocchi has reported[155] that irradiation of an acetonitrile solution of the phthalimide (**239**) produces (**240**), possibly through an oxetane intermediate. A similar photolysis[156] of substrate (**241**) in 8:1 $MeCN/H_2O$ gave, in a 17:43 ratio, δ H-abstraction product (**243**) and spiroazepinedione (**244**), both resulting from initial intramolecular formation of an oxe-



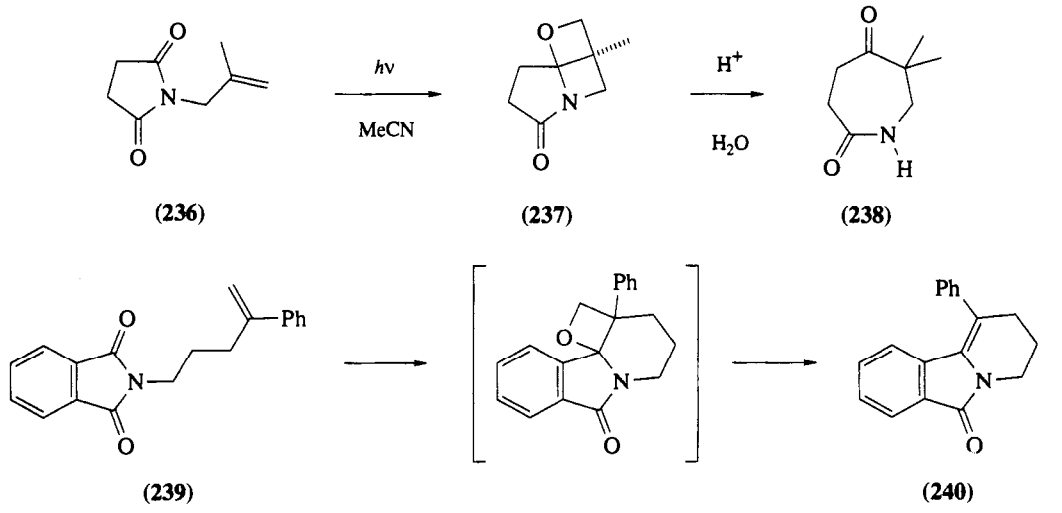
Scheme 22 Efficiency of intramolecular photocycloadditions



Scheme 23 Intramolecular photocycloaddition: asymmetric induction



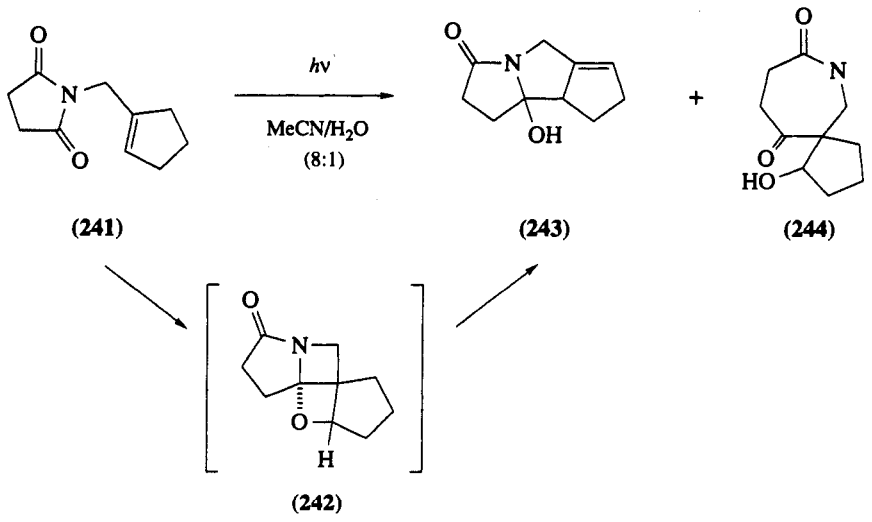
Scheme 24 Functionalization of intramolecular photoproducts



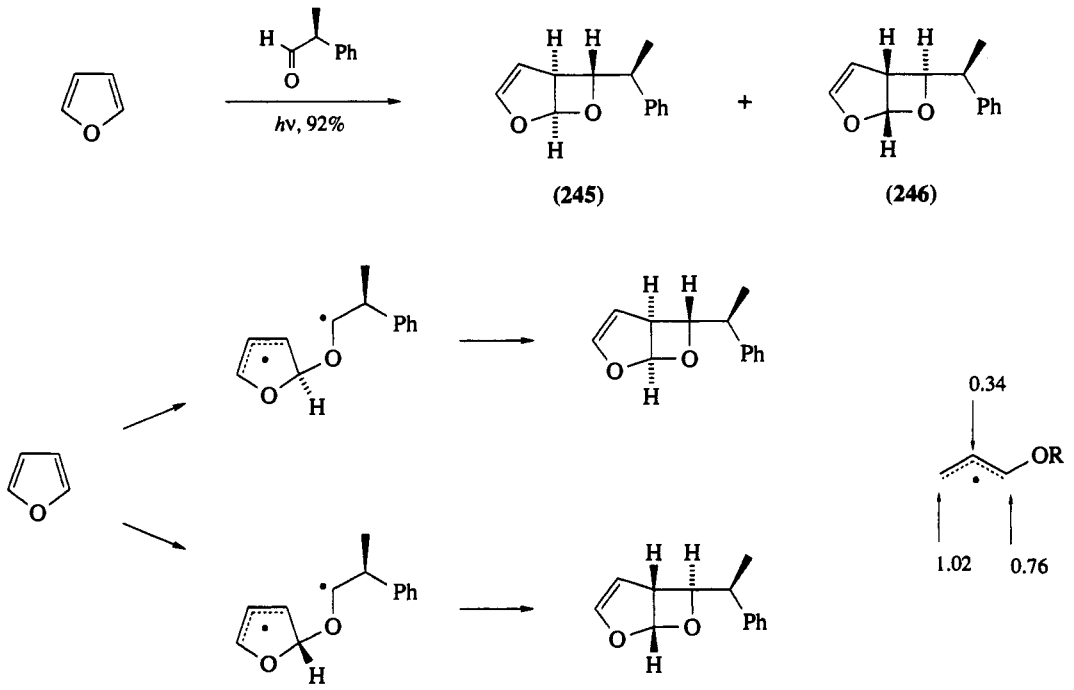
tane, followed by heterolytic cleavage and transannular ring-opening of spiroazetidine intermediate (**242**).

2.4.7 EXCITED-STATE ASYMMETRIC SYNTHESIS[157] USING THE PATERNO–BÜCHI PHOTOCYCLOADDITION

In a previous section (Section 2.4.5), it was noted that the photoreaction of aldehydes containing an asymmetric center adjacent to the carbonyl with furan results in the production of a 1:1 ratio of two *exo* photoproducts. Irradiation of 2-phenylpropanal and furan results in a nearly quantitative yield of *exo* photoproducts (**245**) and (**246**) in approximately a 1:1 ratio. This suggests a mechanism that is insensitive to the substitution pattern of the aldehyde; one such mechanism is depicted in Scheme 25. Reaction of an excited carbonyl and the electron-rich furan proceeds with initial carbon–oxygen bond formation to pro-



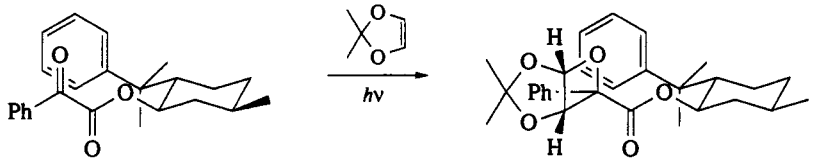
duce either of two diradical species. The newly formed asymmetric center is now in a 1,4-relationship the stereocenter α to the carbonyl and is not expected to exert much influence as a stereocontrol device. Since each cyclization produces a *cis* ring fusion with an *exo*-substituted side chain, the reaction proceeds to form photoproducts in which the stereocenter on the side chain is of no consequence in initial acetal formation or the final diradical ring closure. The site-selectivity of diradical ring closure may be related to the free valency index of the incipient diradical intermediate.[121] The free valency index provides an indication of the amount of π-bonding that is available at each atom of the π system. Scheme 25 also shows a simple Hückel molecular orbital calculation for the 1-methoxyallyl radical and the values of the free valency index at the three carbon centers. The calculation indicates that bond formation with carbon-based radicals would be favored at the C-3 position (oxetane formation), since bonding at C-1 would involve a greater loss of the π-bonding character present in the furanyloxyallyl radical intermediate.



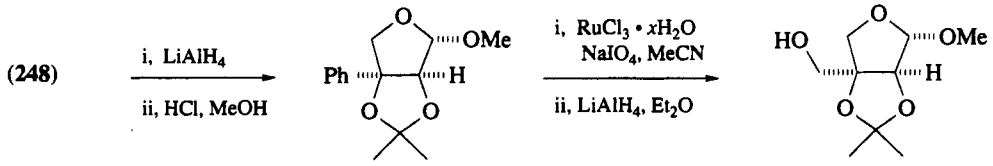
Scheme 25

A direct solution to the problem of enantioselective furan–carbonyl photoproduct synthesis would require a photoaddition that proceeded with enantiofacial selectivity in the aldehyde or furan component and maintained the relative face selectivity that is intrinsic to the reaction. Preliminary work used host–guest chemistry to achieve this objective.[124,158] In aqueous dioxane, a 1:1:1 inclusion complex of unmodified β-cyclodextrin, furan and benzaldehyde is formed. Upon irradiation (Hanovia 450 W lamp, Vycor filter), a rapid photoaddition occurs to afford a photoproduct of 10–20% *ee*.

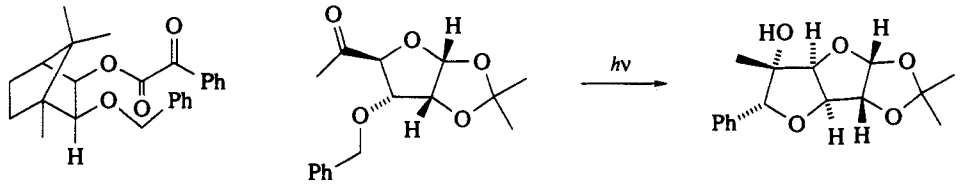
Despite the limited number of examples available on asymmetric induction in the furan–carbonyl photocycloaddition, workers have nonetheless been interested in learning to apply the methods of asymmetric synthesis to the Paterno–Büchi reaction. An early report by Gotthardt and Lenz[159] of optical induction in thietane synthesis using a chiral menthyl methacrylate derivative encouraged examination of the Paterno–Büchi reaction.[160] Optically active phenylglyoxylic (–)-menthyl ester undergoes cycloaddition to 2,3-dimethyl-2-butene to form a diastereomeric mixture, which upon hydrolysis of the chiral auxiliary gave oxetane product with 53% enantiomeric excess. Scharf and coworkers[161] have investigated the effect of chiral auxiliaries on the diastereoselectivity of oxetane formation. Among the cases studied, the phenylglyoxylic acid derivative (**247**) was optimal and gave high *endo* phenyl selectivity.[162] The *endo* selectivity is not a result of the chirality of the ester, as it is also observed in the achiral methyl ester case. Lithium aluminum hydride reduction of adduct (**248**) allows complete recovery of the auxiliary; subsequent acid-catalyzed transacetalization forms furanose (**249**), which is oxidized under the conditions of Sharpless[163] ($RuCl_3 \cdot xH_2O/NaIO_4$) and then reduced with $LiAlH_4$ in ether to form β-1-apiofuranoside derivative (**250**). Side reactions due to the chiral auxiliary were uncovered when attempted use of keto ester (**251**) resulted in competitive transannular photochemical cyclization, indicating a favorable stereochemical arrangement of keto carbonyl and benzylic hydrogens. A similar process has been noted by Araki and coworkers in the photoreaction of hexafuranos-5-ulose derivative (**252**) to form cyclized derivative (**253**).[164]



(247) (248)



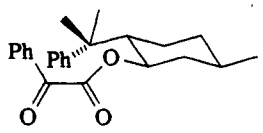
(249) (250)



(251) (252) (253)

Chiral induction in the photochemical reactions of phenylglyoxylic ester (**247**) can be explained by *re* face addition of the alkene to the keto carbonyl in a roughly *s-trans* conformation (**254**).[165] The conformational mobility of the α-keto ester subunit has been implicated by the readiness with which these compounds undergo Norrish type II cleavage, a carbonyl–carbonyl torsional angle of 180° being optimal.[166] In order to understand better the role of the phenyl group in photoreactions of (–)-8-phenylmenthyl glyoxylate derivatives, a crystal structure (–)-(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl phenylglyoxylate was obtained (Figure 3).[167] In the solid state the molecule adopts a conformation wherein the phenyl group is rotated away from the reactive α-keto ester. In addition, the keto carbonyl

points towards the C-8 methyl group of the phenyl menthyl moiety (torsional angle −103.3°), while the ester carbonyl is nearly parallel to the C-1—H bond (deviation 23.2°). The twisting of alicyclic diketo-carbonyl derivatives is well studied,[168] and the UV absorption of the carbonyls has been found to depend on the angle between carbonyl planes. The crystal structure of the (–)-menthyl *p*-bromophenylglyoxylate, shown in Figure 4 for comparison,[169] reveals a similar conformation, except for the reversed sign of the dihedral angle between carbonyl groups (+104°, average of four independent molecules in the unit cell) with the keto carbonyl pointing away from the isopropyl hydrogen.



(254)

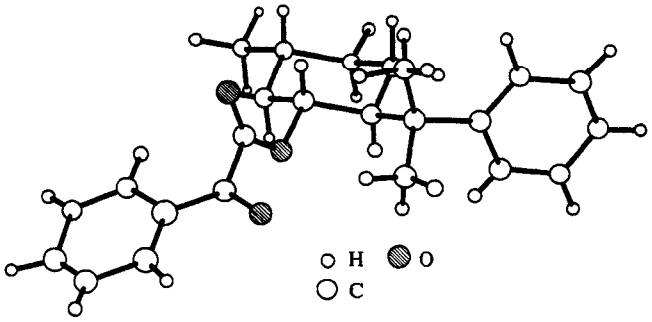


Figure 3

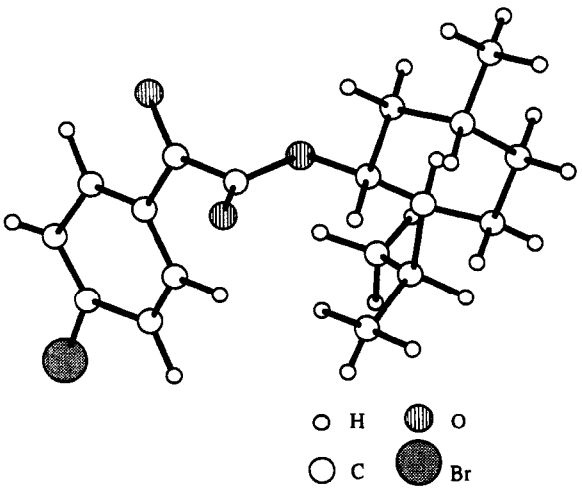
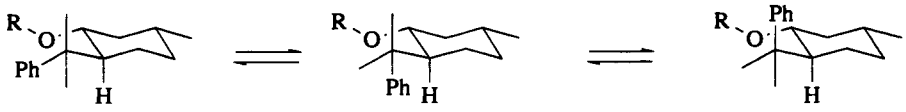


Figure 4

A combination of ^{1}H and ^{13}C NMR showed that a mixture of solution conformations exists. The relative proportion of conformer (**255a**) (P_a) is found to be increased by adding hydrogen-donating solvents and lowered by hydrophobic solvents such as benzene, which indicates that conformation (**255a**) allows for maximum dipole–induced-dipole interaction between keto and aromatic moieties.[170] Although the solid-state conformation of these glyoxylates may not be relevant to solution photochemistry, a difference in solid-state keto orientation may provide insight into the origin of the observed decrease in diastereoselectivities obtained with nonaromatic face-differentiating groups.

A model for stereoselection that has been developed from the analyses of face-discriminating Paterno–Büchi reactions has been reported by Scharf and coworkers.[171] Isoselective relationships[172] were ob-



(255a) (255b) (255c)

served in Eyring plots to change considerably with different chiral auxiliaries and alkenes. Figure 5 shows the isoselective relationship for three phenylglyoxylates (**256a–c**) in photochemically induced oxetane formation with furan. The rate constants k and k' for the formation of diastereomeric oxetanes were found to be highly temperature dependent. In all cases a characteristic inversion temperature (T_{inv}) was noted, and the plots were strictly linear on either side thereof. The existence of inversion temperatures implies that a different selection step dominates in each temperature region. In the low-temperature region, $T < T_{inv}$, entropy-determined selection for the formation of 1,4-diradicals was noted. In the diradical intermediate, energetically unfavorable conformations undergo predominantly retrocleavage instead of ring closure, which results in diastereoselectivity. For $T < T_{inv}$, increase in temperature increases the rate of heterocleavage. In the high-temperature region, $T > T_{inv}$, selection is determined largely by enthalpy. The diastereomeric excess in this region is controlled predominantly by the steric effects of the chiral auxiliaries.

In a related study, Scharf and coworkers have studied isoselectivity relationships in the asymmetric Paterno–Büchi reaction using carbohydrates as chiral auxiliaries.[173] D-Glucofuranose derivative (**257**) underwent photocycloaddition with furan to give an oxetane product in 79% chemical yield, and the stereoselectivity depended linearly on temperature (48% *de* at 20 °C, 70% *de* at –78 °C). The reaction with benzylidene derivative (**258**), on the other hand, gave an oxetane photoproduct in 80% chemical yield and 80% diastereomeric excess upon irradiation at room temperature, but showed linear isoselectivity to produce photoadduct of approximately 75% diastereomeric excess at –78 °C. Cyclohexylidene (+)-galactopyranose compound (**259**) gave an oxetane product of only 6% *de*; previous use of this auxiliary in asymmetric amino acid synthesis[174] involved the use of metal ion chelation to enforce conformational rigidity in the system. The discovered competition between enthalpy- and entropy-determined partial selection steps is very likely general; thus consideration of mechanism may allow for rational optimization of photocycloaddition diastereoselectivity, which bodes well for the future of asymmetric photocycloadditions.

2.4.8 SUMMARY

The Paterno–Büchi [2 + 2] photocycloaddition is becoming increasingly popular as a method for the synthesis of chiral molecules with multiple functionality. Investigations of reaction mechanism have been fruitful and have led quickly to improved procedures and interesting applications. For example, it is through these studies that radical intermediate trapping techniques were developed, and that the temperature dependence of reaction diastereoselectivity was explained. Since photoreactions can be performed on multigram scale and often proceed in high yield and with stereocontrol, these reactions are quite useful and merit special consideration in the early steps of a complex molecule synthesis. Stereocontrolled syntheses of four-membered ring photoproducts have provided efficient, concise syntheses for a number of chemical transformations resulting in the synthesis of naturally occurring substances and analogs, including of carbohydrates and mycotoxins. Further advancements in the Paterno–Büchi process will surely come from the exploitation of the entropic favorability of intramolecular photocycloadditions and a more widespread knowledge of the potential of photochemical, asymmetric synthesis. As an entry point in complex molecule synthesis, the Paterno–Büchi reaction offers the possibility of concise and economic solutions to problems in synthesis involving naturally occurring molecules and also target systems containing modified functionality.

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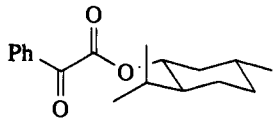
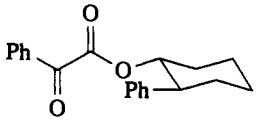
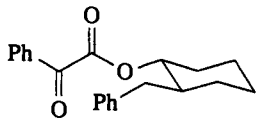


(256a)



(256b)



(256c)

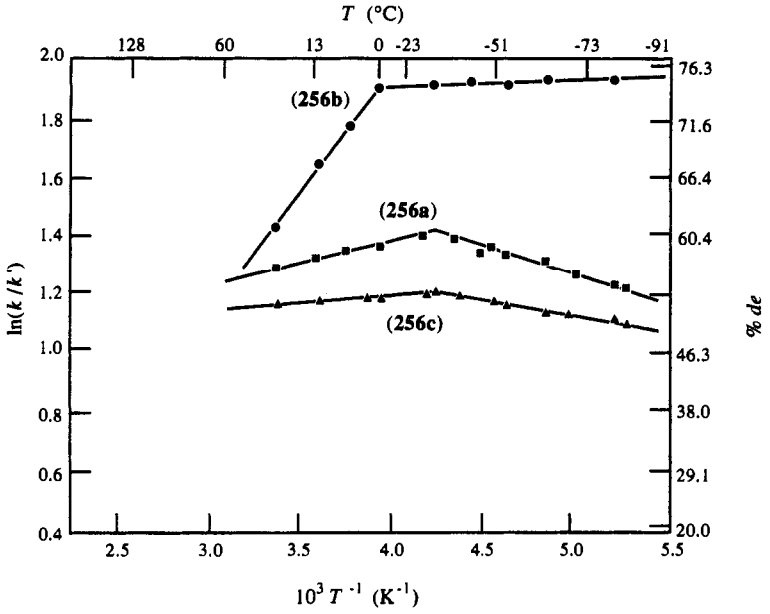
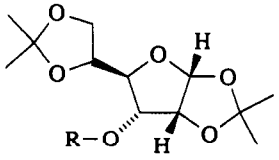
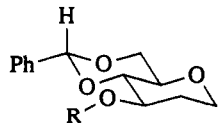


Figure 5



(257)



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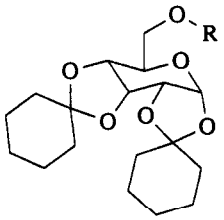

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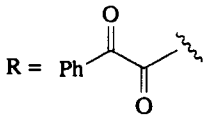

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2.5
Di-π-methane Photoisomerizations

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2.5.1 INTRODUCTION

2.5.1.1 Historical Remarks

The term di-π-methane rearrangement is meant to describe the photoisomerization of 1,4-dienes (*i.e.* two π-systems separated by a methane unit) leading to vinylcyclopropanes. The reaction can be generalized in schematic form as in equation (1). As will be discussed more specifically in the section dealing with mechanism, such a simplistic presentation is not intended as the actual reaction path, but it greatly helps in predicting the reaction products.

(1)

The di-π-methane rearrangement was discovered and conceptually developed by H. E. Zimmerman (University of Wisconsin), one of the earliest examples being the photoisomerization of barrelene (**1**) into semibullvalene (**2**) (equation 2). Through intensive subsequent work, this photoreaction was shown to be quite general for 1,4-dienes. In view of the major contributions by the original author, the rearrangement is also referred to as the Zimmerman rearrangement.

(2)

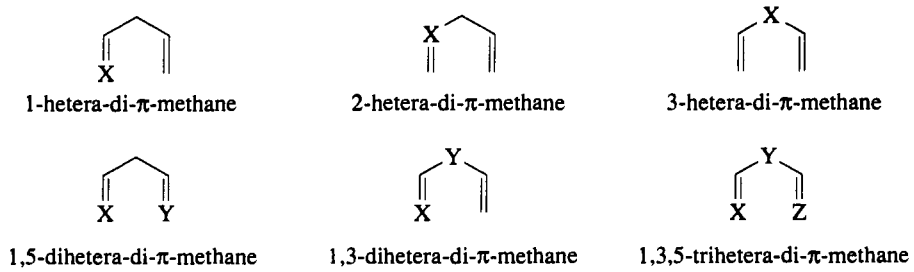
(1) (2)

The 1,4-diene moiety can include atoms other than carbon. Particularly common are oxygen and nitrogen (see later in this chapter and in Chapter 2.6).

Prior to Zimmerman's recognition of the generality of the reaction scheme outlined in equation (1), other photorearrangements falling into the di-π-methane category had been observed. Most of these examples have already been reviewed.[1] The mechanism of the reaction has also been studied in detail for several systems and carefully scrutinized.[2–4]

2.5.1.2 Nomenclature

Owing to the numerous possibilities in which a 1,4-diene can be assembled, especially when heteroatoms are included, a nomenclature issue arises that needs to be addressed from the outset. According to the Hantzsch–Widman nomenclature system in combination with the IUPAC rules,[5] hetera-di-π-methane reactions are those transformations in which a particular heteroatom replaces the carbon atom of the 1,4-diene moiety; the position is specified by means of a numerical prefix. We will use this suggested nomenclature for the di-π-methane photorearrangement as indicated for the substrates shown in Scheme 1.



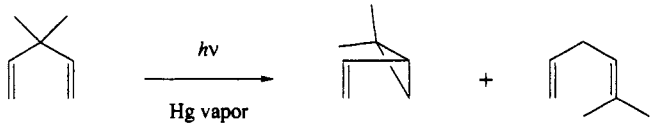
Scheme 1

2.5.2 SCOPE

2.5.2.1 Acyclic 1,4-Dienes

Study of the di-π-methane rearrangement of the parent system is hampered by the low extinction coefficient of the 1,4-pentadiene chromophore. In the practical wavelength ranges, this substrate does not possess a useful chromophore besides the unconjugated π-bonds. The effective wavelength is too energetic so that side products, usually arising from radical chemistry with the solvent, are observed. For this reason the original photoreaction of the parent system was carried out under conditions of mercury sensitization and vapor phase irradiation.[6]

Sensitization by mercury is useful for performing the photoreaction on all those 1,4-dienes that lack chromophoric groups, *e.g.* alkyl and/or cycloalkyl substituted systems. These reactions appear to proceed by triplet energy transfer from the mercury to give vibrationally exited diene triplets. Thus, at variance with solution phase photoreactions, the exited states possess greater vibrational energy and substantially different products are possible. While such comparison is impossible for the parent system because no solution phase photochemistry has been reported, the di-π-methane product (**4**) was not observed when irradiation of the 3,3-dimethyl-substituted diene (**3**) (equation 3) was carried out under acetone sensitization in solution. Hydrocarbon (**4**) was the major component under mercury-sensitized conditions in the vapor phase.[7]

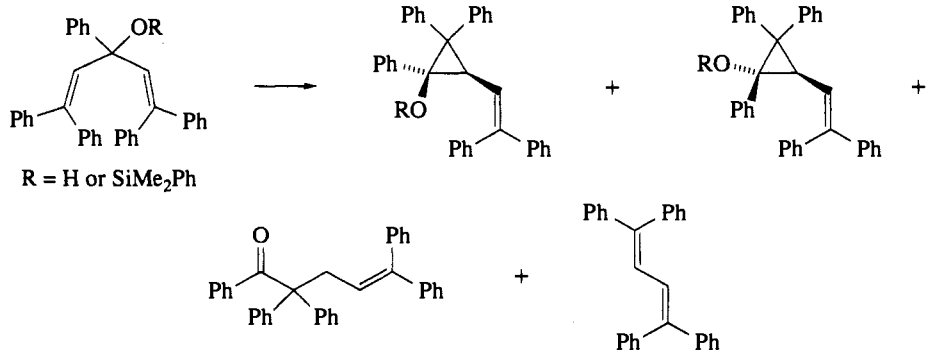


(3) (4) (3)

More recently, the parent system has been investigated under radio frequency plasma conditions. The plasma generated by an electric discharge provides an unusual medium for reactions in the gas phase. The free electrons that are present in the plasma are responsible for the chemical reactions that take place. The electrons are accelerated by an applied electric field and collide with the molecule, thereby activating it for the reaction. Most procedures employ radio frequency (RF) discharges so as to keep the pressure, temperature and energy of the system relatively low. The substrate is usually volatilized into the plasma zone with residence times of the order of a second. Because there is no need of chromophores, the technique has been used to activate those cases that are inert to the normal photoexcitation in solution, *e.g.* the parent 1,4-pentadiene.[8]

It is worth mentioning that direct irradiation of molecules possessing low extinction coefficients at standard wavelengths ($\lambda < 250$ nm) can be accomplished at 185 nm.[9]

Aryl substitution produces a bathochromic shift on 1,4-pentadienes so that standard reaction conditions (in solution at $\lambda > 250$ nm) can be applied. The reaction of equation (4) shows one of the latest examples aimed at understanding the effect of an hydroxy or alkoxy function at the 3-position on the photorearrangement.[10] In the case of the free hydroxy group, two secondary photoproducts were observed besides the two expected vinylcyclopropanes. At variance with this observation, no secondary photoproducts were detected for the phenyldimethylsilyloxy substituent. Direct or benzophenone-sensitized irradiation did not cause significant variation in the reaction products.

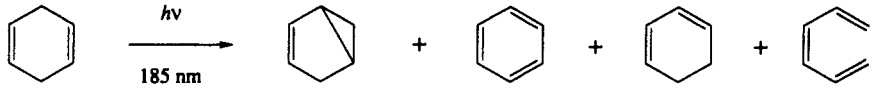


(4)

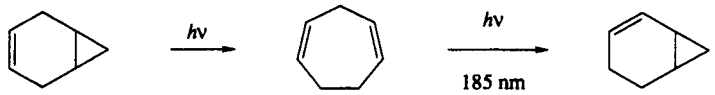
2.5.2.2 Cyclic Dienes

By cyclic dienes are implied those systems in which at least one of the two π-bonds is part of a ring, excluding aromatic rings which will be treated in Sections 2.5.2.4 and 2.5.3.2.

Unsubstituted cyclic dienes, such as 1,4-cyclohexadiene, which contain both double bonds in the same ring, possess very low extinction coefficients at standard wavelengths. The reaction can be carried out by mercury sensitization[11] or under direct irradiation at 185 nm (equation 5).[12] The next higher homolog, *i.e.* 1,4-cycloheptadiene, can be generated in the photolysis of bicyclo[4.1.0]hept-3-ene (**5**) and further transformed into the expected di-π-methane product (**6**) at 185 nm (equation 6).[13]

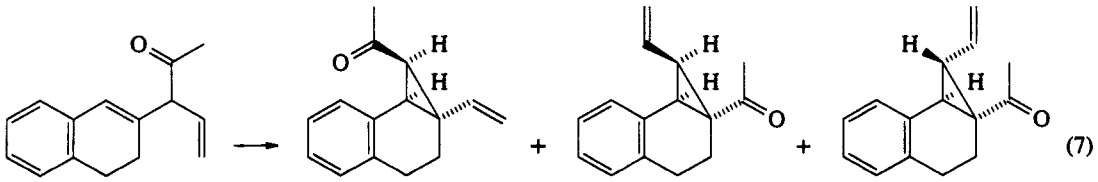


(5)



(6)

When only one of the two double bonds is part of a ring, there are many possible combinations; these have already been reviewed.[1–4] A recently reported representative example involves the photochemistry of (**7**), which contains both the aryl and the acetyl chromophores (equation 7).[14] The observed products arise both from the standard di-π-methane and oxa-di-π-methane rearrangements.

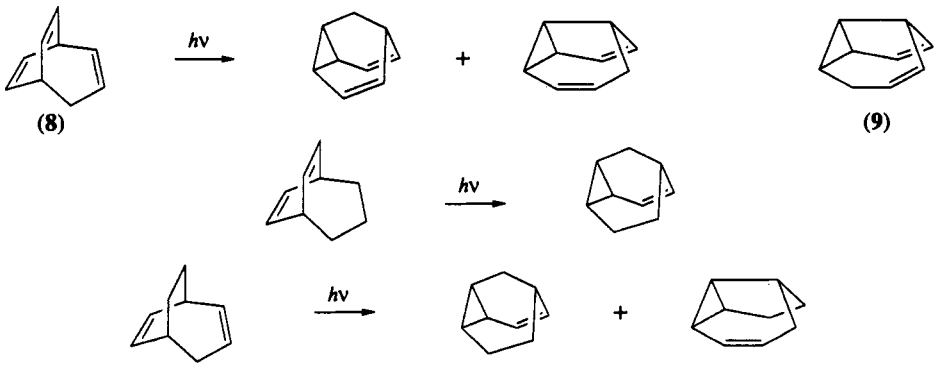


(7)

(7)

2.5.2.3 Polycyclic Dienes

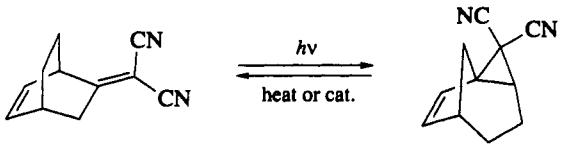
Polycyclic dienes are probably the best represented class of substrates for the di-π-methane rearrangement. The rigid geometry of these molecules places the reacting double bonds in closer proximity, thus allowing for more efficient through-space interaction than is present in acyclic or monocyclic dienes due to conformational mobility. Among the latest examples, the photoisomerization of bicyclo[3.2.2]nona-2,6,8-triene (homobarrelene; **8**) and its dihydro derivatives, which lead to the products illustrated in equation (8), has been reported.[15] The absence of valence tautomer (**9**) in the photoreaction of (**8**) has been attributed to geometrical causes.



(8)

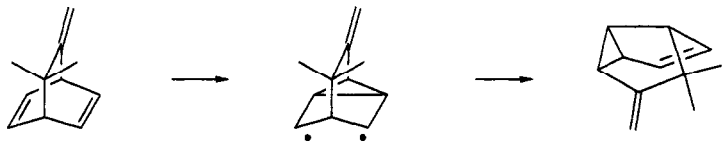
The di-π-methane photoisomerization also occurs with high efficiency when one of the two double bonds is exocyclic.[1–5] A significant effect is exhibited by dicyano substitution on the exocyclic double bond.[16,17] For example, 5,5-dicyanomethylenebicyclo[2.2.2]oct-2-ene (**10**) gives upon direct irradiation

good yields of the highly strained di-π-methane product (**11**).[16] Upon heating or in the presence of catalysts (*e.g.* SiO_2), the latter is quantitatively isomerized back to the starting diene (equation 9).



(10) (11) (9)

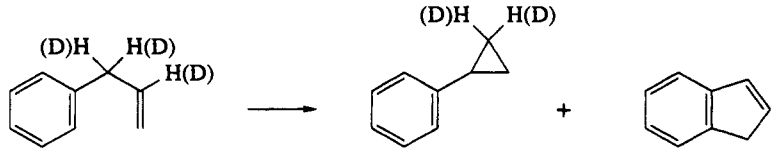
When both the endocyclic and exocyclic systems are present as in (**12**), reaction occurs only at the endocyclic di-π-unit to afford (**13**) (equation 10).[18] Deuterium labeling experiments revealed that this di-π-methane product can be rationalized by postulating the cyclopropyldicarbinyl diradical (**14**) as intermediate.



(12) (14) (13) (10)

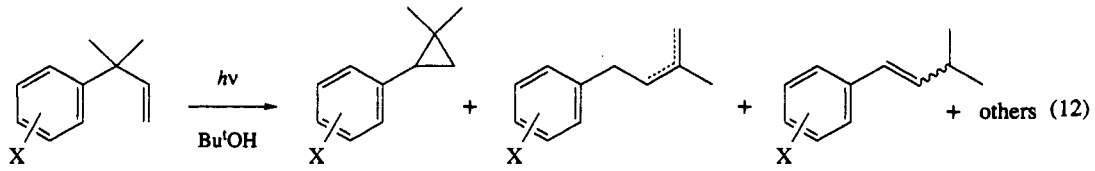
2.5.2.4 Benzo and Dibenzo Systems

The di-π-methane rearrangement readily occurs when one of the two π-bonds is part of an aromatic ring. The aromatic ring substantially increases the extinction coefficient of the substrate and, as expected, these reactions are usually quite efficient, except for the parent system 3-phenylpropene. Indeed, 3-phenylpropene is reported not to photorearrange to di-π-methane products under standard photochemical conditions in solution, but to give the expected vinylcyclopropyl product under RF-generated plasma reaction conditions (equation 11).[8] In the plasma reaction, indene is also produced. The 2-deuterio-substituted analog gave 1-phenyl-1-deuteriocyclopropane, suggesting a reaction pathway consistent with the di-π-methane rearrangement, and thus ruling out the possibility of a 1,2-hydrogen shift.



(11)

Methyl-substituted arylpropenes afford the expected cyclopropanes, but the latter undergo facile ring opening to the corresponding aryl-substituted butenes (equation 12).[19]



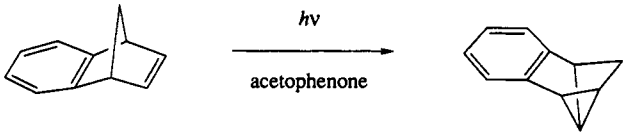
(12)

X = *p*-MeO, *m*-MeO, *p*-CN, *m*-CN

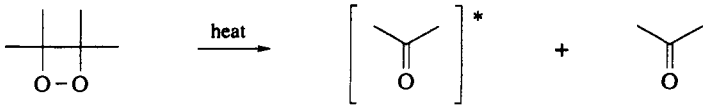
A minimal structural feature for di-π-methane rearrangement of acyclic arylpropenes to occur in solution appears to be the presence of an additional phenyl group.[1-5] A similar requisite seems valid also for cyclic 1,4-systems such as indenes, while the scope for 1,4-dihydronaphthalenes is uncertain.[1-5]

In comparison with acyclic and cyclic substrates, polycyclic systems are far more reactive. The di-π-methane unit *par excellence* is benzonorbornadiene, which affords on triplet sensitization the tricyclic product (**15**) (equation 13).[20] The favorable geometry of this substrate, which by virtue of the methylenic bridge possesses the two π-bonds fixed at an optimal interacting distance, is largely responsible for the

increased reactivity. Interestingly, this di-π-methane photoisomerization can be achieved thermally in the presence of 1,2-dioxetanes.[21] Since the latter decompose thermally to give preferentially triplet state carbonyl fragments (equation 14), such a chemically energized transformation provides rigorous confirmation that the di-π-methane rearrangement of benzonorbornadiene[20] is triplet sensitized.

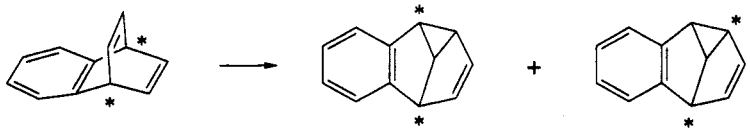


(15) (13)



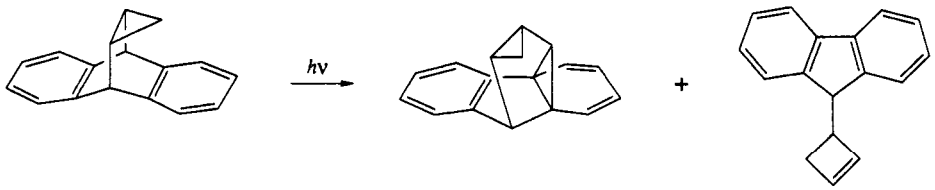
(14)

Bridges other than methylene, *e.g.* those present in benzobarrelene and its dihydro derivative, also provide for reactive di-π-methane systems.[1–5] In the benzobarrelene case, aryl–vinyl or vinyl–vinyl bonding is possible. As shown in equation (15), the products derived from these two pathways are distinctive for the labelled substrate. This aspect has been studied for several barrelenes containing different aromatic groups, including naphthalene (both at the 1,2- and 2,3-positions), anthracene, *etc.*[2] The observed products are rationalized most frequently *via* vinyl–vinyl bridging.[2] Similar behavior is exhibited by dibenzobarrelene[22] and related systems.[2,3]



(15)

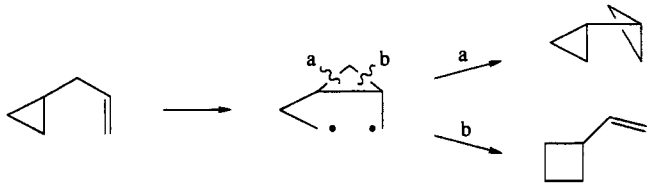
Di-π-methane products arising from aryl–aryl bonding are much more rarely observed. In these cases, the aromaticity of one aryl group has to be sacrificed in the final di-π-methane product. A well studied system is shown in equation (16).[23]



(16)

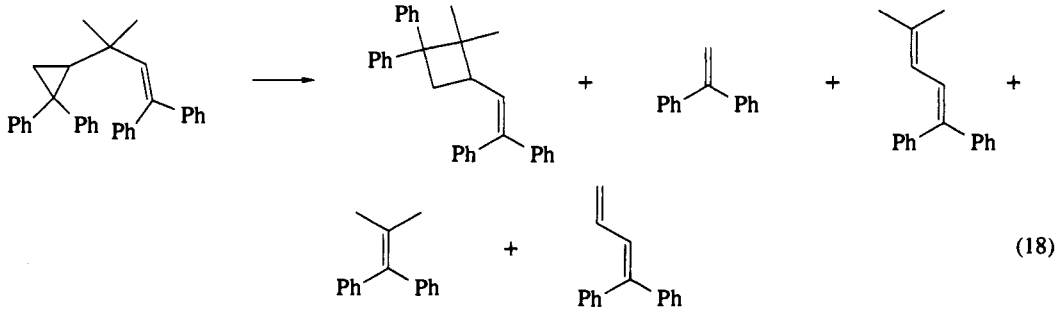
2.5.2.5 Cyclopropyl-π-methane Rearrangements

In this case, one of the two π-bonds is a cyclopropane unit and a vinyl cyclobutane is formed (equation 17), the photorearrangement still resembling closely the di-π-methane process of equation (1). Such an unsymmetric substrate should in principle afford, besides the cyclobutane (path b), also dicyclopropane (path a) by opening of the other σ-bond in the cyclopropyl diradical intermediate; this pathway has not been observed so far.



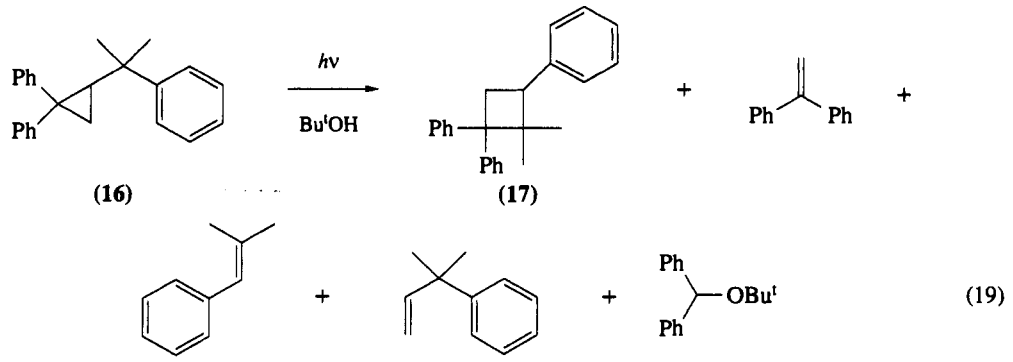
(17)

An example of the photoisomerization of a cyclopropyl-π-methane system is depicted in equation (18). Five products are observed, the first three of which are primary products, while the last two derive from secondary photochemical fragmentation of the vinylcyclobutane.[24]



(18)

The benzo version of the cyclopropyl-π-methane rearrangement has been reported for substrate (**16**).[25] The products are shown in equation (19), of which cyclobutane (**17**) corresponds to the cyclopropyl-π-methane product. The two alkenes are secondary products from the cyclobutane, while the last two products derive from photocycloreversion of the starting material (Griffin fragmentation),[26] the diphenylcarbene being trapped by the solvent (Bu^tOH) in the form of the ether.

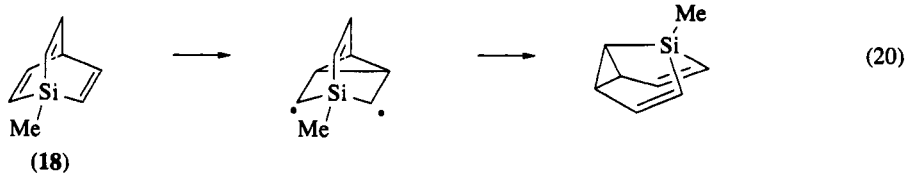


(19)

2.5.2.6 Hetera-substituted Systems

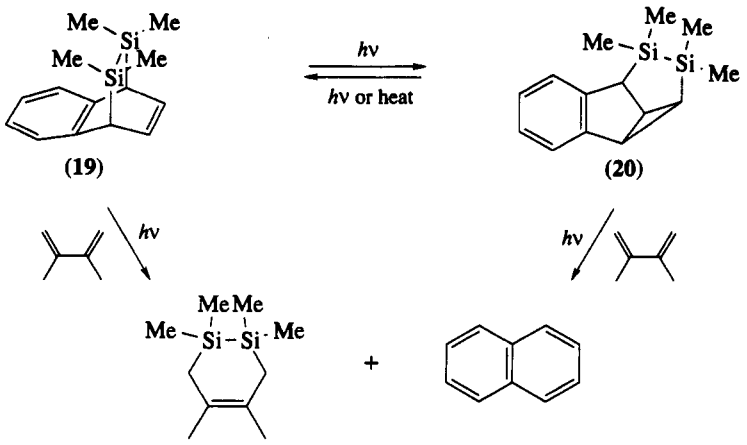
The hetera-substituted di-π-methane rearrangement is currently an active area of investigation. So far, most examples have been reported for oxa and aza substitution. From the available data, it appears that the rearrangement is operative only when the heteroatom is in the 1-position. Replacement of the sp^2 carbon at the 2-position or the sp^3 carbon at the 3-position by heteroatoms such as O, N, S, Se, B, P, *etc.* entails systems which have not been investigated or which have proved incapable of giving di-π-methane products.

An exception is given by silicon as heteroatom. The silabarrelene (**18**) undergoes photorearrangement very similar to barrelene, affording the silasemibullvalene in quantitative yield (equation 20).[27]



(20)

Other types of sila systems also give di-π-methane products. In the case of (**19**), irradiation at 10 K in an argon matrix or at 77 K in a 3-methylpentane glass affords the di-π-methane product (**20**), which on further irradiation or upon heating reverts to the starting material (equation 21). Photolysis of (**19**) at room temperature gives instead retro Diels–Alder fragmentation to tetramethyldisilene, whose intermediacy was established by means of [4 + 2] cycloaddition with 2,3-dimethyl-1,3-butadiene.[28]

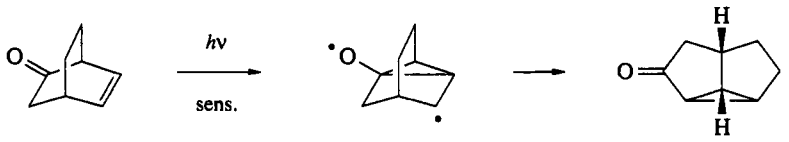


(21)

2.5.2.6.1 *Oxa-di-π-methane rearrangements*

The chemistry of the oxa-di-π-methane rearrangement is covered in Chapter 2.6, so that here, for the sake of completeness, only a few remarks on its more salient features are presented.

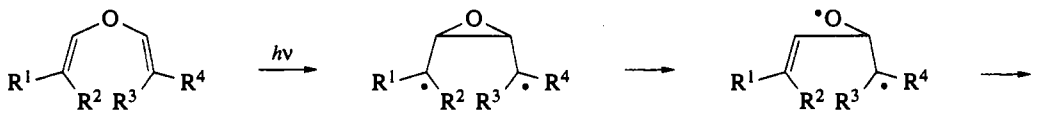
Of the two possible oxa-di-π-methane systems, only the 1-oxa has been extensively studied. The presence of the carbonyl group significantly alters the photophysical characteristics of the 1,4-diene moiety, *e.g.* the type of excitation (from π,π* to *n*,π*), level ordering, spin state, and extinction coefficients. Other reaction pathways such as Norrish type fragmentations become operative and such products often accompany the di-π-methane ones. Of the two possible reaction paths arising from cleavage of the cyclopropyldicarbinyl diradical, usually the one leading to the carbonyl-substituted cyclopropane is observed. An illustrative example is given in equation (22).[29] The triplet sensitized oxa-di-π-methane rearrangement of pure enantiomers of bicyclo[2.2.2]oct-5-en-2-one affords enantiomeric tricyclo[3.3.0.$0^{2,8}$]octan-3-ones, which have been used as building blocks for the synthesis of natural products.



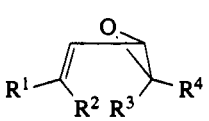
(22)

The 3-oxa-di-π-methane rearrangement is far less common. As a symmetrical system, the product should be a vinyl epoxide (equation 23). So far, no 3-oxa-di-π-methane products have been observed from the divinyl ethers depicted in the equation.[30] It was shown that the solution photochemistry of (**21a**) derives from its singlet π,π*-state and parallels that of the unsubstituted divinyl ether (**21d**) and of furan in the gas phase. All products could be rationalized in terms of the initial formation of a singlet vinyl–vinyloxy radical pair (equation 24). Triplet sensitization brings about *cis–trans* isomerization and consequent deactivation. Had the 3-oxa-di-π-methane product, *i.e.* the vinyloxirane (**22**), been formed, it would have decomposed *via* Griffin fragmentation[26] as confirmed by irradiation of an authentic sample.

An explanation for the lack of formation of 3-oxa-di-π-methane products is offered in terms of Zimmerman's bond order control.[4] Thus, while the 1,4-diene is a four-electron system with bonding between

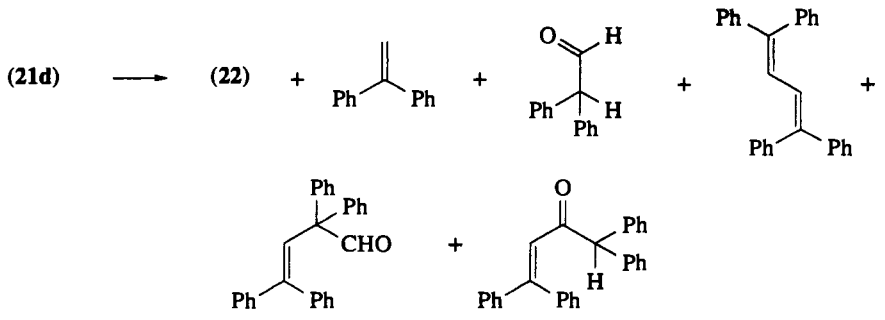


(**21**) **a**: R^{1-4} = Ph
b: R^{1-4} = Tol
c: $R^{1,4}$ = Ph, $R^{2,3}$ = H
d: R^{1-4} = H



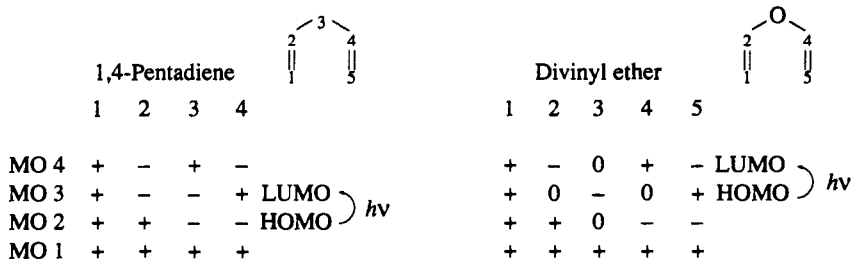
(**22**)

(23)



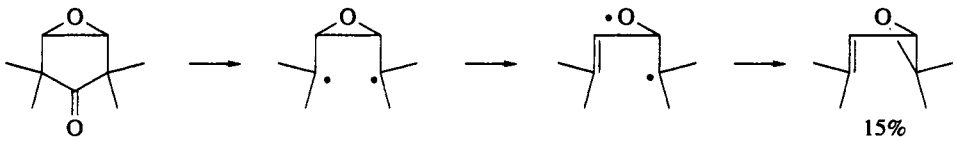
(24)

C-2 and C-4 in the reacting LUMO, the divinyl ether is a six-electron system with antibonding between C-2 and C-4 in the reacting LUMO of the excited states species. Presumably on account of this, the divinyl ether substrate is di-π-methane inactive. This rationalization is shown in Scheme 2.



Scheme 2

Of mechanistic interest in this context is the independent generation of di-π-methane diradicals of 3-oxa-di-π-methane systems which do not give the rearrangement, in order to probe whether such diradicals at least in principle are prone to give di-π-methane products. For this purpose, the cyclopropyldicarbinyl diradical in equation (25) was generated *via* photochemical carbon monoxide extrusion.[31] Indeed, the expected oxa-di-π-methane product 2,5-dimethyl-4,5-epoxy-2-hexene was formed, as well as other products.

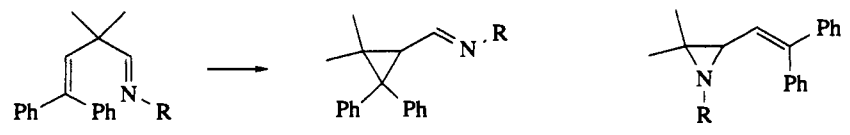


(25)

2.5.2.6.2 Aza-di-π-methane rearrangements

In nitrogen systems, all three arrangements are in principle possible, *i.e.* the 1-, 2- and 3-aza-di-π-methane rearrangements. Only the first of them has recently been investigated, while examples of the 2- and 3-aza-di-π-methane rearrangement appear still missing from the literature.

The first aza-di-π-methane rearrangement to be reported is illustrated in equation (26). The product of the reaction is the imine and not the aziridine; the latter could have formed upon rupture of the alternative bond of the cyclopropyldicarbinyl diradical intermediate.[32] In this regard, the aza-di-π-methane resembles the 1-oxa case, with reestablishment of the imine bond.

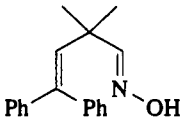


(26)

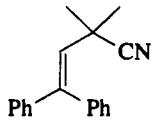
R = CH_2Ph, Ph, OAc

not formed

The 1-aza-di-π-methane rearrangement depends on the type of substitution of the nitrogen atom.[33] For example, aza-di-π-methane rearrangement occurs with aryl-substituted imines and with oxime acetates, but not with the oxime (**23**) or the nitrile (**24**).[34]

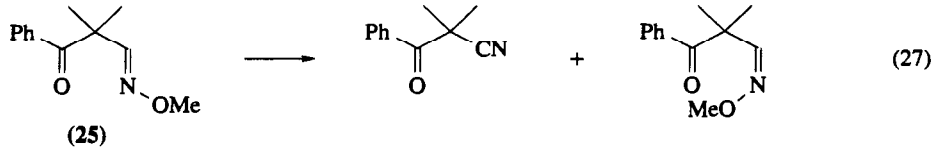


(**23**)

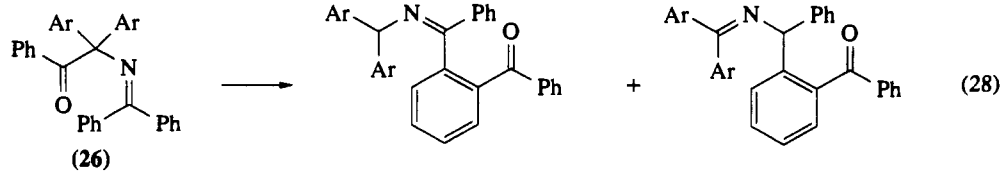


(**24**)

The 1-aza-5-oxa-di-π-methane rearrangement of (**25**) does not occur. Instead, *cis–trans* isomerization and photoelimination of methanol are observed for this oxime (equation 27).[35] Finally, the 1-oxa-4-aza-di-π-methane rearrangement of compound (**26**) also did not take place. This substrate gave rise to the photo-induced 1,5-benzoyl migration shown in equation (28).[36]



(**25**) (27)



(**26**) (28)

2.5.3 MECHANISM

2.5.3.1 General Aspects

The mechanism of the reaction has been extensively reviewed on several occasions.[2–4] We intend, therefore, to highlight only the essential features. Moreover, it should be kept firmly in mind that, in most instances, diradical intermediates have been postulated for mechanistic convenience and rigorous experimental confirmation of their intervention is often lacking.

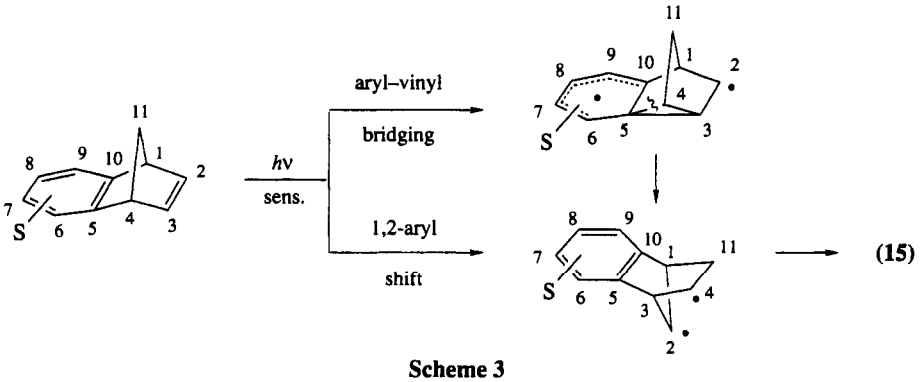
Recent achievements in the elucidation of the mechanism have been obtained by computational methods. The results of a SINDO1 study[37] are in agreement with the general mechanistic pathway suggested by Zimmerman.[2] For the parent 1,4-pentadiene system the calculated correlation diagrams suggest that opening of the cyclopropyldicarbinyl diradical is prevented by a high barrier on the singlet surface. Thus the rate of formation of the parent vinylcyclopropane should be negligible under direct irradiation. However, the singlet-state reaction becomes efficient where no barriers appear in the first excited singlet state, *e.g.* the case of *gem*-dimethyl substitution at the central carbon atom. For this substrate, calculations predict that the cyclopropyldicarbinyl diradical is not an intermediate.[37]

On the other hand, these calculations suggest that the triplet-state process can be efficient only if the cyclopropyldicarbinyl triplet intermediate is avoided during the reaction because of high vibrational energy. If the ground-state triplet cannot be circumvented, back reaction to the ground-state reactants should be observed.[37] However, the existence of the cyclopropyldicarbinyl diradical on the triplet energy surface has been advanced by Borden *et al.*,[38] who compared the calculated geometries and energies of reactants, intermediates and products.

The general impression of the present computational status on this complex photochemical rearrangement is that the results are still contradictory. Presumably the mechanistic details depend on the system under consideration, so that a spectrum of possibilities applies. More intensive efforts should be invested in the future to resolve this perplexing situation.

2.5.3.2 Divinyl *versus* Benzo–Vinyl Bridging

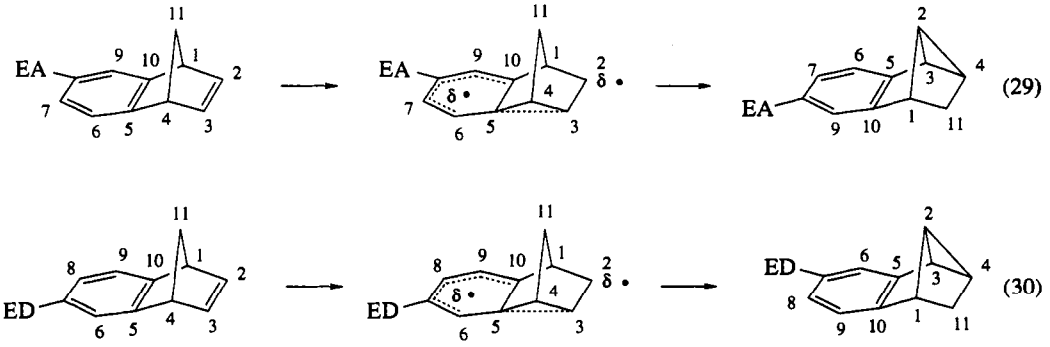
The question arises whether there is any need for formation of the cyclopropyldicarbinyl diradical in the aryl di-π-methane rearrangement. In the event that this intermediate is indeed formed, one has to keep in mind that the aromaticity of the aryl moiety has to be sacrificed along the reaction coordinate. Alternatively, a 1,2-aryl shift with direct formation of the 1,3-diradical may operate, which irreversibly cyclizes to the di-π-methane product. In Scheme 3 these mechanistic alternatives are illustrated for benzonorbornadienes, which have been studied in great detail by Paquette *et al.*[39]



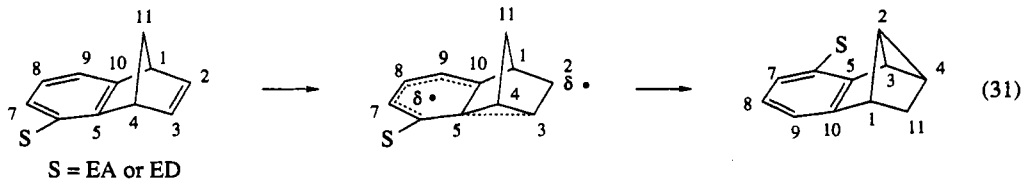
Scheme 3

Experimental scrutiny of this mechanistic problem has been approached from several points of view; substituent effects on the aromatic ring have been investigated with special intensity (Scheme 3). The significant features can be summarized as follows.

(a) Substitution at C-7 by electron-acceptor groups (S = EA) results in rebonding *via* the *para* position in the rearrangement (equation 29),[39a,b] while electron-donor groups (S = ED) at C-7 favor rebonding *via* the *meta* position (equation 30).[39a,b]



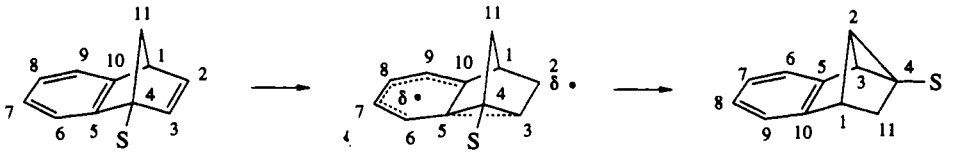
(b) Substitution at C-6 favors rebonding *via* the *ortho* carbon atom, irrespective of the electronic nature of the group (equation 31).[39c,d]



S = EA or ED

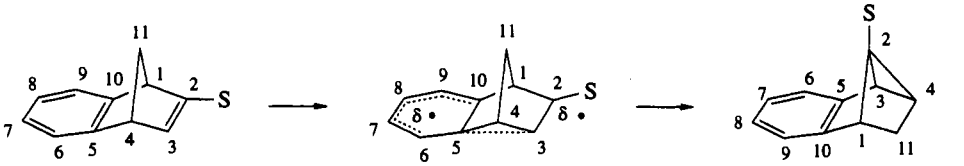
(c) Bridgehead substitution at C-1 promotes regiospecific migration of the proximate aryl site (equation 32), except for Br (heavy atom effect) and D (isotopic control).[39e,f]

(d) In the case of 1-methoxy-4-substituted benzonorbornadienes, with few exceptions the reaction channel involving the aryl carbon atom proximate to the substituent is favored.[39g]



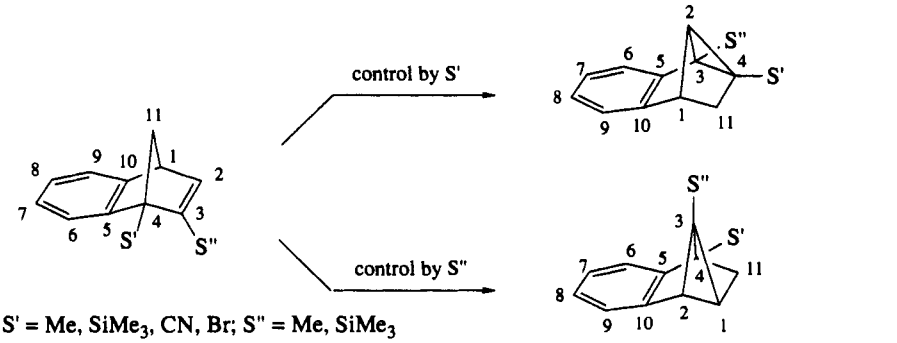
S = EA or ED (32)

(e) A cyano group in the 2-position strongly induces migration of the distant aryl site;[39h,i] the effect of a methyl group at the same position is less pronounced (equation 33).[39j]

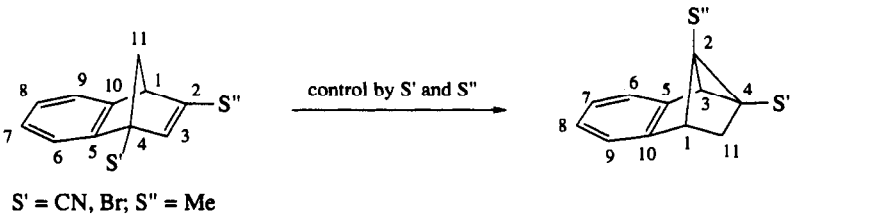


S = CN or Me (33)

(f) In 1,2-dimethyl- and 1,2-bis(trimethylsilyl)-benzonorbornadienes, both the possible reaction channels operate, showing that the substituent effects in the two positions are matched. Bridgehead cyano substitution overwhelms the effect of a vinylmethyl group, while bridgehead bromine augments the ratio of product derived from rebonding at the distal site of the methyl group (equations 34 and 35).[39k]



S' = Me, $SiMe_3$, CN, Br; S" = Me, $SiMe_3$ (34)



S' = CN, Br; S" = Me (35)

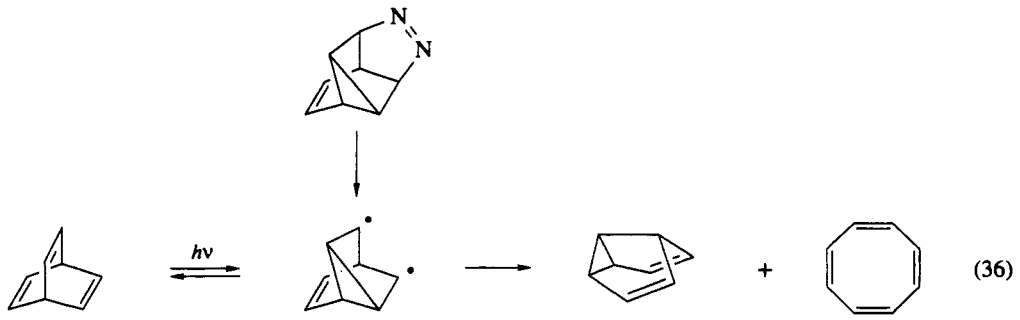
(g) In bridgehead-substituted 6-methoxybenzonorbornadienes, electron acceptors have a dominant effect over the methoxy substituent; for electron donors, competition with the directing control by the methoxy group in the aryl ring is observed.[39l]

(h) The deuterium isotope effect associated with the triplet state di-π-methane rearrangement of [1-D]- and [2-D]-benzonorbornadiene has been determined to be quite large, *i.e.* k_H/k_D = 1.27 and 1.34, respectively.[39l] These findings strongly support a mechanistic pathway *via* 1,2-aryl migration (Scheme 3).

2.5.3.3 Independent Generation of the Diradical Intermediates

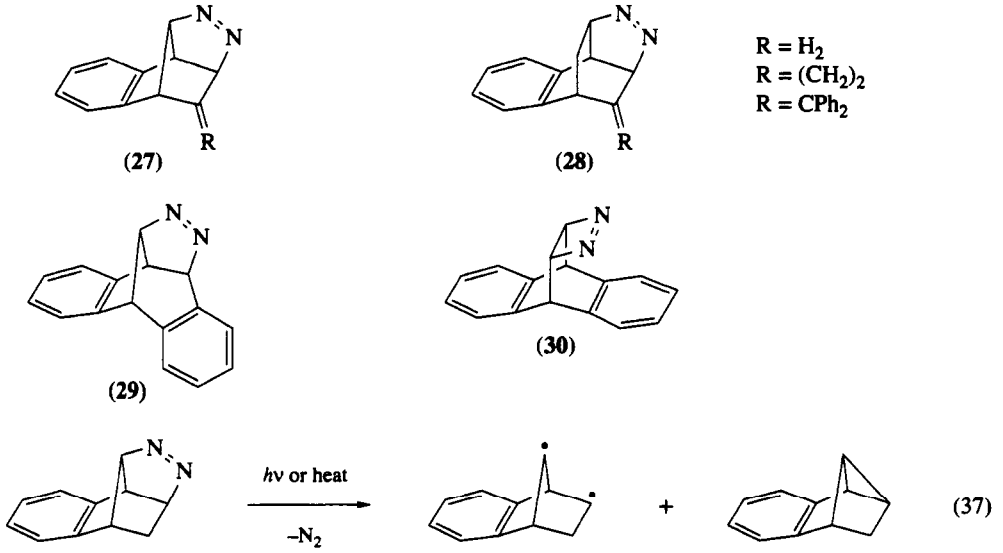
A useful mechanistic probe for the diradical intermediates postulated in the di-π-methane rearrangement entails generating them *via* authentic routes and elucidating their chemical behavior. One of the early examples concerns the cyclopropyldicarbinyl diradical postulated in the photoisomerization of barrelene into semibullvalene by nitrogen extrusion from the appropriate azoalkane.[40] Indeed, as shown in

equation (36), beside the expected semibullvalene, barrelene and cyclooctatetraene were also formed, thereby suggesting that the postulated cyclopropyldicarbinyl diradical is a reasonable intermediate in this photoreaction.



(36)

In a similar way, the 1,3-diradicals postulated in the di-π-methane rearrangement of several benzonorbornadienes and related species have been produced *via* denitrogenation of the appropriate azoalkanes (**27**)–(**30**).[41] The products obtained in the thermal and photochemical denitrogenation of (**27**), for example, are the norbornadiene and the tricyclic di-π-methane product (occasionally other products not derived from denitrogenation have been observed).[42] The latter hydrocarbon, which derives from direct collapse of the 1,3-diradical, is formed almost exclusively (equation 37).



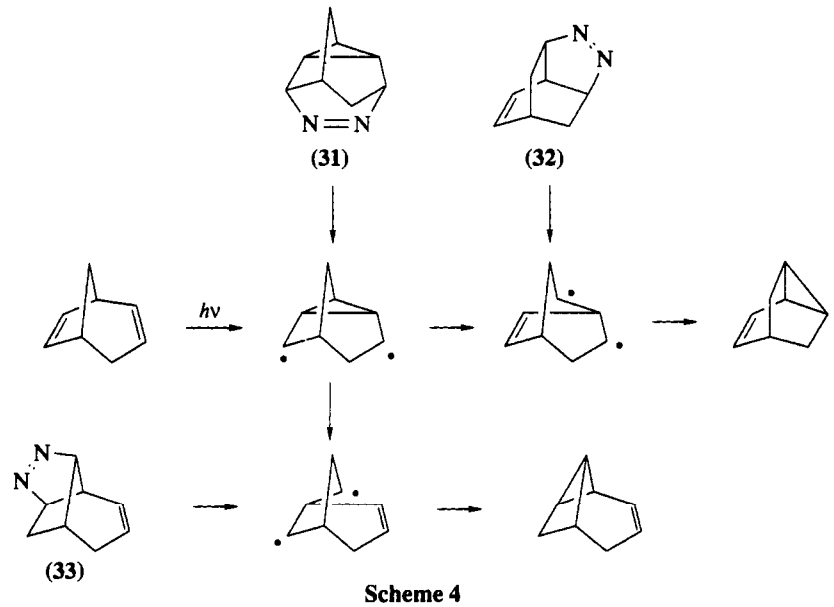
(**27**) (**28**) (**29**) (**30**)

R = H_2
R = $(CH_2)_2$
R = CPh_2

(37)

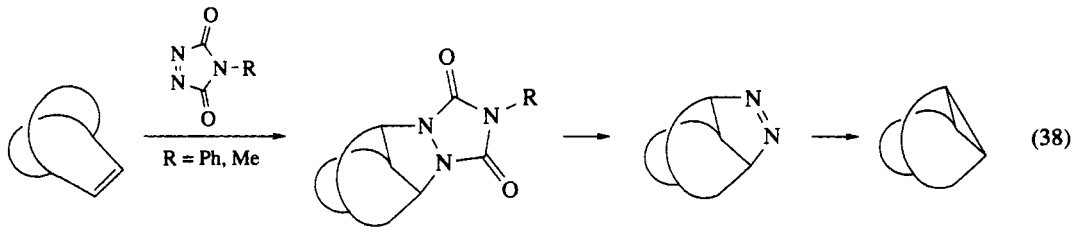
The question arises whether the generated diradicals are indeed the same as the ones involved in the photoreaction. Recent investigations on bicyclo[3.2.1]octa-2,6-diene (Scheme 4) and its benzo analog[43] have brought into focus a more complicated picture. The product compositions derived from thermal and photochemical denitrogenation of the three azoalkanes (**31**)–(**33**) and of some deuterated species, all potential entry points into the same diradical manifold, suggest that the di-π-methane rearrangement and the photochemical denitrogenation of the azoalkanes are disjointed chemical events.[43] The retro di-π-methane product (the octadiene) obtained in the azoalkane photolyses is better explained by postulating diazenyl diradicals (stepwise bond cleavage of the azoalkane). However, the major pathway leading to the di-π-methane products unquestionably involves cyclization of the 1,3-diradicals postulated in the di-π-methane rearrangement, so that their intermediacy is secured. In this context, it is immaterial whether the 1,3-diradical is formed directly or *via* the diazenyl diradical in the photolysis of the azoalkane. Nonetheless, caution should be exercised in using azoalkanes as mechanistic probes for elucidating the diradical manifolds postulated in photochemical reactions because the intermediate diazenyl diradical may lead to unexpected products.

Although the utility of azoalkanes as mechanistic probes is being questioned, their utilization in synthesis is well documented.[44] The sequence of reactions shown in equation (38) is definitely a useful alter-



Scheme 4

native for preparing unusual di-π-methane products. This fact rests on the interesting feature that triazolinediones cycloadd to polycyclic dienes *via* the same skeletal modifications that occur in the di-π-methane rearrangement.[45] In this sense, triazolinedione cycloaddition, coupled with hydrolysis of the resulting urazole to the azoalkane and subsequent denitrogenation (thermal or photochemical), represents a synthetic equivalent to the di-π-methane rearrangement. An illustrative example is given in equation (39), in which the di-π-methane product was prepared *via* these two distinct routes.[46]



(38)

(39)

2.5.4 SELECTIVITY

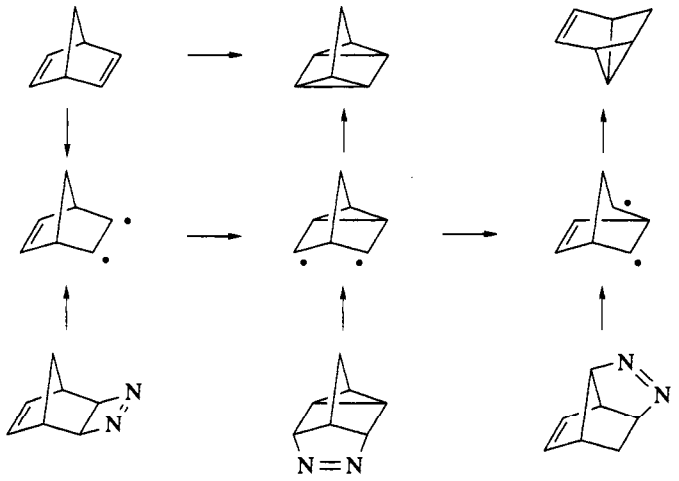
2.5.4.1 Chemoselectivity

Several processes are known to be capable of competing with the di-π-methane rearrangement. The following list is, however, by no means exhaustive and refers only to those side reactions that are more frequently encountered.

2.5.4.1.1 [2 + 2] Photocycloadditions and/or photoreversions

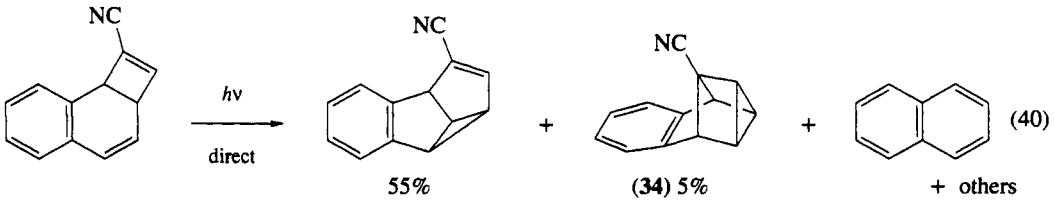
[2 + 2] Photocyclizations are usually observed with symmetric systems. Indeed, when vinyl–vinyl bridging is equally possible for the four alkenic carbons, a [2 + 2] photocyclization can occur. As an example, norbornadiene prefers to give quadricyclane *via* photocyclization rather than the tricyclic di-π-methane product.[47] The latter, however, has been generated from the appropiate azoalkane as shown in

Scheme 5.[48] It should be noted that for this substrate all three possible diradical species have been prepared from the respective azoalkanes.[49]



Scheme 5

More complicated nonsymmetric systems can sometimes produce [2 + 2] cycloadducts, although this is usually a very minor process. The example of equation (40) illustrates one such case where [2 + 2] cycloaddition (product **34**) as well as [2 + 2] cycloreversion (formation of naphthalene) are observed simultaneously with the di-π-methane rearrangement.[50] Cycloreversion can usually only be observed when one of the double bonds of the 1,4-diene is part of a cyclobutene.



The possibility must be considered as well that triplet sensitization with carbonyl sensitizers can lead to competition by the Paterno–Büchi reaction, *i.e.* the [2 + 2] cycloaddition of the sensitizer to the substrate. To the best of our knowledge this possibility has not yet been observed.

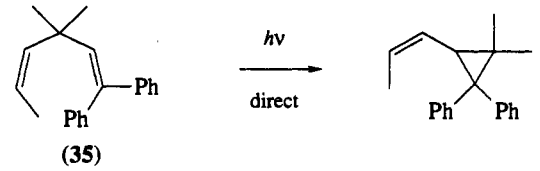
2.5.4.1.2 Cis–trans *isomerizations*

Such isomerizations can only be observed in open-chain structures and, of course, medium–large ring systems. The mode of irradiation is important, as illustrated in the representative example of equation (41),[51] *i.e* the direct and sensitized irradiation of the 1,4-diene (**35**). While direct photolysis leads to the expected di-π-methane product, sensitized irradiation brings about *cis–trans* isomerization before cyclization, resulting in products with inverted stereochemistry at the double bond.[51]

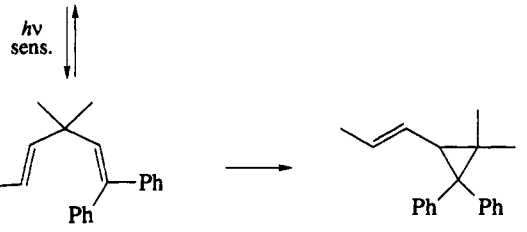
2.5.4.1.3 1,3-Sigmatropic shift

This photochemical transformation, shown in equation (42), is a process that occurs especially frequently in the oxa-di-π-methane rearrangement. This isomerization may proceed *via* a Norrish type I reaction.

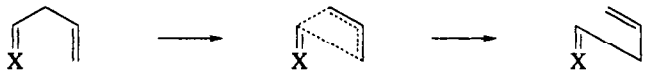
An extension of the simplistic but practical diradical mechanism of equation (1) leads to the generalized di-π-methane process given in equation (43).[41] Thus, the initial 1,3-diradical, instead of cyclizing across C-3 and C-5 to the final vinylcyclopropane, bonds across C-2 and C-5 to generate a cyclopropyldicarbinyl diradical, which on opening of the C-2/C-4 bond affords the isomerized 1,4-diene. A num-



(35)



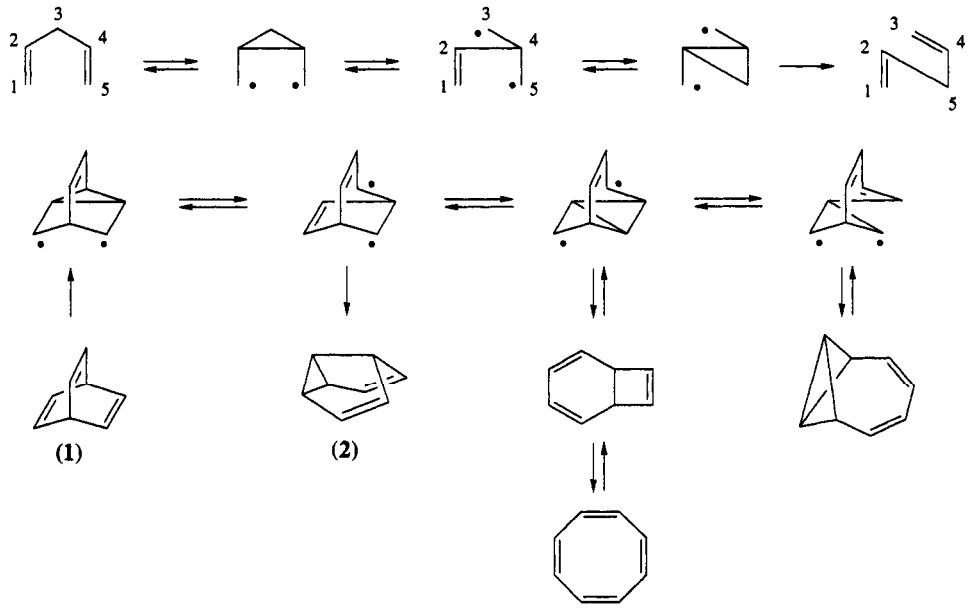
(41)



(42)

X = CH_2, O

ber of photochemical transformations may be rationalized *via* the reversible generalized di-π-methane process of equation (43), but have so far not been scrutinized from this mechanistic perspective. As a significant example the photoisomerization of the C_8H_8 hydrocarbon series, depicted in Scheme 6, is illustrated. The mechanistic postulate in equation (43) helps to predict and to rationalize photoisomerized 1,4-diene products in the di-π-methane process.

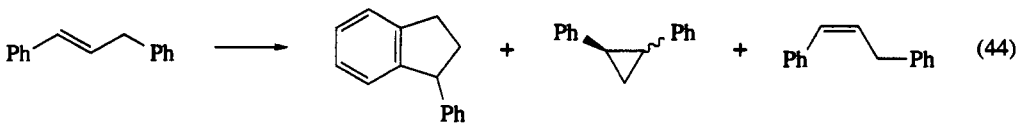


(43)

Scheme 6

2.5.4.1.4 Radical-type rearrangements

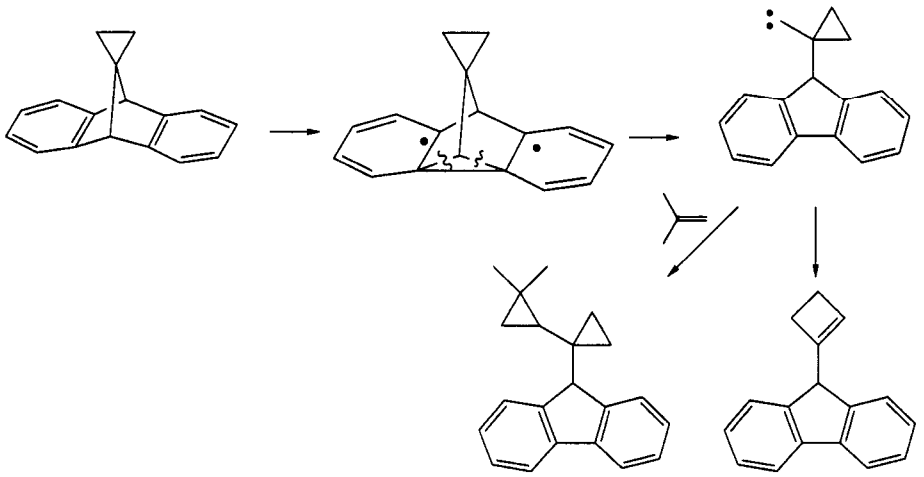
Such processes have been encountered in the photolysis of highly aryl-substituted systems. Representatively, 1-phenylindane is formed in the photolysis of *trans*-1,3-diphenylpropene (equation 44).[52] To the best of our knowledge, no cases have as yet been reported in which radical-type hydrogen abstractions compete with the di-π-methane rearrangement.



(44)

2.5.4.1.5 Fragmentations

In some cases the initial cyclopropyldicarbinyl diradical fragments into a carbene. Such diradical–carbene fragmentations are quite common in the 185 nm photochemistry of alkenes,[9] but seldom in photolyses under long wavelength conditions. An example, however, is given in equation (45), in which the driving force of the fragmentation is rearomatization.[53] An analogous process constitutes the photofragmentation of triptycenes.[54]

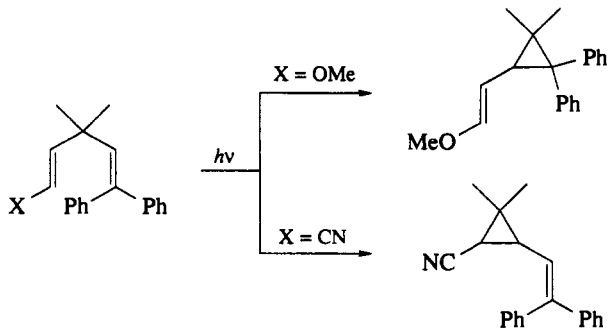


(45)

2.5.4.2 Regioselectivity

The regioselectivity that arises from unsymmetrically substituted dienes has already been discussed for several systems in the cited reviews.[2–4] For acyclic 1,4-dienes substituted with alkyl and/or aryl groups, the general rule applies that the product with the less substituted vinyl moiety (conversely the higher substituted cyclopropane) is formed. This type of regiochemistry derives from the need for producing the more stable 1,3-diradical intermediate. In the arylpropene cases the resultant regiochemistry is mandated by the need for maintaining the aromaticity of the aryl ring.

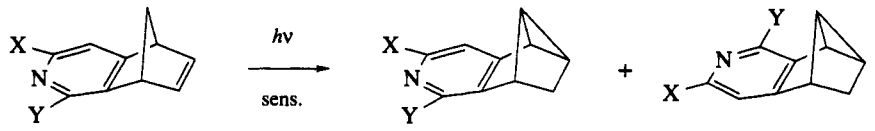
The general trend for acyclic 1,4-dienes substituted with functional groups possessing electron donor or acceptor characteristics is highlighted by the examples shown in equation (46).[55] The polarity of the intermediates plays a major role in determining the regiochemistry. From an empirical viewpoint, the more electron-rich double bond in the substrate remains as the double bond in the product.



(46)

The regioselectivity associated with *ortho,meta*-substituted, bridgehead- and alkene-substituted benzonorbornadienes has already been discussed in Section 2.5.3.2. These studies by Paquette *et al.*[39] have

provided valuable insights into the mechanism of the complex di-π-methane process. Latest reports concern the regioselectivity exhibited by the pyridine ring in the heterobenzonorbornadiene series (equation 47).[56] The ring nitrogen atom in the parent system favors migration of the distal carbon. The '*meta*' chloro and methoxy substituents act cooperatively with the ring nitrogen atom and cause a higher proportion of the same product. An '*ortho*' methoxy group acts in an antagonist fashion and the only observed product reflects total control by the methoxy substituent. These results consolidate the mechanistic rationales developed in the study on the substituted benzonorbornadienes.[39] The regioselectivities associated with substituted benzo-[57] and dibenzo-barrelene[58] systems are also in line with these mechanistic notions.



(47)

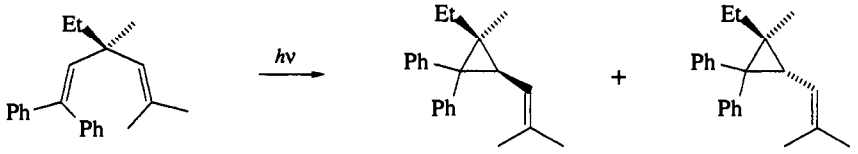
X = Y = H; X = OMe, Y = H; X = Cl, Y = H; X = H, Y = OMe

2.5.4.3 Stereoselectivity

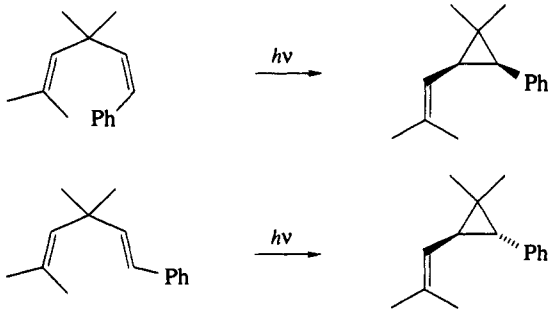
The stereochemistry of the di-π-methane photorearrangement has been reviewed in detail.[1,2] The general trend is that configuration at C-1 is retained, while that at C-3 and C-5 is inverted (equation 48). The disrotatory motion at C-3 and C-5 is responsible for inversion, provided that no untoward geometric factors operate.

(48)

The retention of stereochemistry at C-1, as, for example, in the direct photolysis in equation (41), implies that rotation between C-1 and C-2 in the cyclopropyldicarbinyl diradical does not occur. Study of the stereochemical event at the central carbon atom requires optically active substrates containing an asymmetric C-3 carbon atom. The example of equation (49)[59] and all other cases studied[2] demonstrate that in the two diastereomeric vinylcyclopropanes which form, the central carbon atom has inverted its configuration. Knowledge of the stereochemical fate of C-5 can be gained by inspection of the examples shown in equation (50).[60] Rearrangement of the *cis* and *trans* isomers of the diene gave the *cis* and *trans* vinylcyclopropanes, respectively.[60]



(49)

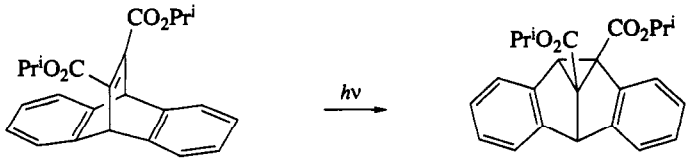


(50)

Recent efforts have focused also on the possible realization of enantioselective reactions. The use of organized chiral media has met with some success. Benzonorbornadiene forms stoichiometric complexes

with β-cyclodextrin. These β-cyclodextrin–benzonorbornadiene complexes, either in solution or in the solid state, gave on acetophenone sensitization optically active tricyclic product (**15**).[61] No quantitative data are available, however. In view of the rapid equilibrium between the free substrate and its complexed form, the major problem with such experiments is the difficulty of ascertaining whether the photoreaction has occurred for the complexed or free substrate. Another problem is the difficulty experienced by the sensitizer in approaching the complexed substrate.

Finally, a few di-π-methane reactions have been reported to occur in the solid state using chiral crystals. The success of such experiments rests on the fact that racemic, but more significantly nonchiral, compounds form chiral crystalline lattices. An example is the dibenzobarrelene (**36**) (equation 51).[62] The enantioselective photoreaction occurs on the crystal surface with a high degree of asymmetric induction. It is worth noting that reactions within the crystalline state also exhibit a marked regioselectivity as the result of augmented steric interactions in the lattice compared with isotropic liquid media.[63]



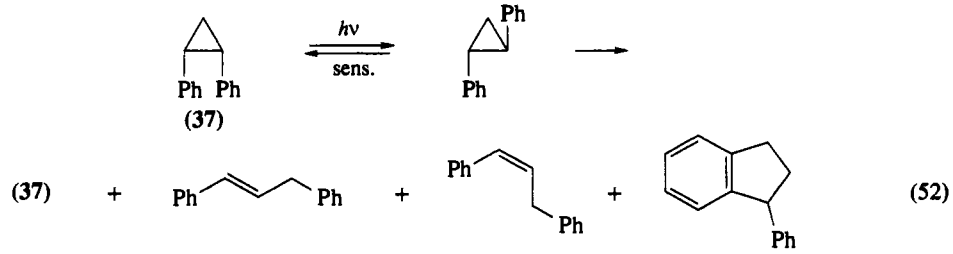
(**36**) $P2_1P2_1P2_1$ crystals — 100% *ee* (51)

2.5.5 SYNTHETIC UTILITY

So far the di-π-methane photoisomerization has found few applications in synthesis, despite the fact that vinylcyclopropanes are versatile intermediates. Several reviews discuss these compounds from a general point of view.[64] For example, vinylcyclopropanes are prone to rearrange to cyclopentenes. Hence, in sequence, these two rearrangements may serve as a way to produce cyclopentenes from 1,4-dienes.[65]

It is perhaps worth pointing out that the di-π-methane rearrangements of 1,4-cycloheptadienes produce bicyclo[4.1.0]alkenes which are present in several natural products (*e.g.* in carenes). However, the most striking utility is perhaps evident in polycyclic transformations. The di-π-methane rearrangement remains the most efficient and effective method for synthesizing semibullvalene and its benzo and dibenzo derivatives. It is, indeed, surprising that this synthetic protocol has found so little utilization, especially in the subsequent transformation of products into useful complex target molecules.

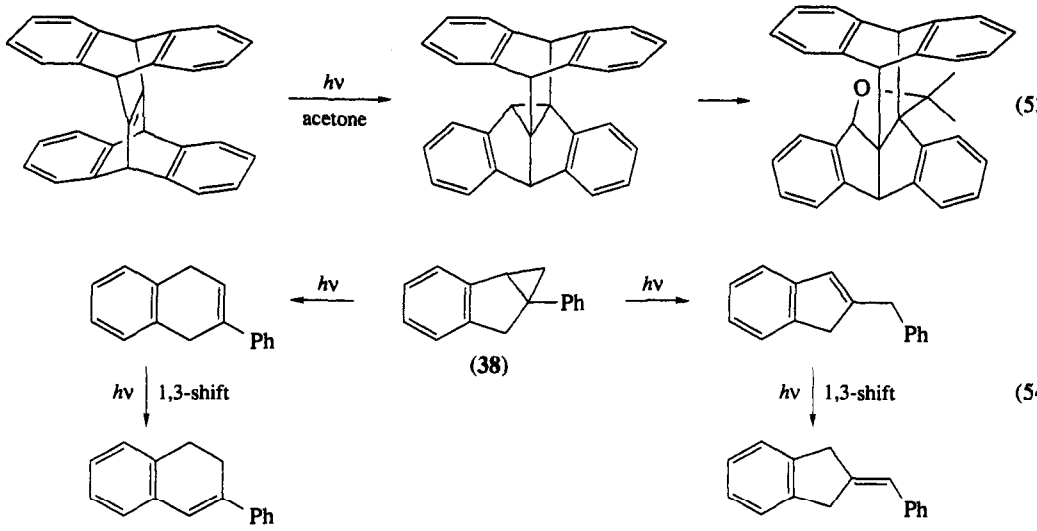
For synthetic applications, the stability of the di-π-methane product is very important. Generally, vinylcyclopropanes exhibit different extinction coefficients from the starting dienes, but frequently they are not inert photochemically. This is especially crucial in aryl vinyl systems where the radiation wavelength excites the aryl chromophore and hence both reagent and products. For example, arylcyclopropane photochemistry affords alkenes and indane, as illustrated by 1,2-diphenylcyclopropane (equation 52).[66]



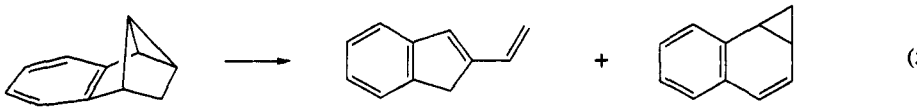
(52)

In other cases the addition of the ketone sensitizer to the cyclopropane moiety has been observed (equation 53).[67] This secondary reaction is probably occurring because of the notably stable benzyl radical center that results upon rupture of the cyclopropane.

On the other hand, retro-di-π-methane rearrangements have been observed. For example, the rearrangement of (**38**) has been rationalized in terms of a reverse di-π-methane reaction, followed by 1,3-hydrogen shift (equation 54).[68]



Even more complex is the mixture of products which arises from the direct irradiation of benzotricyclo[3.1.0.0^{2,6}]hex-3-ene (**15**), the di-π-methane product of benzonorbornadiene (equation 12). In cyclohexane as solvent, 2-vinylindene and benzonorcaradiene are the major primary products (equation 55).[69]



(**15**)

2.5.6 PRACTICAL ASPECTS

The di-π-methane rearrangement, being a photochemical process, is subject to all basic practical considerations important in routine photochemical work. These are well described in books dealing with this topic.[70] General considerations which are possibly valid for classes of substrates are given in this section.

Apparatus. Exploratory and mechanistic photochemistry does not need large quantities of material (up to 1 g) and can be accomplished with external light sources. The Rayonet photoreactor is a typical apparatus. The merry-go-round device allows for more uniform irradiation and simultaneous photolysis of larger amounts (10–100 g) of material. In this simple photoreactor, the radiation intensity can be augmented or diminished by removing light bulbs. Another advantage is the possibility of directly irradiating NMR tubes in order to monitor the progress of the reaction.

Problems arise with this apparatus when low temperatures are needed and when stirring of larger quantities of material is necessary. In these cases, immersion-well photoreactors are more useful. Cooling jackets permit the use of low temperatures and external magnetic stirring can provide good agitation. The latter can be also achieved by passage of a vigorous inert gas stream, most usually pure, dry nitrogen gas, into the solution.

Lamps and filters. The combination of radiation source and filter accounts for the actual radiation wavelength to which the reaction mixture is exposed. An unavoidable filter is the glass type of the reaction vessel. In the direct irradiation of substrates not containing functionality other than the phenyl groups, wavelengths in the 280 nm region are needed. Typically a Hanovia 450 W medium-pressure mercury lamp and a 2 mm Corex cylindrical filter ($\lambda > 270$ nm) are employed. Triplet-sensitized reactions need a higher cut-off, which can be obtained by the use of the same lamp with a 2 mm Pyrex filter ($\lambda > 300$ nm). The Rayonet photoreactor can be equipped with 254, 300 and 350 nm lamps.

Solvents, concentration and sensitizers. Purity standards for solvents to be used in photoreactions may differ substantially from those in usual preparative chemistry. It is of outmost importance that absorbing impurities and radical initiators are avoided. Furthermore, the reaction mixtures should be purged with pure, dry nitrogen before and during the irradiation.

Common solvents for direct di-π-methane reactions are hexane, cyclohexane or acetonitrile. The substrate concentrations depend on the extinction coefficient of the substrate.

Acetone and acetone–benzene are standard solvent systems for triplet-sensitized reactions. Alternatively, acetophenone or benzophenone (depending upon the triplet energy required) can be used in hydrocarbon solvents, acetonitrile or benzene. The presence of benzene is particularly useful to avoid adsorbance by aryl groups present in the substrate. For example, in the reaction of the benzonorbornadienes, in order to guarantee triplet sensitization the irradiation should be carried out in dilute benzene solutions (*ca.* 10^{-2} M) containing acetophenone (*ca.* 10^{-2} M) and using a 3500 Å light source. The excited triplet energy of benzophenone (E_T = 73.6 kcal mol^{-1}) ensures sufficient energy for most rearrangements. In all cases the isomerizations for these substrates are rapid (complete within 20–40 min) and essentially quantitative.

Hazards. Eyes and skin can be severely injured by ultraviolet radiation. One should avoid looking at the reaction mixture when the irradiation source is activated. The photochemical apparatus, especially when using immersion set-ups, must be wrapped appropriately to avoid exposure to the ultraviolet radiation. In view of the high temperatures produced by the lamp, efficient cooling is mandatory. Special care must be exercised when flammable solvents are used. Ozone is also produced, so that working in an efficient hood is essential. Furthermore, proper electrical safety is necessary to avoid high voltage shocks.

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2.6
Oxa-di-π-methane Photoisomerizations

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2.6.1 INTRODUCTION

The knowledge and body of β,γ-enone photochemistry have continued to grow rapidly during the past decade following the last comprehensive reviews.[1–4] One main interest in this area is the oxa-di-π-methane (ODPM) photoisomerization, a reaction that has become a powerful synthetic tool and has hence served successfully in natural product synthesis.[5–11] Based on detailed investigations, a convincingly consistent picture of the mechanistic events of the reaction has evolved and predictions of the reactivity of new substrates can nowadays be made with reasonable assurance.

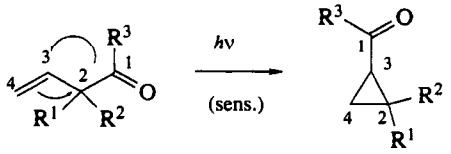
ODPM rearrangements can be readily controlled by the use of appropriate triplet sensitizers and selection of the wavelength. Excellent reproducibility is assured since the optimum reaction conditions are not sensitive to small changes of the experimental parameters (light source, concentration, irradiation time, and temperature). In this context it should be pointed out that the ODPM reaction is typically run at ambient temperature, bringing about rearrangements even of substrates with complex functionality patterns. Very often the rearrangement can be achieved with unprotected functional groups, an aspect which is certainly not restricted to the area of ODPM chemistry but is a valuable bonus for a large number of

phototransformations compared with most ground-state processes. This offers a solution to a very prominent goal of modern synthetic methodology.

The chemical yields of ODPM transformations are generally high, *i.e.* yields of 80–95% are achieved in several cases together with quantum efficiencies of 0.5–1.0. In summary, the title reaction has the essential characteristics of a general synthetic method permitting easy and safe handling and has the potential to be employed in medium- to large-scale applications, at least on a multigram to kilogram scale.

2.6.2 MECHANISTIC ASPECTS

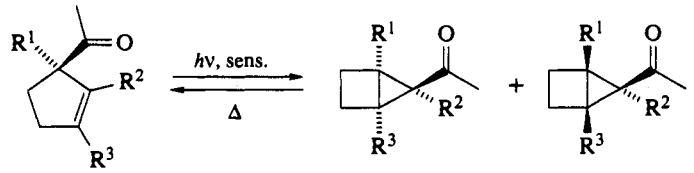
Most β,γ-unsaturated ketones rearrange upon triplet sensitization to cyclopropyl ketones *via* the so-called oxa-di-π-methane (ODPM) rearrangement, the result of which is an overall 1,2-acyl shift as schematically shown for (**1**) → (**2**).[1] β,γ-Enone arrangements in which the alkene moiety is further conjugated to either phenyl or C=O sites also undergo this transformation upon direct excitation, *i.e. via* the singlet excited state.



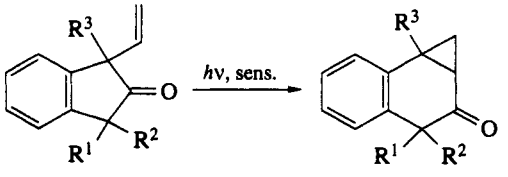
(**1**) (**2**)

2.6.2.1 Correlation of Excited States and Reactivity

As shown for the transformations of the cyclopentenyl methyl ketones (**3a–d**) to mixtures of (**4a–d**) and (**5a–d**) (Scheme 1), the ODPM rearrangement occurs from the lowest electronically excited β,γ-enone triplet state.[12,13] The π,π* configuration has been assigned to this state on the basis of CNDO-MO calculations,[12,14] phosphorescence studies at 77 K,[15,16] and mechanistic examinations.[16,17] The phosphorescence data together with sensitization experiments have revealed a T_1 energy range of 289–310 kJ mol^{-1} (4.18 kJ = 1.0 kcal) for (**3a–c**) and a much lower T_1 of 253 kJ mol^{-1} for (**3d**).[16]

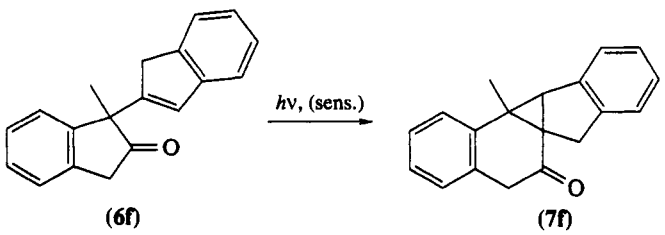


(**3a–d**) (**4a–d**) (**5a–d**)



(**6c,e**) (**7c,e**)

a: R^1 = Me, R^2 = R^3 = H
b: R^1 = R^2 = Me, R^3 = H
c: R^1 = R^2 = R^3 = Me
d: R^1 = R^2 = H, R^3 = Ph
e: R^1 = R^2 = H, R^3 = Me

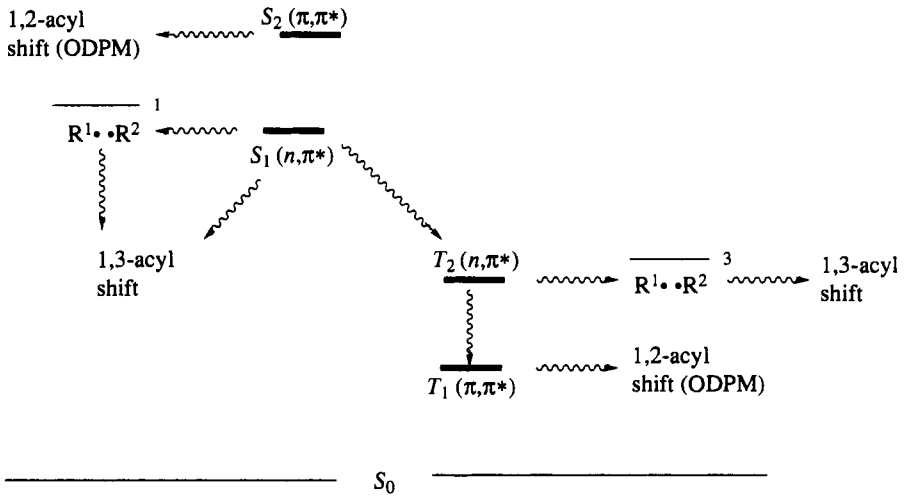


(**6f**) (**7f**)

Scheme 1

Further detailed information on the reactive excited states of β,γ-unsaturated ketones has been acquired with (**3a–c**). Inefficient intersystem crossing from the singlet to the triplet state precedes population of $T_2(n,\pi^*)$ from which the 1,3-acyl shift, induced by Norrish type I cleavage, occurs more readily than internal conversion to T_1.[2] T_2 has been estimated to lie within 8 kJ mol^{-1} of the acetone triplet (335 kJ mol^{-1}).[18] That the 1,3-acyl shift is coupled not only with singlet-state but also T_2-state reactivity has been unequivocally shown by two methods. Thermal decomposition of a dioxetane, a derivative of (**3a**), generates predominantly the T_2 state from which the 1,3-acyl shift product is formed concurrently with the ODPM products (**4a**) and (**5a**) *via* $T_1(\pi,\pi^*)$.[17] A photo-CIDNP study has independently demonstrated that the 1,3-shift with (**3a–c**) originates from both excited states, S_1 and T_2, on direct excitation.[19,20] This correlation of excited-state multiplicity and electronic configuration, at least with regard to the ODPM reaction, has recently been supported by more examples such as the rearrangements of (**6c,e**) to the corresponding cyclopropyl ketones (**7c,e**).[21] Furthermore, this latter investigation has uncovered a novel facet of ODPM photochemistry. Whereas (**6c**) rearranges exclusively to (**7c**) upon direct irradiation, the analogs (**6e**) and (**6f**) afford, under the same conditions, products derived from multiple reaction paths, *i.e.* three reaction channels: decarbonylation, 1,3-migration, and the ODPM rearrangement to (**7e,f**). Interestingly, the formation of (**7f**), but not of (**7c**) and (**7e**), is efficiently suppressed by triplet quenchers, a finding that parallels the results of experiments employing triplet sensitizers in which (**6f**) cleanly undergoes the rearrangement to (**7f**) but, in contrast, no reaction occurs with (**6c,e**). The authors conclude that on direct excitation of (**6f**) the ODPM product (**7f**) is formed from the $T_1(\pi,\pi^*)$ state *via* intersystem crossing from $S_1(n,\pi^*)$. Both (**7c**) and (**7e**), however, are thought to originate from the $S_2(\pi,\pi^*)$ state. A reason for the selective $S_2(\pi,\pi^*)$ reactivity of (**7c**) and (**7e**) may be that triplet excitation of (**6c**) and (**6e**) does not extend to the vinyl group, *i.e.* is preferably localized on the benzo ketone part.

Scheme 2 summarizes all the knowledge available up to the present time of the energetic order, spin multiplicity, and configuration of excited states involved in the photochemistry of β,γ-enones.

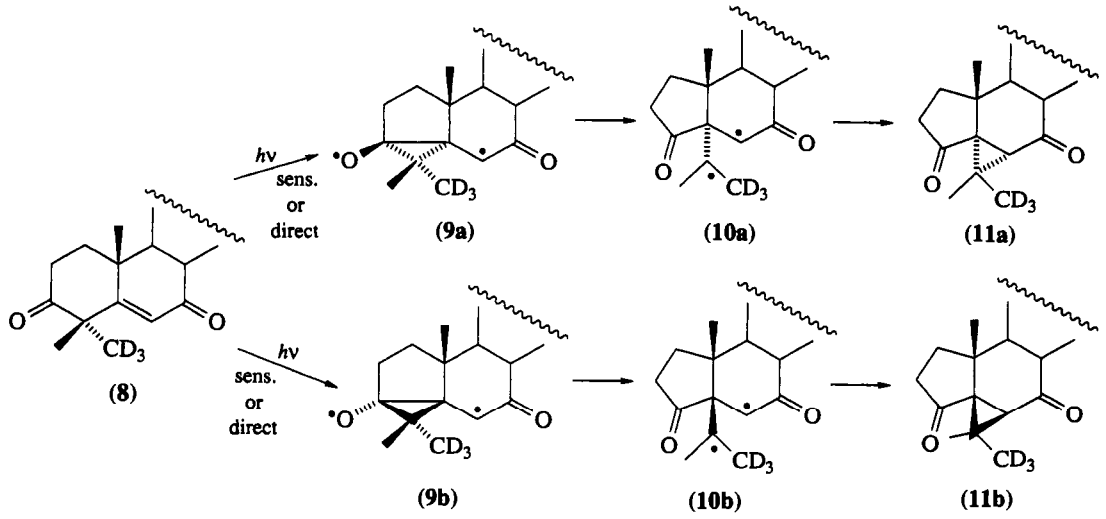


Scheme 2

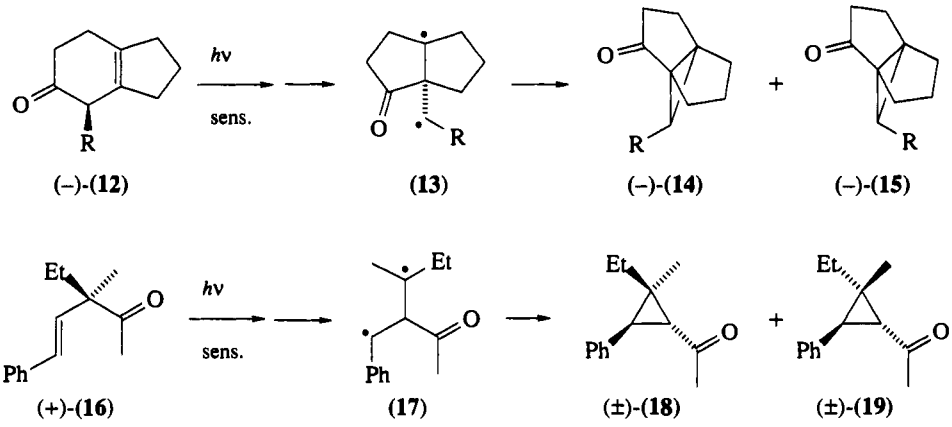
In sole conflict with this coherent picture of the correlation of excited states and reactivity in the ODPM context is the claim that a representative of the 1-methoxy-substituted bicyclo[2.2.2]octenones [*cf.* (**66a**) in Scheme 13, Section 2.6.3.4.2] may not necessarily rearrange from the T_1 state but rather from T_2.[22,23]

Evidence in favor of a stepwise rather than a concerted mode of rearrangement is gained from the three examples (**8**) → (**11**) (Scheme 3),[24] (**12**) → (**14**) + (**15**) (Scheme 4),[25] and (**16**) → (**18**) + (**19**) (Scheme 4),[26,27] in which the reaction paths can most satisfactorily be described by a sequence of diradical intermediates. In the first case, complete stereochemical scrambling of the isotopically labelled geminal methyls of the products (**11a,b**; 1:1 ratios) during the ODPM rearrangement requires the formulation of a stepwise reaction mode. The depicted sequences of diradicals *via* (**9a,b**) and (**10a,b**) are proposed as the likely reaction cascades fitting the experimental findings. Similarly, the ODPM products resulting from the rearrangements of (–)-(**12**) and (+)-(**16**) demand, by analogy with the previously postulated intermediacy of (**10**), transients such as (**13**) and (**17**), respectively, to account for scrambling of the substituents prior to permanent bond formation, *i.e.* the assembly of the cyclopropane [→ (–)-(**14**) + (–)-

(**15**) and (±)-(**18**) + (±)-(**19**)]. In summary, one may suggest that the majority of ODPM reactions be classified as stepwise processes.



Scheme 3



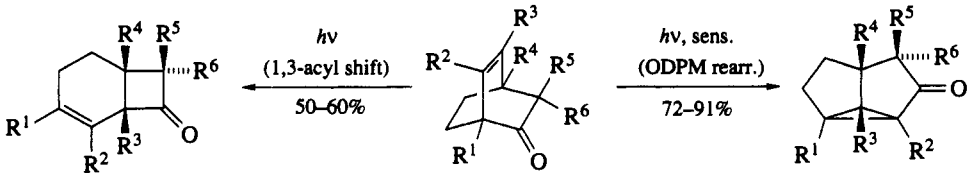
Scheme 4

Nevertheless, several examples are interpreted to be in accord with either of the two allowed concerted modes of the rearrangement, a [$_{\sigma}2_a + {}_{\pi}2_a$] or [$_{\sigma}2_s + {}_{\pi}2_s$] process. Whereas the suprafacial case involves retention[28] of the methane carbon, the antarafacial variant gives rise to inversion[29–35] of this center. However, serious doubts[1,36] about the interpretation of some of the results must be raised since geometrical restrictions may also lead to a stereoselective reaction course in the case of stepwise pathways.

2.6.2.2 Selective Population of Excited States: The Clue to Reaction Selectivity

High quantum and chemical yields of ODPM rearrangements are obtained with substrates in which the β,γ-enone chromophore is part of a conformationally rigid molecular assembly which at the same time guarantees adequate orbital overlap of the C=C and C=O π-bonds. Whereas in bicyclic and bridged β,γ-unsaturated ketones these prerequisites are widely met, acyclic β,γ-unsaturated ketones usually rearrange inefficiently since other channels of energy dissipation from the triplet state predominate. Exceptions to this rule are substrates in which the C=C π-bond is part of a styrene or an α,β-enone moiety (Section 2.6.3.1). In this context it should also be noted that β,γ-unsaturated aldehydes, except for one case, are ODPM unreactive (Section 2.6.3.2).

The principle of efficiency and selectivity control of the 1,2-acyl shift can best be demonstrated by the bicyclo[2.2.2]octenone transformations given in Scheme 5.



(22) (20) (21)

a: R^{1-6} = H (refs. 5–11, 39, 40; available enantiomerically pure)

b: R^1 = Me, R^{2-6} = H (refs. 5–11, 39)

c: $R^{1,4}$ = Me, $R^{2,3,5,6}$ = H (ref. 5)

d: $R^1 = CH_2CH(OMe)_2$, $R^{2,3,5,6}$ = H, R^4 = OMe (refs. 8, 41)

Scheme 5

As mentioned previously, the energy of the lowest and, at the same time, ODPM-reactive triplet state of structurally plain β,γ-unsaturated ketones is in the range of 289–310 kJ mol^{-1}.[12–17] This means that sensitization of the 1,2-acyl shift starts to be effective with acetophenone or acetophenone-type donors, known to possess a T_1 energy of 302–310 kJ mol^{-1}.[37,38] Most efficient energy transfer is guaranteed with sensitizers transferring their energy exothermically, *e.g.* a quantum yield close to unity is determined for the conversion (**20a**) → (**21a**) in 1–2% acetone solution [$E(T_1)$ of acetone approx. 335 kJ mol^{-1}] when irradiating at λ_{irr} 300 nm; Φ = 0.3 is found for the same transformation when sensitized by acetophenone [20% of acetophenone added to acetone, benzene or cyclohexane solutions of (**20a**); λ_{irr} > 340 nm].[39] The chemical yields are uniformly high, 86–91%, under either condition at 94–96% conversions of starting enone. The reaction run in pure acetone solution at λ_{irr} 300 nm is, in addition to its efficiency, very attractive from a practical viewpoint. Acetone serving both as solvent and sensitizer renders the work-up and purification preparatively easy: no separation procedure is required. It should be noted, however, that the substrate concentration under the latter conditions should not exceed 2–4% because another reaction path, the 1,3-shift induced by Norrish type I cleavage, becomes noticeably competitive, affording the cyclobutanone (**22a**). This side reaction is a consequence of direct light absorption by (**20a**) competing increasingly with absorption by the acetone at the wavelength employed. For the same reason, even greater direct absorption of light renders the yield of (**21a**) much lower (34%) when the acetone solution of (**20a**) is irradiated with 254 nm light.[40]

Cyclobutanone formation becomes more bothersome in the acetone-sensitized rearrangements of the homologs (**20b–d**) to (**21b–d**) in which approximately 10% of (**22b–d**) are already formed as by-products when 1–2% acetone solutions are irradiated. For these substrates, and generally for all 1-substituted bicyclooctenones of type (**20**), it is therefore advantageous to employ acetophenone sensitization at >340 nm, where the absorbance of the enone chromophore is negligible. Preparatively attractive high substrate concentrations of up to 10% of (**20**) can be employed under the latter conditions.

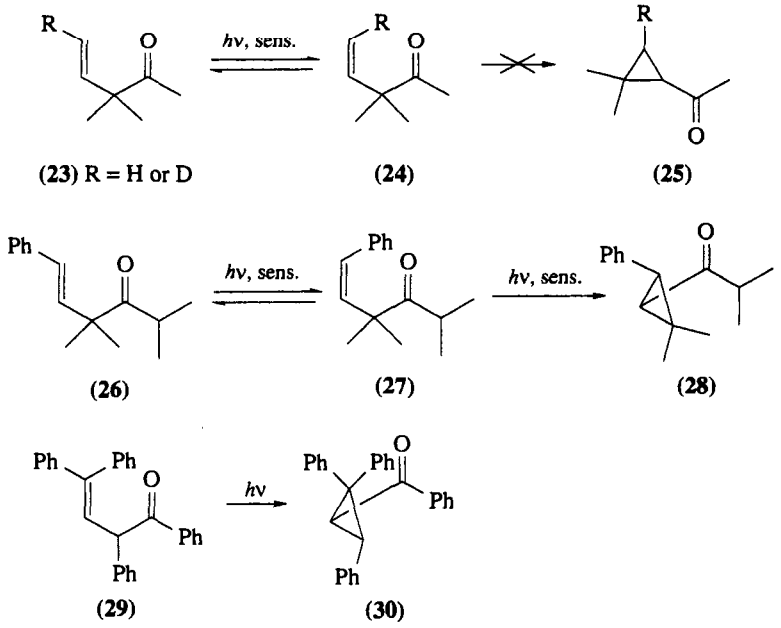
2.6.3 CLASSES OF ODPM-REACTIVE SUBSTRATES

Semicyclic, bicyclic and among these especially bridged β,γ-unsaturated ketones give rise to ODPM products in good to excellent yields. This does not only apply to the simplest case of ODPM chromophores, but also to those which are conjugated additionally either at the ketonic or at the alkenic site. These latter two arrangements undergo efficient singlet to triplet intersystem crossing and hence also 1,2-acyl migration upon direct excitation. Besides exclusive ODPM arrangements, mixed chromophores have been investigated in which additional di-π-methane (DPM) reactive sites[42] are present. Such combinations, however, react highly selectively *via* the DPM route rather than following the ODPM option (Section 2.6.4.3).

With respect to the preparative usefulness of the ODPM reaction, it should be noted that the chemical yields depend strongly on the skeletal arrangement and substituents of the reactants; the yields increase, at least as a general trend, in the order of Sections 2.6.3.1–2.6.3.4.

2.6.3.1 Acyclic β,γ-Unsaturated Carbonyls

Acyclic β,γ-unsaturated aldehydes do not undergo the ODPM reaction and acyclic β,γ-unsaturated ketones rearrange efficiently only if the C=C π-bond is further conjugated, *e.g.* part of a styrene moiety. In all the other cases where the vinyl group is less favorably substituted, other channels of deactivation from the triplet state are more important than the ODPM path. The main process then becomes twisting around the carbon–carbon double bond, resulting in *cis–trans* isomerization. This form of energy dissipation has been called the 'free rotor effect' for β,γ-unsaturated ketones, adopting an earlier formulation made for unconstrained DPM arrangements.[43–45] This process is the main event in the case of irradiation of the isomers (**23**) and (**24**) (R = D) (Scheme 6), which interconvert with a quantum efficiency of 0.12; the potential ODPM product (**25**) is not formed at all.[46] Successful competition of the 1,2-acyl migration with the free rotor effect is suggested to depend on the degree of orbital mixing in the T_1 state, which in turn is reflected by an enhanced $n \rightarrow \pi^*$ absorption.[1] If the vinyl group is part of a styrene moiety, ODPM reactivity, in competition with *cis–trans* isomerization, is again encountered. One example of this type is the transformation of the *cis*/*trans* isomers (**26**)/(**27**), which affords the sole product (**28**) in 93% yield.[47]



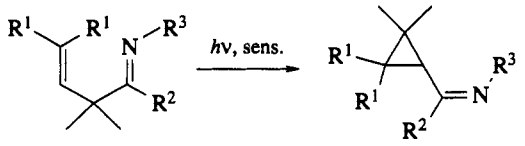
Scheme 6

A number of cases have been found where the ODPM rearrangement also occurs on direct excitation, *e.g.* compounds in which the alkene is further conjugated to either C=O or phenyl sites. It should be noted that the first example of an ODPM reaction belongs to the latter category: (**29**) rearranges without sensitizer to (**30**) in 7% yield[48] (for further examples of ODPM reactions on direct excitation, see the following Sections 2.6.3.2 and 2.6.3.3). Introduction of a ^{14}C label has shown that the rearrangement to (**30**) proceeds by migration of the benzoyl group. A closely related analog of (**29**) that bears a methyl ketone instead of the benzoyl group also undergoes *cis–trans* isomerization exclusively from the triplet state,[49] a result that may reflect enhanced susceptibility of the methyl derivative to vibrational energy dissipation.

The reluctance of the acyclic substrates to undergo the ODPM reaction, apart from the few exceptions cited above, represents a methodological gap, at least from a synthetic viewpoint; it can, however, be overcome by resorting to the respective imine derivatives of such β,γ-unsaturated aldehydes and ketones (Section 2.6.3.1.1).

2.6.3.1.1 Aza-di-π-methane rearrangement

Specific imine derivatives of otherwise reluctant (see preceding section) β,γ-unsaturated aldehydes and ketones are again photochemically reactive and cyclize in high yields when irradiated in the presence of a triplet sensitizer: they undergo the aza-di-π-methane rearrangement, typical examples of which are shown for (**31**) → (**32**) (R^1 = alkyl or phenyl).[50,51]



(31) **(32)**

a: R^1 = Ph, R^2 = H or Me, R^3 = OAc

b: R^1 = Me, R^2 = H, R^3 = OAc

no reaction (*hν*, direct or sens.) in case of R^1 = Ph, R^2 = H or Me, R^3 = OH or OMe

This reaction depends on the type of nitrogen substitution and it is proposed that the reactivity may correlate with the ionization potential of the imine.[52] Oxidized derivatives, *i.e.* the oxime (**31**; R^3 = OH)[53] and the oxime ether (**31**; R^3 = OMe),[54] fail to undergo the aza-di-π-methane reaction. Instead, isomerizations around the C=N and C=C bonds are the main paths of deactivation. Only for one oxime, a cyclic and additionally constrained derivative, has aza-di-π-methane reactivity been reported.[55]

In order to increase the ionization potential of the oxime group, oxime acetates have been prepared and investigated recently.[56] The acetophenone-sensitized rearrangement of (**31a**) turns out to be highly efficient, providing the cyclopropane (**32a**) in 79% yield in addition to the nitrile derivative, which derives from elimination of acetic acid, to the extent of 11%. The aza-di-π-methane reaction also proceeds in benzene; direct excitation, on the other hand, fails to trigger this process. The authors suggest that initial energy transfer to the 1,1-diphenylalkene moiety may be responsible for the success of cyclization. This notion is substantiated in the same work[56] by the lack of rearrangement of (**31b**) in the presence of acetophenone. The sole product formed under these conditions is an oxetane. The aza-di-π-methane reaction path, on the other hand, is again activated when (**31b**) receives the energy from acetone to form (**32b**), a result which confirms the necessity for exothermic energy transfer to the alkene moiety of the starting material.

In a synthetic context, it is important to note that liberation of the carbonyl from the respective imine photoproducts has so far not yet been probed. A potential 'drawback' of this step could be simultaneous cleavage of the cyclopropane[57,58] under the necessary hydrolytic conditions, a transformation which is, however, by itself part of the synthetic strategy in many instances.[59]

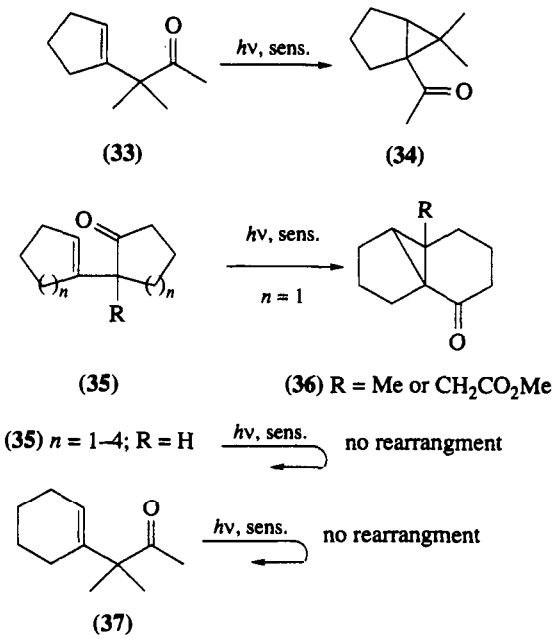
2.6.3.2 Semicyclic β,γ-Unsaturated Carbonyls

In cases where either the C=C, the C=O or both moieties of a β,γ-unsaturated enone are part of a cyclic system, the ODPM reactivity is noticeably enhanced and less substituent-dependent compared with the previously discussed acyclic arrangement of the chromophore. Two examples of this category have already been given earlier in Section 2.6.2.1 (Scheme 1): the transformations of (**3a–d**) to a mixture of (**4a–d**) + (**5a–d**)[12,13,16,30] and (**6c,e,f**) to (**7c,e,f**)[21] which proceed in yields as high as 65% and 84%, respectively.

Efficiency and limitation of the ODPM reaction are strongly coupled to the degree of flexibility of the alkene moiety. The energy dissipation from the triplet state *via* twisting of the C=C bond is indicated by a comparison of the following examples. When the C=C bond is geometrically constrained, for example being part of a five-membered ring, the rearrangement proceeds smoothly, as documented by the representative reactions of (**3a–d**) and (**6f**), cited above, as well as (**33**) → (**34**)[46] and (**35**) → (**36**) (Scheme 7).[35,59] On the other hand, no rearrangement occurs when the vinyl group is embedded in a six-membered ring such as in (**37**).[46] In this connection it should be pointed out that strong evidence for the existence of alkene twisting has recently been gained in a closely related field, the photochemistry of α,β-unsaturated cyclohexenones.[60]

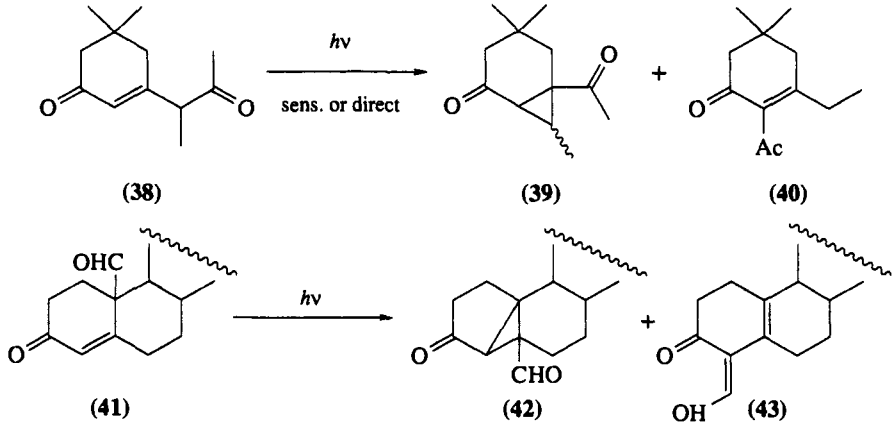
Substrates in which the methane carbon is not fully substituted, for example in (**35**; R = H), are similarly ODPM unreactive, irrespective of the ring size of the alkene moiety; β,γ → α,β isomerization of the C=C bond appears to constitute a major path of chemical energy dissipation.[61] One exception in this category is, however, the earlier cited (**3d**) in which the alkene is part of a styrene moiety.[16]

When the C=C bond is part of an α,β-unsaturated ketone moiety as in (**38**) (Scheme 8), direct (*i.e.* π,π* excitation) triggers the ODPM reaction: a stereoisomeric mixture of (**39**) and the 1,3-shift product (**40**) is formed in 93% and 6% yield, respectively, at 91% conversion of starting material.[62] Compounds (**40**) and (**39**) are suggested to be generated from the singlet and triplet state, respectively.[62] This finding



Scheme 7

of 1,2-acyl migration *via* the singlet state seems to be characteristic for various categories of substrates with an extended chromophore (additional conjugation of the vinyl group to either phenyl or C=O sites). Examples of this type are also encountered with bicyclic (**8** and **16** in Schemes 3 and 4, respectively), acyclic (**29** in Scheme 6) and bridged chromophores (**20l** in Scheme 11).



Scheme 8

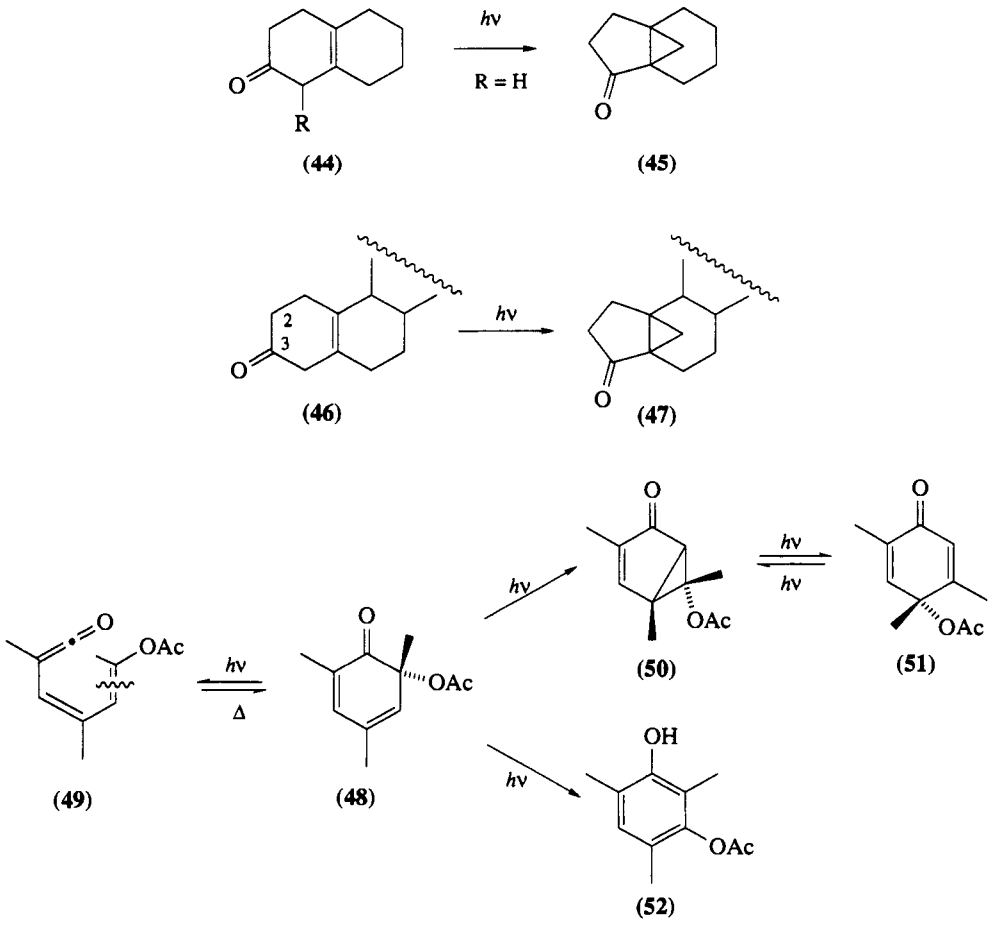
A concluding result, albeit of little synthetic value, should still be mentioned because of its uniqueness. One congener (**41**) of the otherwise ODPM-resistant β,γ-unsaturated aldehyde class exhibits ODPM reactivity on direct excitation, giving rise to the formation of (**42**), albeit in moderate yield, besides decarbonylation and 1,3-acyl migration (→ **43**) as the major reactions (Scheme 8).[63]

2.6.3.3 Mono-, Bi- and Spiro-cyclic β,γ-Unsaturated Ketones

Representative examples of conversions of bicyclic β,γ-enones have previously been cited in the mechanistic context: the efficient transformation of (**8**) into (**11**) (Scheme 3),[24] the reaction of an analog of (**8**) lacking the C-7 carbonyl,[64,65] and ultimately the preparation of (**14**) and (**15**) from (**12**) (Scheme 4).[25]

In agreement with the findings concerning the reactivity of (**38**) and (**41**) (Scheme 8), the O=C—C—C=C—C=O chromophore in (**8**) also undergoes the 1,2-acyl shift on direct excitation.[24,66] This rearrangement has been shown to occur from the lowest triplet state (π,π^*) in the energy range typical of α,β-enones.[66]

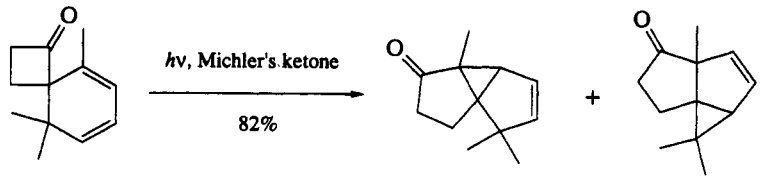
Two unusual findings concern ODPM reactions encountered on direct excitation of structurally simple β,γ-enone chromophores as in (**44**; R = H; Scheme 9) and in the steroidal analog (**46**), which rearrange to (**45**)[67–69] and (**47**),[68,69] respectively. Intriguingly, a number of closely related compounds do not rearrange to ODPM products in the absence of a sensitizer,[64,65,70] two examples of which are (**44**; R = Me)[68] and the 2-keto isomer of (**46**).[68,69] It has been suggested that the dihedral angle between the carbonyl and the vinyl group in the enones controls the efficiency by which the $^3(\pi,\pi^*)$ state is populated on direct irradiation; hence the reaction selectivity of 1,2- *vs.* 1,3-acyl migration.[1,71]



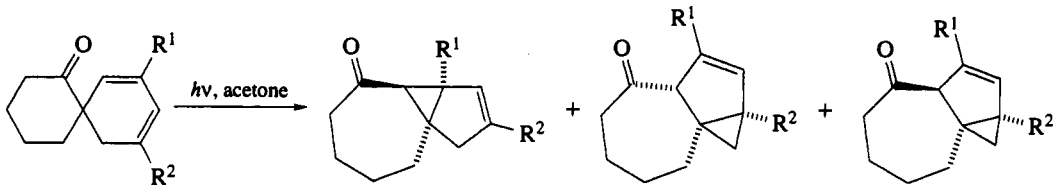
Scheme 9

In the monocyclic series, the 2,4-cyclohexadienones rearrange to photoproducts of potential synthetic value.[72] However, for efficient 1,2-acyl migration, only a relatively small number of substrates are suitable. These must be highly substituted, for example (**48**). Whereas on direct excitation in methanol, cleavage to the isomeric ketenes (**49**) ($\Phi \geq 0.42$) predominates,[73] the remarkably stereoselective 1,2-acyl shift to the bicyclohexenone (**50**) is found either in trifluoroethanol or when the dienone is adsorbed on silica gel.[74] The conversion to (**50**) is followed by a reversible phototransformation to the cross-conjugated dienone (**51**)[75,76] and accompanied by aromatization to (**52**) to a minor extent.[77] Such reactivity has also been verified for tetra- and penta-methylated 2,4-cyclohexadienones.[78,79] The only photoreaction of the hexamethylated homolog, on the other hand, is ketene formation.[78,80,81]

In a third category of cyclic β,γ-enones of synthetic potential, the chromophore moieties are linked by a spiro carbon; typical examples are a β,γ-unsaturated δ-diketone[82] and β,γ;δ,ε-unsaturated spirocyclic ketones.[83–86] A representative of the latter category is (**53**), which upon triplet sensitization with Michler's ketone affords the isomers (**54**) and (**55**) in a ratio of about 2:1 and a total yield of 82% (Scheme



(53) (54) 71% (55) 29%



(56) (57) (58) (59)

total yield:	74%	**a**: R^1 = Me, R^2 = H	75%	20%	5%
	60%	**b**: R^1 = H, R^2 = Me	68%	24%	8%
	51%	**c**: $R^1 = R^2$ = H	33%	55%	12%
	95%	**d**: $R^1 = CO_2Me$, R^2 = H	100%	0%	0%

Scheme 10

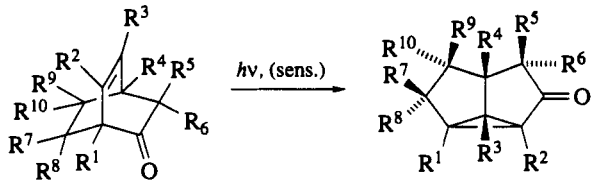
10).[83] Analogous homoconjugated spirocyclobutanones in which the diene moiety is part of a seven- or eight-membered ring have similarly been rearranged.[83] Analogously, the acetone-sensitized rearrangement of (**56a,b**) leads to a mixture of vinyl cyclopropyl ketones, the major isomers of which are (**57a,b**) besides two minor components (**58a,b**) and (**59a,b**).[84] Reduced selectivity and yield have been found for the conversion of (**56c**).[84] However, a preparatively attractive result is reported for the sensitized reaction when R^1 is an electron-withdrawing group such as the methyl ester in (**56d**): the *trans* isomer (**57d**) is obtained exclusively in 95% yield.[85] The rearrangement of (**56d**) is also highly selective when direct irradiation is employed (>340 nm light): the *trans* product (**57d**) is formed solely.[85] Interestingly, if the irradiation is conducted with 254 nm light, other reaction channels are activated, *i.e.* electrocyclic opening of the diene moiety predominates.[84,85] With regard to potential synthetic exploitation of this chemistry, the smooth thermal isomerization of (**57d**) to (**59d**) is worth mentioning.[85] The photochemical results with (**56a–d**), *i.e.* the striking wavelength dependence of the reactions, are interpreted as being indicative of the mechanistic involvement of more than one excited state with exceptionally high selectivity.[86]

2.6.3.4 Bridged β,γ-Enones

2.6.3.4.1 General

Since the efficiency of the ODPM reaction depends strongly on the degree of potential twisting of the C=C moiety of the β,γ-enone in the excited state (*cf.* Sections 2.6.3.1 and 2.6.3.2), the conformationally rigid [2.2.1]- and especially the [2.2.2]-bridged skeletons are generally excellent candidates for good performance. Synthetically very useful examples of bicyclo[2.2.2]octenone transformations *via* the ODPM path have already been given in Scheme 5; for the extension of the list, further analogous conversions are cited in Scheme 11 (for older examples, consult refs. 1–4).

The rearrangement of bicyclo[2.2.1]heptenone (**60a**) in acetone affords mainly the 1,2-acyl shift product (**61a**) accompanied by a small amount of the 1,3-shift isomer (**62a**),[32,99] the latter being convertible to (**61a**) photochemically by acetone sensitization (Scheme 12).[99] In accord with the results discussed in Section 2.6.2, formation of (**62a**) can be suppressed if acetophenone (λ_{irr} > 340 nm) is employed as the sensitizer. Identical photoreactivity has been found for the two higher-substituted congeners (**60b**)[100] and the spiro-2-norbornenone (**60c**).[31,32] A mechanistic study has revealed that (**60a**) and (**62a**) both give (**61a**) on triplet sensitization and that the triplet diradical (**63**), generated independently by benzophenone-sensitized nitrogen extrusion from the parent ketoazoalkane, is a common intermediate.[101]



(20) (21)

a–d: *cf.* Scheme 5

e: $R^{1,4,7-10}$ = H, $R^{2,3}$ = CO_2Me, $R^{5,6}$=Me (76% yield) (refs. 87, 88)

f: $R^{1,2,4,7-10}$ = H, R^3 = CO_2Me, $R^{5,6}$ = OMe (ref. 89)

g: $R^{1-6,9-10}$ = H, R^7 = Me, R^8 = CH_2OH (91% yield) (ref. 90)

h: $R^{1-6,8,10}$ = H, $R^{7,9}$ = CH=CH (66% yield) or CBr=CH (80% yield) (ref. 91)

i: $R^{1-3,5-8}$ = H, $R^{4,9}$ = cycle, R^{10} = Me (structure *cf.* Scheme 21, 70% yield) (refs. 92–94)

j: R^{1-7} = H, $R^{8,10}$ = cycle, R^9 = Me (structure *cf.* Scheme 21, 72% yield) (refs. 92–94)

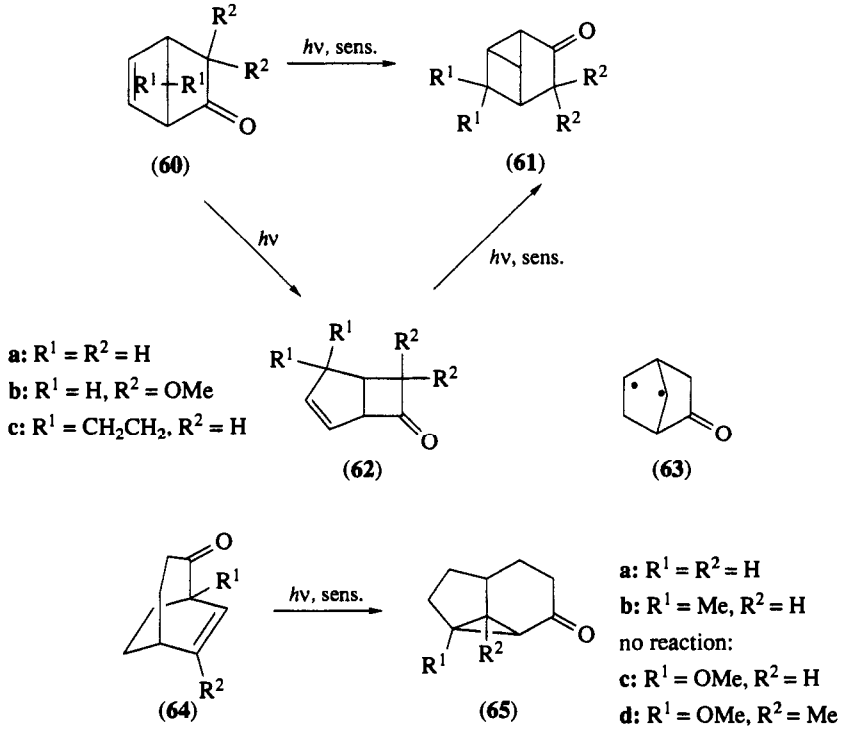
k: R^1 = Me, R^2 = H, $R^{3,4}$ = cycle, R^{5-10} = H (structure *cf.* Scheme 21, 50% yield) (ref. 95)

l: $R^{1,4-8}$ = H, $R^{2,3}$ = $CMe_2(CH_2)_2CO$, $R^{9,10}$ = Me (direct or sens., 78% yield) (ref. 96)

m: $R^{1,4,7-10}$ = H, $R^{2,3,5 \text{ or } 6}$ = CO_2Me, $R^{5 \text{ or } 6}$ = Me or CH_2Ph (51–65% yield) (ref. 97)

n: $R^{1-4,7-9}$ = H, R^5 = CO_2Me, $R^{6,10}$ = four-, five- or six-membered cycles (66–89% yield) (ref. 98)

Scheme 11



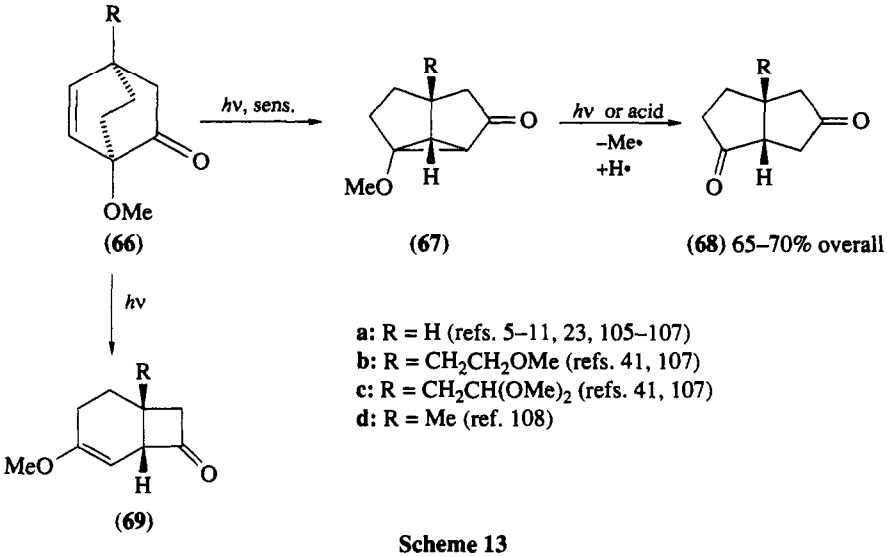
Scheme 12

While the bicyclo[2.2.1]heptenones and bicyclo[2.2.2]octenones are both excellent ODPM reactants, the higher homolog bicyclo[3.2.2]nonenones (**64**)[102–104] are rather reluctant regarding the 1,2-shift. In acetone solution (λ_{irr} > 290 nm), (**64a**) and (**64b**) rearrange in moderate yields of 18% and 23%, respectively, to the cyclopropyl ketones (**65a,b**) besides formation of the 1,3-shift products in about equal amounts.[104] Surprisingly, the 1-methoxy derivatives (**64c,d**) do not undergo the 1,2-shift at all.[104] Specific patterns of substituents in the enone can sterically control or even alter the course of ODPM reactions. Similarly, additional unsaturation in the starting enone gives rise to competitive reaction modes

(DPM reaction), yielding products which are of great synthetic value as well. The following classes of substrates exhibit such reaction properties: 1-methoxy-substituted β,γ-unsaturated ketones (Section 2.6.3.4.2), β,γ-unsaturated ε-diketones (Section 2.6.3.4.3), β,γ;β′,γ′- and α,β;β′,γ′;δ,ε-unsaturated ketones (Section 2.6.4.3).

2.6.3.4.2 *1-Methoxy-substituted cyclic β,γ-unsaturated ketones*

The rearrangement of 1-methoxy-substituted bicyclo[2.2.2]octenones (**66a–d**) follows a mechanistic variant of the ODPM reaction, which includes two consecutive single-step phototransformations, *i.e.* the ODPM path to (**67a–d**), again triplet sensitized, and conversion to the final 1,4-diketones (**68a–d**) (*cf.* Scheme 13).[5–11,105–108] The second step involves cleavage of the transient cyclopropane in (**67a–d**) accompanied by loss of the methoxy methyl, most likely *via* methyl radicals, and transfer of a hydrogen atom from the solvent.[107]



a: R = H (refs. 5–11, 23, 105–107)
b: R = CH_2CH_2OMe (refs. 41, 107)
c: R = $CH_2CH(OMe)_2$ (refs. 41, 107)
d: R = Me (ref. 108)

Scheme 13

Notably, diquinane products of type (**68**) are of particular synthetic interest. Firstly, their rings are conveniently functionalized by keto groups that can be chemically distinguished and allow further individual elaboration of the functionality pattern into polyquinanes (*cf.* Section 2.6.6). Secondly, the starting materials (**66a–d**) are readily available, each in about 30% yield, from anisole, *p*-methoxytoluene, *p*-methoxyphenylacetic acid and *p*-methoxybenzyl cyanide, respectively.[41,105–108] The optimum reaction conditions, resulting from detailed mechanistic studies,[107] are as follows. Irradiation with 300 nm light (Rayonet) of argon-flushed 1% solutions of (**66a–d**) in 2:1 mixtures of acetone and isopropyl alcohol at room temperature affords 65–70% yields of (**68a–d**) and 5–10% of cyclobutanones (**69a–d**). The latter 1,3-shift products are accessible as the main components in yields of 50–60% on direct irradiation of the starting enones.[41]

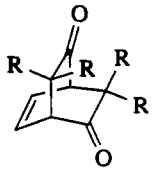
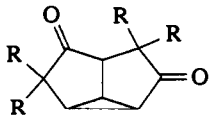
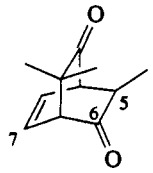
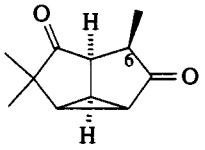
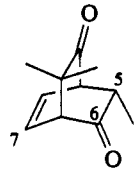
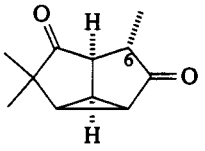
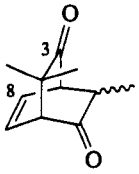
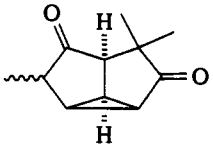
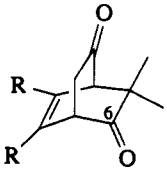
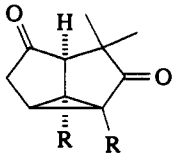
It has been proposed that the sensitized conversion (**66a**) → (**68a**) proceeds *via* the 1,2-acyl shift product (**67a**).[105,106] The three-membered ring in (**67a**) is photolytically cleaved,[109,110] followed by loss of the methoxy methyl and addition of a hydrogen atom to give (**68a**).[105–107] In neat acetone, serving both as solvent and triplet sensitizer of the homologous (**66b**), and in benzene containing acetophenone, the formation of a transient in low concentration has actually been observed.[41,107,108] The analytical data and chemical behavior are clearly in favor of the proposed tricyclic structure (**67b**).[41,107] However, the donor/acceptor substitution of the three-membered ring[58,111,112] renders the compound too labile to allow its isolation. Compound (**67b**) reacts not only photochemically to give (**68b**) but also undergoes this transformation in protic media.[41,107]

The ODPM reactivity of higher homologs in the series of bridged 1-methoxy compounds, *i.e.* bicyclo[3.2.2]nonenones, has also been investigated.[104] In contrast to the nor-methoxy analogs (**64a,b**) (*cf.* Scheme 12), which undergo the 1,2-migration in moderate yield, a 1,3-shift is observed exclusively for the derivatives (**64c,d**) [note: the substituents Y and Z in structure (**4**) of ref. 104 are erroneously interchanged].

2.6.3.4.3 β,γ-Unsaturated ε-diketones

The ODPM rearrangement has been very successfully probed with extended chromophores such as β,γ-unsaturated ε-diketones (Table 1). The ε-diketones (**70**), (**72**) and (**75**) afford the tricyclo[3.3.0.$0^{2,8}$]octane-4,7-diones (**71**),[113,114] (**73**) + (**74**)[113–115] and (**76**),[116] respectively, upon triplet sensitization. The rearrangements of (**70**) and (**72**) have been carried out in acetone at λ_{irr} = 300 nm and the conversion of (**75**) to (**76**) has been achieved in acetophenone employing 350 nm light. These rearrangements proceed efficiently with quantum yields of 0.17–0.93 and deliver the products in 60–95% yield.[114]

Table 1

β,γ-Unsaturated ε-diketone	*Photoproduct*	*Quantum yield (Φ)*	*Chemical yield (%)*	*Ref.*
 (**70**)	 (**71**)			
R = H		0.93	75	113, 114
R = Me		0.34	60–75	113, 114
 (**72a**)	 (**73a**)	0.36		
			70–74	113, 114
 (**72b**)	 (**73b**)	0.17		
 (**72a,b**)	 (**74a,b**)	—	Minor product	113, 114
 (**75**) R = CO_2Me	 (**76**)	—	95	116

A preparatively attractive aspect of this chemistry is the exceptionally high enone concentration of more than 20%, as shown with (**72**), at which the transformations can still be run without noticeable formation of side products. In the case of the trimethyl derivative (**72**), a regioselective photochemical rearrangement favoring the formation of (**73**) over (**74**) has been encountered. The course of the reaction seems to be sterically controlled by the methyls. *In situ* photochemical equilibration of the C-5 epimers (**72a,b**) allows preferential rearrangement involving the C-6 (→ **73a,b**) rather than the C-3 (→ **74a,b**) keto group.[114,115]

It has been argued that bridging in the primary photochemical step between C-6 and C-7 of (**72a**), on the way to (**73a**), should be the sterically least-hindered ODPM path since the C-5 methyl occupies the '*exo*' position with respect to the bonding sites.[114] In contrast, the corresponding bridging in (**72b**) should be impeded by the secondary methyl now occupying the '*endo*' position. The same argument should apply to the bridging process between C-3 and C-8 of (**72a,b**) which leads to (**74a,b**). Quantum yield measurements indeed support the notion of steric hindrance exerted by the '*endo*' methyls; decreasing values are found in the order of the reactions (**70**) → (**71**; R = H), (**72a**) → (**73a**) and (**72b**) → (**73b**). The efficiency of the tetramethyl homolog (**70**) → (**71**; R = Me), that has the option of two identical bridgings yielding a single product, is greater than for (**72b**) → (**73b**) which competes with the process (**72a,b**) → (**74a,b**).

In conflict with this coherent picture of steric control of the ODPM rearrangement of the ε-diketones (**72a,b**) is the course of the transformation of (**75**).[110] This compound is reported to yield cleanly the 1,4-diketone (**76**) which is the isomer derived from bridging between the vinyl and C-6 in (**75**). In the previously described examples this reaction path has been shown to be unfavorable — an open mechanistic riddle!

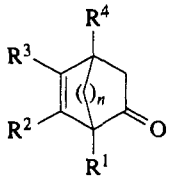
2.6.4 LIMITATIONS OF THE METHOD

2.6.4.1 General

Skeletal arrangements, substituents and ring size of the β,γ-enones are key parameters controlling the ODPM reactivity. As outlined in Section 2.6.3.1, the reactivity of acyclic β,γ-unsaturated carbonyls depends strongly on the pattern of substituents since *cis–trans* isomerization of the C=C bond is often competitive, disfavoring ODPM reactions. They are even suppressed in cases where no phenyl group is attached to the enone γ-position, such as in (**23**) of Scheme 6. The semicyclic arrangements, discussed in Section 2.6.3.2, suffer from ODPM inertness under two circumstances: incorporation of an isolated vinyl moiety in a ring of size larger than a five-membered one (**37** in Scheme 7) or absence of a quaternary methane carbon as in example (**35**; R = H).

2.6.4.2 Bridged Bicyclic β,γ-Enones

Generally excellent ODPM substrates are encountered in the classes of mono-, bi- and spiro-cyclic as well as bridged α,β-unsaturated ketones (Sections 2.6.3.3 and 2.6.3.4). In the latter category, the bicyclo[2.2.1]heptenones and bicyclo[2.2.2]octenones, with the exceptions (**20o–q**) (Scheme 14), undergo the 1,2-acyl shift much more readily than the homologous bicyclo[3.2.2]nonenones (**64**) in Scheme 12. The enones of type (**64a,b**) rearrange in moderate yields to (**65a,b**), but most interestingly the 1-methoxy derivatives (**64c,d**) do not give any ODPM product, a result which is yet difficult to rationalize. The switch of reactivity from the [2.2.1] and [2.2.2] skeletons to the [3.2.2] homologs, however, could reasonably be explained by enhanced skeletal flexibility (see the discussion of the acyclic series) or unfavorable orbital overlap, or both.



(**20**)

o: $n = 2$, R^1 = Me, $R^{2,3}$ = H, R^4 = OMe (refs. 8, 41)
p: $n = 2$, R^1 = CO_2Me, CO_2H or CO_2Na, $R^{2,3,4}$ = H (ref. 5)
q: $n = 1$, $R^{1,2,4}$ = H, R^3 = OMe (ref. 124)

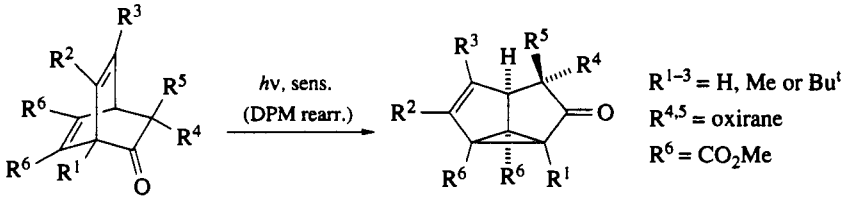
Scheme 14 ODPM unreactive substrates

Only with compounds (**20o–q**) are bicyclooctenones found which are unreactive either on direct excitation (λ_{irr} = 300 nm) or by triplet sensitization (acetone or acetophenone as sensitizer).[5,8,41,124] On comparison of these exceptional cases with the substrates in Schemes 5 and 11, it becomes apparent that ODPM reactivity *vs.* inertness is influenced by very subtle differences in the substitution pattern. For example, shortening of the acetal chain of (**20d**) to R^1 = Me for (**20o**) renders a photoreactive substrate (**20d** → **21d**; 90% yield) photochemically inert.[8,41]

A model has been proposed which allows an empirical prediction of reactivity for this class of compound.[7] Accordingly, if R^1 or R^2 are donor-type substituents or R^3 or R^4 acceptors, the substrates (**20**) are ODPM reactive. The complementary pattern of substituents (R^1 or R^2 = acceptors or R^3 or R^4 = donors) is characteristic of the unreactive enones. Bicyclo[3.2.2]nonenones (**64c,d**; no reaction, Scheme 12, Section 2.6.3.4.1) and mixed bicyclo[2.2.2]octenones (**20e** → **21e**; Scheme 11, Section 2.6.3.4.1) need not fit into this reactivity scheme.

2.6.4.3 β,γ;β′,γ′- and α,β;β′,γ′;δ,ε-Unsaturated Ketones

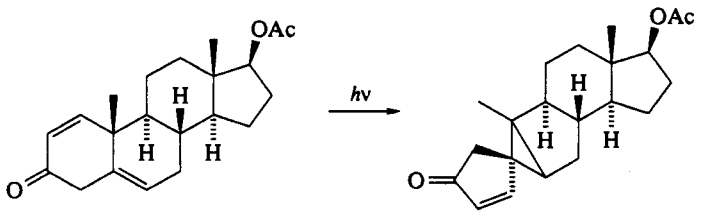
Besides parent ODPM arrangements, mixed chromophores have also been investigated in which DPM-reactive sites can compete with the ODPM reaction. β,γ;β′,γ′-Unsaturated ketones, *i.e.* barrelenones of type (**77**), rearrange to the corresponding unsaturated cyclopropyl ketones (**78**) upon acetophenone sensitization *via* a highly regioselective DPM process, rather than the optional ODPM variant, in 42–73% yields.[117,118] These results contrast with the observations in a benzobarrelenone series[119,120] but are in full agreement with the following mechanistic investigation. The question as to which of the two possible mechanisms is operative has been answered by the acetone-sensitized reaction of labelled material (**77**; $R^{2,3}$ = D, $R^{4,5}$ = Me).[121] The products must derive from a DPM process rather than from the alternative ODPM reaction paths.



(**77**) (**78**)

In summary, the above results reveal relative bridging 'rates' between the optional chromophoric sites in bicyclo[2.2.2]octadienone-type substrates (**77**) in the following order: vinyl–vinyl > keto–vinyl > benzo–vinyl bridging.[117–121]

Similarly, α,β;β′,γ′;δ,ε-unsaturated ketones react in a DPM fashion as shown for the rearrangement of steroidal dienones, *e.g.* (**79**) → (**80**).[122,123]



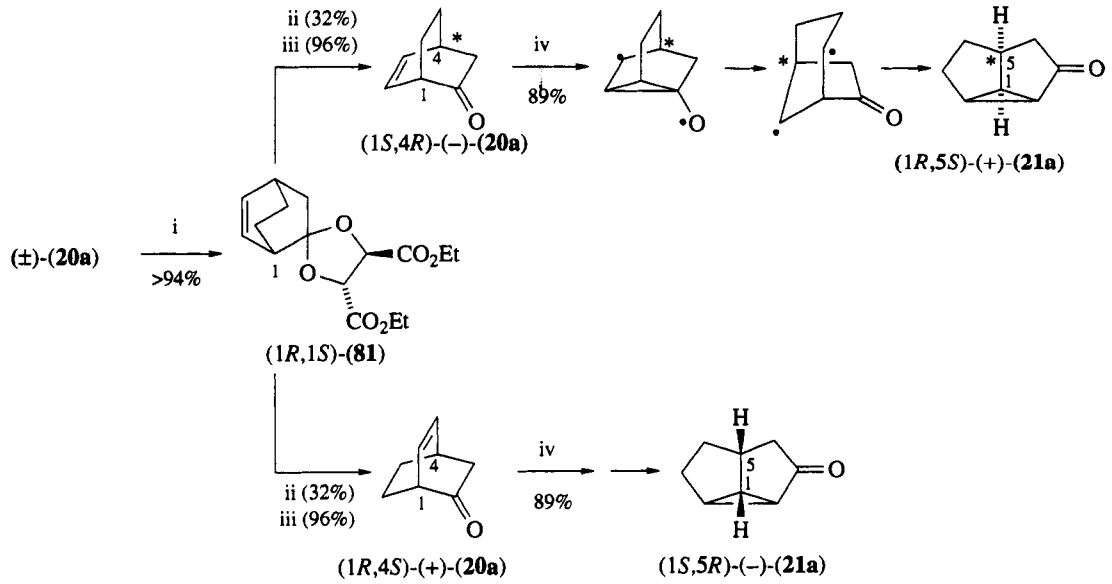
(**79**) (**80**)

2.6.5 APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

The search for efficient methods for the construction of five-membered rings with the aim of gaining access to polycondensed cyclopentanoids, which are also found in nature, has been a major concern in synthesis during the past 15 years.[125,126] Preparatively attractive routes to a remarkable number of struc-

tural variants of such natural products have been established by the use of tricyclooctanone-type building blocks and congeners thereof, all products of high-yield ODPM transformations.

A considerable number of ODPM products have been made available in optically pure form. Resolution techniques prior to the photorearrangement as well as the use of enantiomerically pure starting materials in general provide ready access to such building blocks. In contrast, enantioselection *via* sensitization has so far turned out to be preparatively of little value. The latter possibility has been probed with a racemate of (**20a**), the rearrangement of which has been sensitized by an optically active hexahydrofluorenone.[39] The enantiomeric excess of (–)-(**21a**) after 7–44% conversion of (±)-(**20a**) reaches 4.5% in benzene or in ethyl acetate at ambient temperature, and 10% in ethyl acetate at low temperature. Interestingly, the same degree of induction can be achieved when racemic sensitizer is employed for the rearrangement of (**20a**) in optically active solvent, *i.e.* in diethyl (+)-tartrate (Scheme 15).[39]



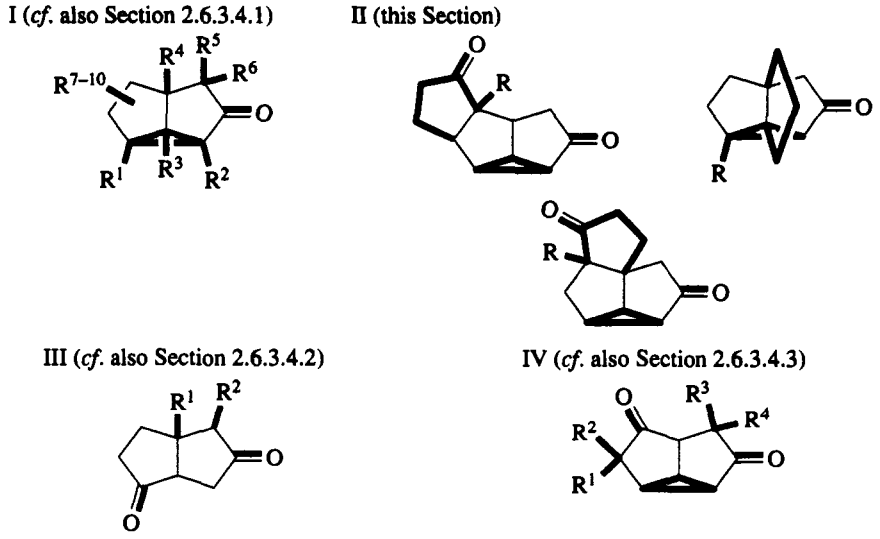
i, diethyl (*R,R*)-tartrate, *p*-TsOH, toluene, reflux; ii, chromatography; iii, 1N HCl, THF, 40 °C; iv, *h*v (300 nm), acetone

Scheme 15

The ODPM transformation of bridged β,γ-unsaturated ketones is, as expected on mechanistic grounds, enantiospecific. This aspect has been first documented by the production of (+)-(**21a**) and (–)-(**21a**) from the pure enantiomers (–)-(**20a**) and (+)-(**20a**), respectively, without loss of optical activity; this implies that the configuration of the starred carbon (see scheme above) is retained throughout the reaction cascade.[39] This circumstance has paved the way to ready access to enantiomeric target materials simply by the choice of the appropriate optically pure precursors of the photochemical step or starting materials. The enantiomers of (**20a**)[127–129] and (**70**)[114,115] are obtained in >98% enantiomeric excess and in multigram amounts *via* a resolution step which involves ready chromatographic separation of diethyl tartrate derivatives such as (**81**), followed by their hydrolysis to the enantiomers. The use of the photoproducts (**21a**), (**71**) and (**73**), which can be functionalized in a manifold manner by cleavage of the cyclopropane, *e.g.* reductively, *via* nucleophile addition or rearrangement,[57,114,115,130,131] offers a conceptually new approach to the synthesis of enantiomerically pure cyclopentanoid natural products.[5–11]

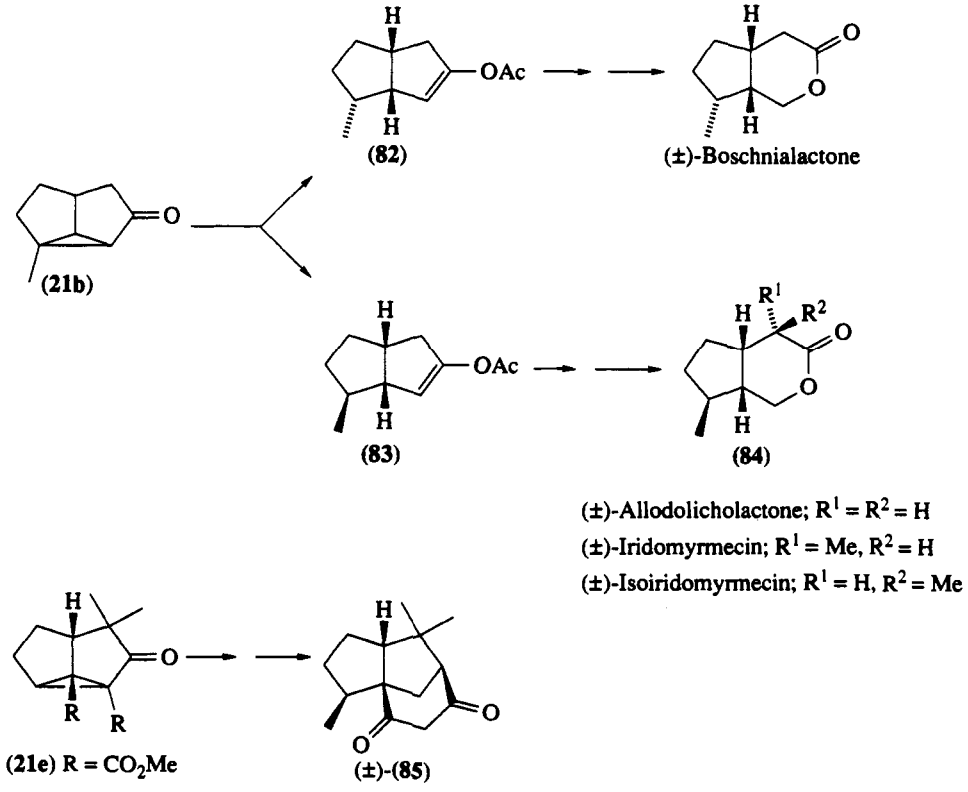
Four basic structural arrangements as shown in Scheme 16 have so far proven to be of broad utility in synthesis: a parent type (I), with a minimal but very variable set of functionalities, and three more target-oriented complexer units (II)–(IV). The bold lines in the formulae depicted emphasize the functionality pattern characteristic of each representative, constituting in sum a fully flexible and complementary set of possible synthetic modifications at the diquinane core.

Among the first synthetic achievements, based on the use of tricyclooctanones, are the following preparations of mono- and sesqui-terpenes. Four members of the monoterpene iridoid family have been obtained by a single approach (Scheme 17). The disadvantage of the stereo*non*selective reduction of (**21b**), affording (**82**) and (**83**) in a 1:1 ratio, is compensated for by the benefit of simultaneous access to four natural products: (±)-boschnialactone and the epimer (**84**), this being a suitable precursor to attain (±)-al-



Scheme 16

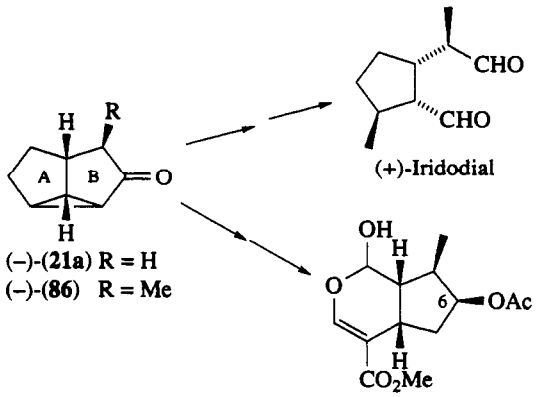
lodolicholactone, (±)-iridomyrmecin and (±)-isoiridomyrmecin.[5] The sesquiterpene cedrol and more highly oxygenated cedranoids, in racemic form, have been accessed from the Stork–Clarke β-diketone (**85**), which in turn can be assembled in a novel way *via* the 76% yield rearrangement of (**20e**) to (**21e**) (*cf.* Scheme 11).[87,88,132] In 10 steps and in a 15% overall yield, a synthesis of (±)-forsythide aglucone dimethyl ester has recently been accomplished by similarly exploiting the potential of ODPM photochemistry for the key step.[133]



Scheme 17

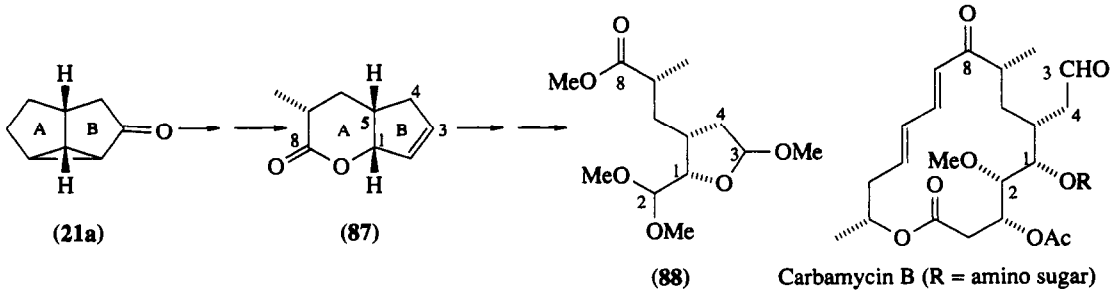
An enantioselective access to a number of different structural variants of the cyclopentanoids is given by the use of the tricyclooctanone building blocks (–)-(**21a**) and (+)-(**21a**), both of which are available in

optically pure form as mentioned previously. These particular photoproducts offer an alternative to earlier exercised principles aiming at individually designed target-oriented syntheses. The enantiomers (**21a**) exhibit structural features allowing for a multitude of synthetic transformations of predictable regio- and stereo-selectivity.[57,130,131] As part of this concept, the first stereocontrolled assembly of natural iridodial has been achieved from (–)-(**86**) *via* oxidative ring B cleavage in the last step of the sequence (Scheme 18).[129] Five steps are required for the elaboration of the target material from the intermediate (–)-(**86**), which is the product of exclusive *exo* methylation of (–)-(**21a**). Rearrangement of the cyclopropane moiety of the latter intermediate constitutes the basis for extensive ring A functionalizations, including oxidative enlargement, on the way to (+)-loganin aglucone 6-acetate.[127] This synthesis is distinguished by a higher overall yield of 7%, starting from 1,3-cyclohexadiene and acrylonitrile, than previous efforts and the lack of separation problems.



Scheme 18

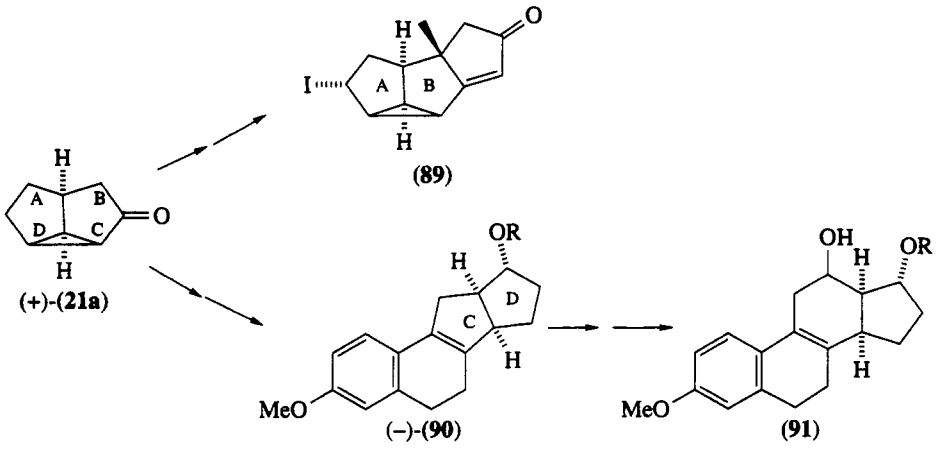
The cleavage of all rings of (**21a**) has led to stereocontrolled access to (**88**; Scheme 19), which is viewed as a segment to serve in the construction of the 16-membered lactone carbamycin B.[134] The numbered carbons in the target derive from the respective centers of the intermediate (**87**), which has been prepared from (**21a**) in a high-yield sequence involving consecutive rearrangement of the cyclopropane, Baeyer–Villiger oxidation and methylation. Evidently the correct absolute configuration, as depicted for (**88**), should derive from (–)-(**21a**) in the final version of the synthesis.



Scheme 19

The enantiomer (+)-(**21a**) has been considered configurationally suited as starting material to approach *cis,anti,cis* tricycloundecane-type targets, *e.g.* the antitumor and antibacterially active coriolin, a potential progenitor (**89**) of which has been synthesized, at first in racemic form (Scheme 20).[135,136] However, this route has been abandoned in favor of a much shorter synthesis outlined later (see Scheme 22). Two-step transformations from (+)-(**21a**) to a number of c,18-bisnor-13α,17α-dehydroestrone derivatives (–)-(**90**; R = OTs, $OCOCF_3$, Cl) have been elaborated;[131,137] these are intermediates from which ring c enlargement to (**91**) can be achieved in three further steps which are all realized in high yields (Scheme 20).[138]

In an extension of the previous concept, starting materials which are readily available in enantiomerically pure form have served for the construction of bridged β,γ-enones with an additional five-membered ring.[92,93] In this way the first total synthesis of enantiomerically pure (–)-silphiperfol-6-en-5-one



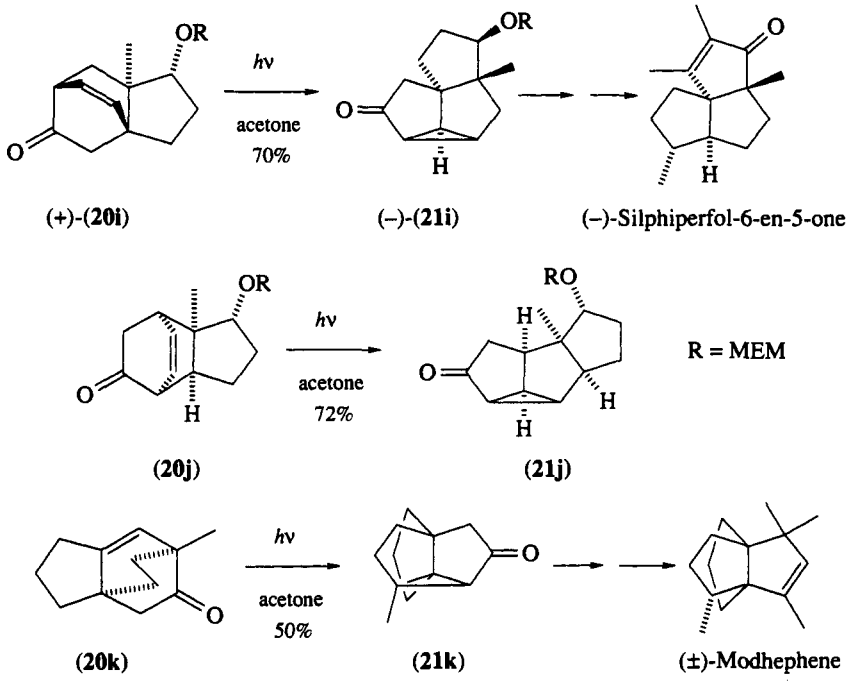
Scheme 20

has been accomplished.[92,94] The acetone-sensitized photorearrangement at λ_{irr} = 300 nm of (+)-(**20i**) cleanly furnishes the angularly fused (–)-(**21i**; 72% yield of purified product), the structural features of which have allowed economic elaboration into the silphiperfolenone target (Scheme 21). A by-product, which results from a 1,3-acyl migration, is formed to a negligible extent (4%) under the reaction conditions employed. Such a smooth rearrangement of (+)-(**20i**) is *a priori* not predictable in view of some β,γ-enones bearing bridgehead substituents known to be unreactive under ODPM conditions (see Section 2.6.4.2). Similarly efficient is the conversion of (**20j**) to the linearly arranged *cis,syn,cis* tetracycloundecanone (**21j**), for which the initially wrongly assigned *cis,anti,cis* structure[93] has later been revised on the basis of an X-ray analysis.[92,94] *Cis,anti,cis* fusion of the five-membered rings in tetracycloundecanone-type skeletons has been achieved by the rearrangement of appropriately assembled tricyclo[5.2.2.$0^{2,6}$]undecanediones in racemic form.[139] A very economic preparation of racemic modhephene, a unique natural product with [3.3.3]propellane structure, has been prepared from (**21k**), which in turn is obtained in 50% yield upon irradiation of (**20k**) in acetone solution.[95] These results are complementary in that three types of important cyclopentanoid ring fusions, *i.e.* the [3.3.3]propellane assembly, linearly and angularly fused skeletons (*cf.* Scheme 16: structures type II), can be attained by resorting to a common class of bridged β,γ-enones (**20i,j,k**). These enones are accessible *via* thermal [4 + 2] cycloadditions in an efficiently regio- and stereo-controlled manner. Whereas the stereochemical result of the addition of the etheno bridge is responsible for the ultimate *syn/anti* relation of the rings in the photoproducts, the regiochemical location of the C=C bond in the enones determines whether a propellane, a linearly or angularly fused photoproduct results.

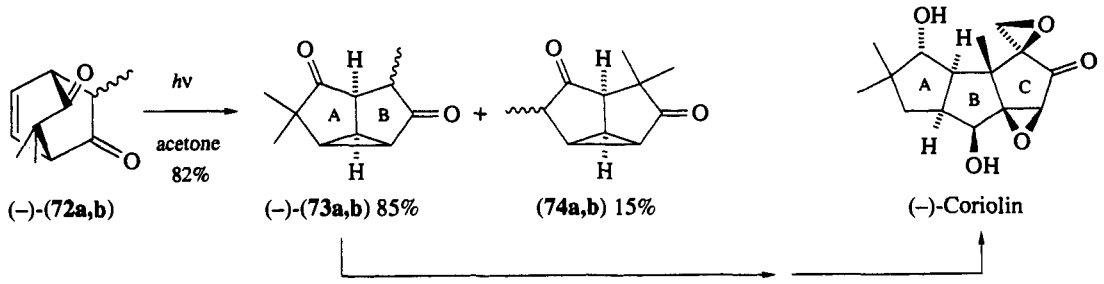
The acetone-sensitized (λ_{irr} = 300 nm) preparation of a mixture of enantiomerically pure (–)-(**73a,b**) in 70–74% yield (*cf.* Table 1), besides the minor regioisomers (**74a,b**), has opened access to the first total synthesis of the antitumor agent coriolin in its natural configuration (Scheme 22).[113–115] The key step is characterized by a novel facet of ODPM photochemistry, steric control by the methyls in (**72a,b**) giving rise to a site selective rearrangement to (**73a,b**) (*cf.* Section 2.6.3.4.3). Both epimeric photoproducts (–)-(**73a,b**) are equally suitable for the A + B → ABC building-up principle of the target. Concurrent with the ODPM reaction and favoring the most efficient ODPM channel, a second and fast photoreaction results in a 5:1 equilibration of the epimers (**72a**) and (**72b**). Although the mechanism of this process has not been fully identified, it has at least been shown that Norrish type I cleavage and reclosure is unlikely to be responsible for the epimerization.[114] The earlier mentioned, preparatively attractive, high substrate concentrations of more than 20% at which the transformation of (**72a,b**) can still be run without noticeable side reactions (1,3-acyl shift) have to be stressed again at this point. This preparation of (–)-coriolin comprises 14 steps in all, entirely from readily available starting materials; the sequence compares favorably with the shortest synthesis of the racemate achieved earlier.

Similarly, the photorearrangement of β,γ-unsaturated ε-diketone (**75**) (*cf.* Table 1) has been probed in view of its potential application as a key step for the synthesis of cedranoids.[116] Although the tricyclooctanedione (**76**) is cleanly accessible, the scheme has been abandoned in view of difficulties in assembling the ultimately required functionalities; routine β,γ-enone photochemistry has been employed instead.

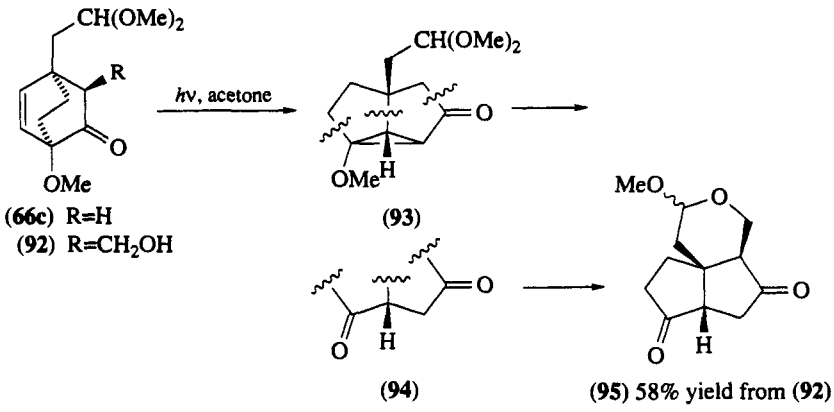
In a final example, use has been made of a mechanistic variant of the ODPM reaction: the conversion of a 1-methoxy-substituted bicyclo[2.2.2]octenone (**92**) to the bicyclo[3.3.0]octadione (**94**; Scheme 23). The highly substituted β,γ-enone (**92**) is accessible *via* hydroxymethylation of (**66c**), a compound which



Scheme 21



Scheme 22



Scheme 23

itself is photoreactive (*cf.* Scheme 13). Enone (**92**) rearranges in two consecutive single-step photoreactions to (**94**) *via* (**93**). The photoproduct (**94**) cyclizes smoothly upon purification on silica gel, affording a potential progenitor (**95**) of pentalenolactone G in good yield.[9,10,41,140] This natural product is a member of a family of antibiotic and tumor inhibitory agents. The photorearrangement (**92**) → (**94**), which is

mechanistically in accord with the reactions (**66a–d**) → (**68a–d**), can be performed either in acetone with 20% acetophenone added ($\lambda_{irr} \geq 340$ nm) or by following the procedure described in Section 2.6.3.4.2.[41]

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3.1
Thermal Cycloadditions

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3.1.1 INTRODUCTION

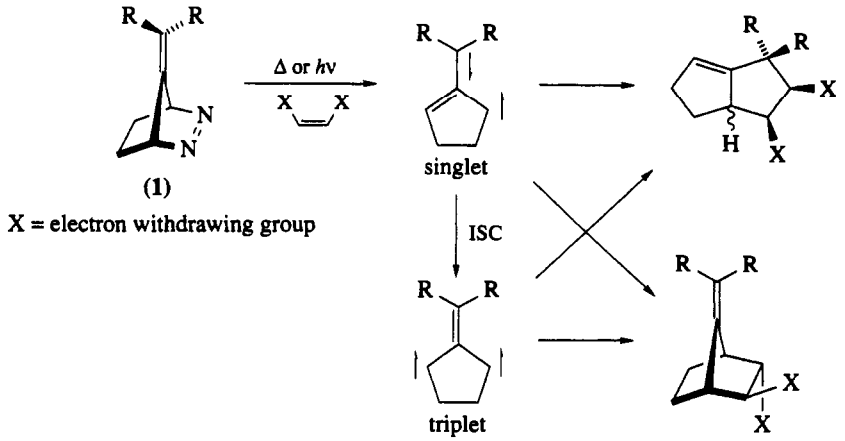
The past 15–20 years have witnessed a tremendous growth in the number and type of reactions which are applicable to the synthesis of five-membered rings. The underlying reasons for the growth, and for the continued activity one finds in this area of research, have been elegantly described by others and will not be recounted here.[1] The material which follows focuses primarily upon the use of derivatives of a very reactive diradical, trimethylenemethane (TMM), to construct carbocyclic systems through use of the 1,3-diyl trapping reaction, and upon the use of 1,3-dipolar cycloaddition reactions to synthesize both carbocyclic and heterocyclic ring systems. The latter field is, of course, very rich, intricate and extensive. The present treatment provides only a brief overview of it and, unfortunately, many elegant pieces of work have not been discussed.

3.1.2 TRIMETHYLENEMETHANE (TMM)

3.1.2.1 Regioselectivity

3.1.2.1.1 Fused versus *bridged (intermolecular 1,3-diyl trapping)*

Both the thermally and the photochemically initiated extrusion of nitrogen from bicyclic diazene (1) leads to the formation of a 1,3-diradical (diyl) which is structurally related to trimethylenemethane.[2] As shown in the cascade mechanism illustrated, two forms of the diyl can be intercepted by alkenes bearing electron-withdrawing groups (diylophiles), *viz.* the open form of the singlet diyl and the triplet diyl which is formed *via* intersystem crossing from the singlet (Scheme 1).[2]



(1)

X = electron withdrawing group

Scheme 1

Fortunately, for synthetic purposes, the diyls are sufficiently long lived to be trapped in high yield.[2,3] Of equally good fortune, the singlet undergoes cycloaddition with maintenance of diylophile stereochemistry and with a marked regiochemical preference for formation of fused adducts. The triplet, on the other hand, undergoes cycloaddition with loss of the diylophile stereochemistry and with the formation of both bridged and fused cycloadducts; little preference is expressed for the formation of either product type (Table 1).[2a,b]

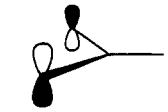
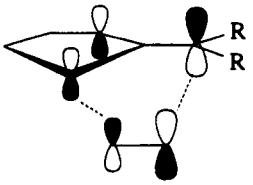
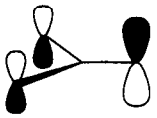
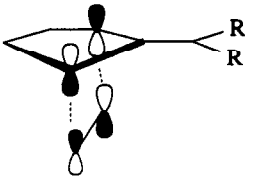
Table 1 Product Composition as a Function of Diyl Spin State

Diyl spin state[a]	*Diylophile*	*Fused bridged ratio*	*Trans:cis ratio*[b]
Singlet	Dimethyl fumarate	65.7	*Trans* only
Triplet	Dimethyl maleate	0.72	88:12
Triplet	Dimethyl fumarate	0.72	92:8

[a]From diazene (1) when R = Me. [b]Refers to relationship between esters in the product.

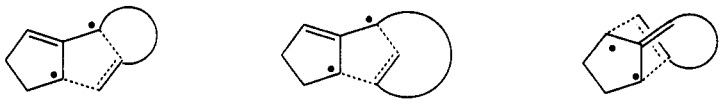
Frontier orbital theory has been used successfully to rationalize the regiochemical course of the singlet diyl chemistry (Table 2).[2a] To do so, the assumption is made that the formally degenerate nonbonding molecular orbitals of TMM are perturbed, placing the symmetric form below the antisymmetric and making the former the HOMO. Only when the exocyclic carbon of the diyl is substituted with two strongly electron-donating methoxy groups is it suggested that the antisymmetric orbital lies below the symmetric. In this case, bridged cycloadducts are formed preferentially, in accord with expectations based upon this ordering of frontier molecular orbitals.

Table 2 Frontier Molecular Orbital Analysis of Intermolecular Diyl Trapping

TMM nonbonding molecular orbitals (symmetry)	*HOMO/LUMO combination*	*Predicted product*
Symmetric diyl HOMO with diylophile LUMO		
 (Antisymmetric, *a*)		Fused cycloadduct
Antisymmetric diyl HOMO (R = OMe) with diylophile LUMO		
 (Symmetric, *s*)		Bridged cycloadduct

3.1.2.1.2 Linear versus *bridged (intramolecular 1,3-diyl trapping)*

Like its intermolecular counterpart, the intramolecular diyl trapping reaction can, in principle, afford either fused or bridged cycloadducts.[4] Because of the geometric constraints imposed by the intramolecular variety, however, one might anticipate that bridged products, strictly analogous to those produced in the intermolecular cycloaddition, would form only when the length of the tether is long enough to minimize the angle strain which would be associated with maintaining a double bond at C-7 of the bicyclo[2.2.1] cycloadduct. When the length of the tether is three or less, therefore, one might safely dismiss from consideration the formation of products of this type, the type II bridged products. Indeed, no evidence is available to suggest that these products have ever been produced (Figure 1).



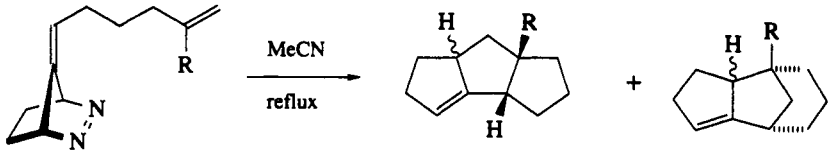
Linear Type I bridged Type II bridged

Figure 1

Both linear and type I bridged cycloadducts can be produced selectively and by design.[5] The regioselective formation of linearly fused cycloadducts occurs from the singlet state of the diyl when the diylophile is substituted with an electron-withdrawing group at either the internal or terminal carbon, and also when the diylophile bears the tether as its only substituent. It has recently been firmly established that type I bridged cycloadducts arise from the triplet diyl and that they can be formed regioselectively when the internal carbon of the diylophile is substituted with a large alkyl group.[5] The mere presence of an alkyl group at this carbon is sufficient to ensure the formation of the bridged cycloadduct. However, it is not sufficient to ensure the formation of synthetically useful amounts. Table 3 clearly indicates[5] that the selectivity increases as the size of the substituent increases, and eventually to a value where synthetically useful amounts of the bridged cycloadduct are obtained. The trend is reminiscent of the way in which the 6-*endo,trig* to 5-*exo,trig* cyclization ratio increases as the size of the substituent on the internal carbon of the 5-hexenyl monoradical increases.[6]

These results suggest that when an electron-withdrawing substituent is placed on the internal carbon of the diylophile, then the diyl HOMO–diylophile LUMO energy gap is small enough such that the singlet form of the diyl is trapped at a rate which significantly exceeds the rate of intersystem crossing to the

Table 3 Influence of Diylophile Substituents Upon Bridged *versus* Linear Regioselectivity



R	*Bridged:linear ratio*	*Yield (%)*
CH_2OH	1.2:1	90
$CH(OMe)_2$	2:1	93
$CMe(OMe)_2$	16:1	83
COMe	1:7	98
CO_2Me	1:19	85

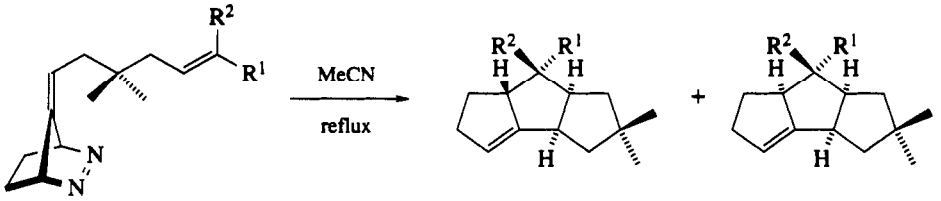
triplet manifold. On the other hand, when an alkyl group occupies the same site, then the rate of trapping of the singlet decreases sufficiently to allow intersystem crossing and the expression of triplet diyl chemistry. Provided the alkyl group is large enough, type I bridged cycloadducts form regioselectively. This discovery promises to be of utility in a variety of synthetic endeavors.

3.1.2.2 Stereoselectivity (Intramolecular)

3.1.2.2.1 Diylophile stereochemistry

Diylophile stereochemistry is nearly always maintained. This generalization is adequately exemplified by the chemistry of the diradicals derived from diazenes (**2**) and (**3**), the former possessing a diylophile with (*E*) geometry, the latter (*Z*) (Table 4).[7] The observed stereospecificity suggests either that the two new σ-bonds are formed in concert or, assuming a nonconcerted process wherein the σ-bond is formed first between the exocyclic carbon of the diyl and the β-carbon of the diylophile, that rotation about the C_α—C_β bond with concurrent loss of diylophile stereochemistry is not competitive with formation of the second σ-bond.

Table 4 Maintenance of Diylophile Stereochemistry

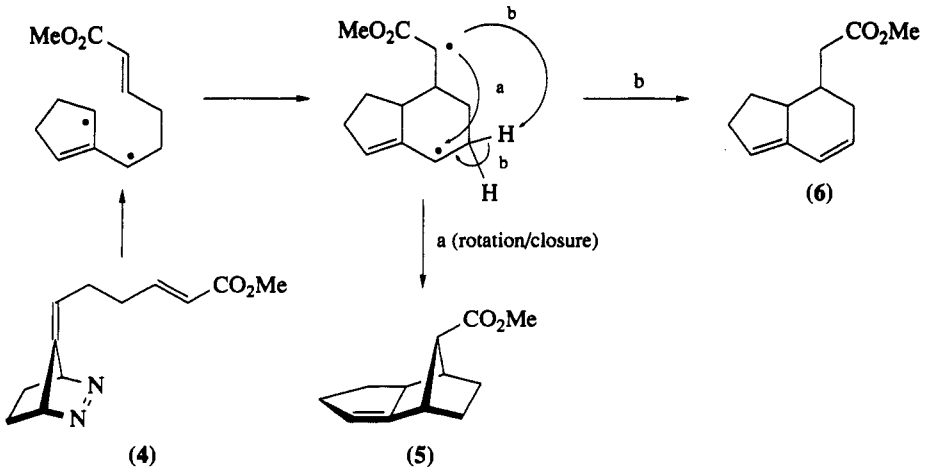


(2, 3) *cis,anti* *cis,syn*

	R^1	R^2	*Cis,anti:cis,syn ratio*[a]	*Yield (%)*
(2)	CO_2Me	H	87:13	≥85
(3)	H	CO_2Me	75:25	87

[a]Both the *cis,anti* and the *cis,syn* products are formed with retention of diylophile stereochemistry.

The only instance wherein the diylophile stereochemistry is lost was recorded upon examination of the chemistry of the diyl derived from diazene (**4**), one possessing a two-carbon tether.[8] In this case, four products were isolated in an 83% yield and in the ratio 16:5:1.5:1. Formation of tricycle (**5**) as the major product, as well as the diene (**6**), argue convincingly for the existence of a stepwise pathway where rotation about the C_α—C_β bond with loss of diylophile stereochemistry and hydrogen atom abstraction occur in competition with formation of the second σ-bond (Scheme 2).

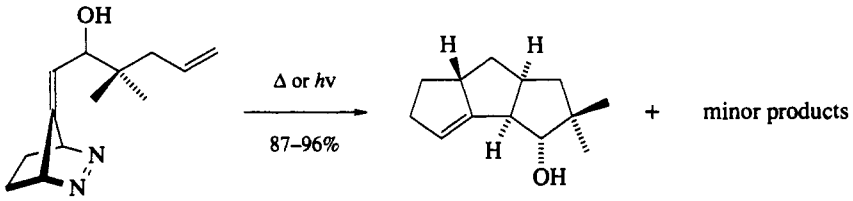


Scheme 2

3.1.2.2.2 Ring junction stereochemistry

Linearly fused tricycles are produced stereoselectively, the major product corresponding to one with the *cis,anti* ring junction stereochemistry. This selectivity made the intramolecular diyl trapping reaction well-suited for the synthesis of several natural products, including the mold metabolite hirsutene,[7,9] the marine natural product $\Delta^{9(12)}$-capnellene,[10] and the antitumor agents coriolin and hypnophilin.[4b,11] Table 5 shows how the degree of stereoselection, expressed by the *cis,anti*/other products ratio, is a function of the temperature at which the diyl trapping reaction is conducted;[11] the highest selectivity is obtained when the diyl is generated photochemically at temperatures below 0 °C.

Table 5 Ring Junction Stereoselectivity in Intramolecular Diyl Trapping Reactions

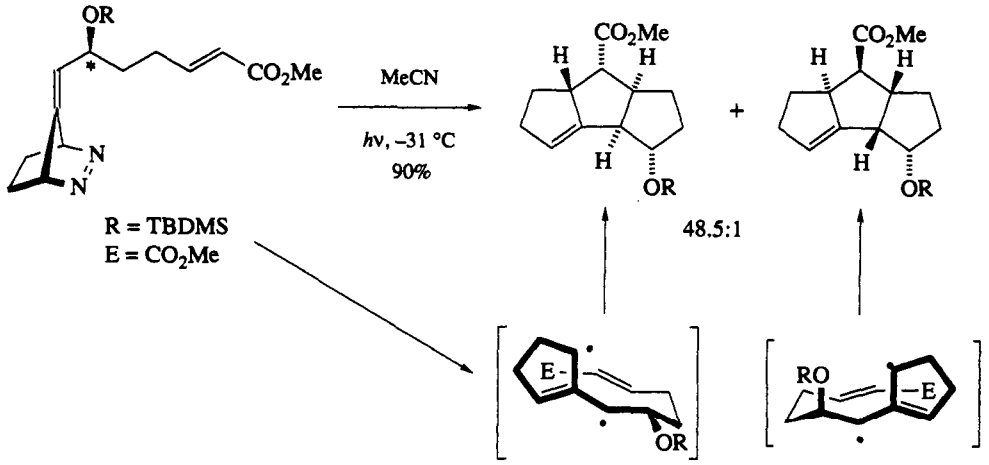


Solvent	*Temp. (°C)*	*Δ or hν*	*cis,anti:minor products*
MeCN	81	Δ	3.8:1
MeCN	6	*hν*	9.1:1
MeOH	61	Δ	4.7:1
MeOH	6	*hν*	9.1:1
MeOH	–60	*hν*	30:1

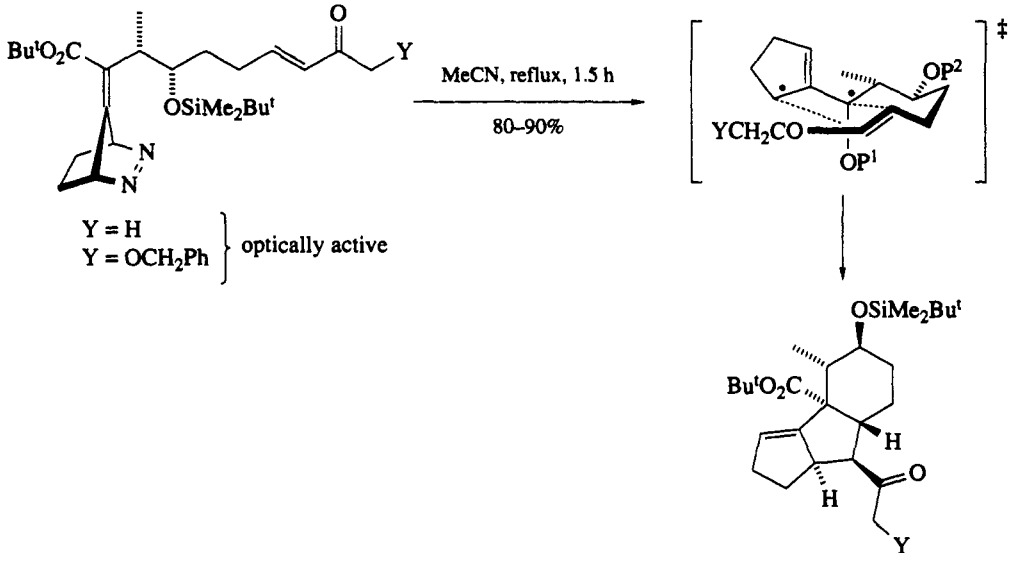
Both the relative and the absolute stereochemical outcome of the intramolecular diyl trapping reaction can be predicted by assuming that the cycloaddition is kinetically controlled. The objective, then, is to formulate a model of the alternative transition states and to choose among them the one of lowest energy. Two examples, each dealing with optically active diazenes, are illustrated in Schemes 3 and 4. In the first case,[12] the major diastereomer arises *via* the extended pseudochair transition-state formulation wherein the diylophile and tether coil to the rear, in a manner which places the OR unit in a pseudoequatorial orientation. Coiling to the front forces OR to assume an energy-raising pseudoaxial orientation (Scheme 3).

In the second example the diazene possesses a four-carbon tether with two stereogenic centers.[13] The major product can be viewed as arising *via* a pathway where the tether coils to resemble a chair form of cyclohexane with the methyl, silyl ether and five-membered ring occupying pseudoequatorial positions. That the observed stereospecificity is due to the preference for the substituents to orient themselves

pseudoequatorially is exemplified by the failure to observe any stereoselection in the diyl trapping reaction originating from a diazene possessing an unsubstituted four-carbon tether (Scheme 4).[13,14]



Scheme 3



Scheme 4

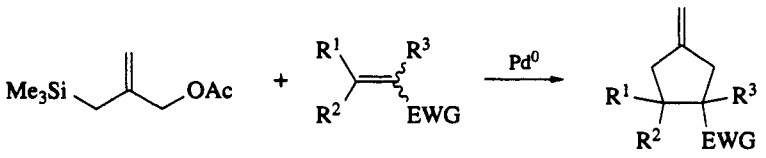
3.1.3 TRIMETHYLENEMETHANE SYNTHETIC EQUIVALENTS[15]

3.1.3.1 Palladium Trimethylenemethane Complex [(η^3-TMM)PdL$_2$]

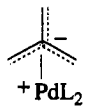
An exceptionally powerful means of constructing five-membered rings surfaced in 1979 with the report of the reaction between 2-acetoxymethyl-3-allyltrimethylsilane and electron-deficient alkenes in the presence of Pd^0.[16] Through this process, one can conduct the equivalent of a [3 + 2] cycloaddition between trimethylenemethane and an alkene,[17] a reaction which otherwise occurs in low yield.[2c,18] Several sources of Pd^0 have been utilized including (a) $(Ph_3P)_4Pd/Ph_2PCH_2CH_2PPh_2$ (DPPE) and (b) $Pd(OAc)_4/(Pr^iO)_3P$, the latter generating Pd^0 *in situ* and often leading to higher yields. Typically, 0.1–10 mol % of the resulting catalyst, $\{(Pr^iO)_3P\}_nPd$, is used in a 'typical' laboratory-scale reaction. Table 6 provides several examples of the cycloaddition.[17]

Evidence clearly indicates that trimethylenemethane (TMM) is not an intermediate in these reactions and establishes, instead, the existence of a trimethylenemethane–palladium complex with dipolar character, *viz.* (η^3-TMM)PdL$_2$ (7).[16,19]

Table 6 Examples of Cycloaddition with (η^3-TMM)PdL_2

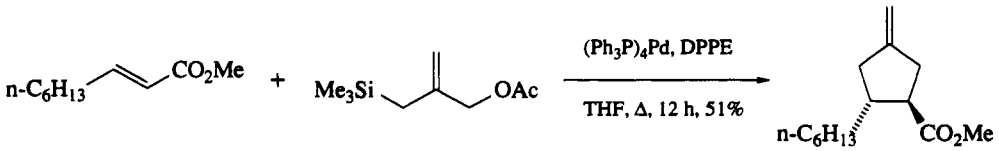


$R^1R^2C{=}CR^3EWG$	*Solvent*	*Temp. (°C)*	*Time (h)*	*Yield (%; comment)*
Methyl acrylate	PhMe	85–90	43	68
Acrylonitrile	PhMe	60	150	35
Coumarin	PhMe	115	14	52
Cyclohexenone	THF	reflux	20	17 (*cis* fused)
Chalcone	PhMe	115	11	85 (with retention of alkene geometry)
1-(Phenylsulfonyl)cyclopentene	THF	reflux	40	58 (*cis* fused)

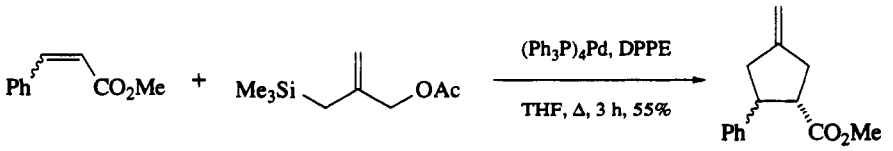


(7)

The cycloadditions proceed stereoselectively with the geometry of (*E*)-alkenes being preserved, but that for (*Z*)-alkenes being partially lost (equations 1 and 2).[20] Excellent diastereofacial selectivity has been observed in cycloadditions to cyclic alkenes,[17] the major product resulting from the addition of the TMM–PdL_2 complex to the least-hindered face of the alkene (equations 3–5). Modest (4:1) to high (>99:1) diastereoselectivity is also observed when enantiomerically pure acyclic alkenes are used (equations 6, 7).[21]



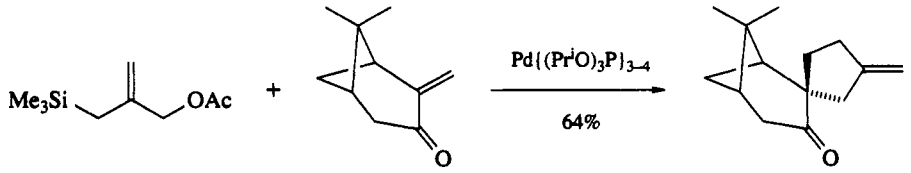
(1)



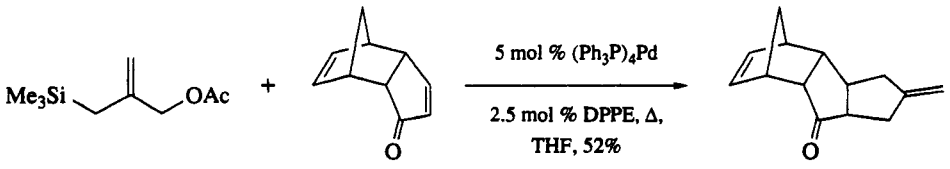
(2)

E/*Z* 1:10

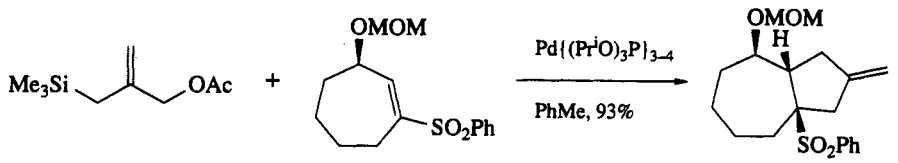
trans:*cis* 1:1.3 to 1:1.2



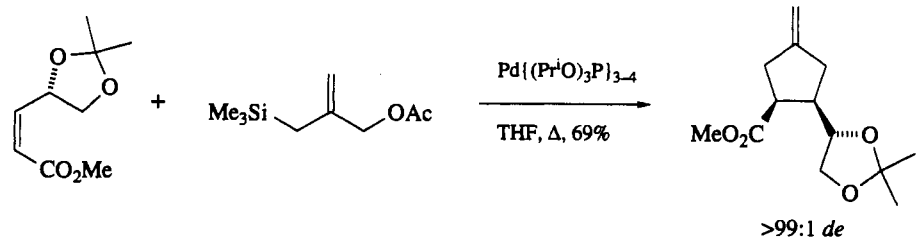
(3)



(4)

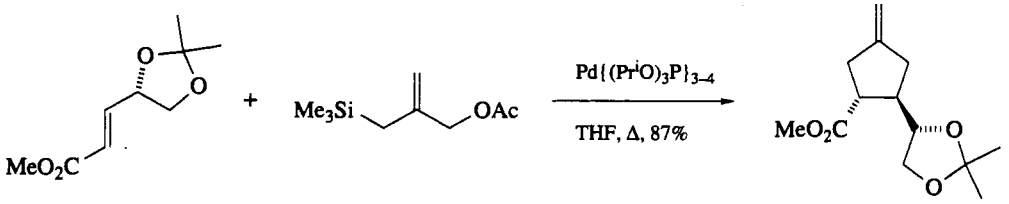


(5)



(6)

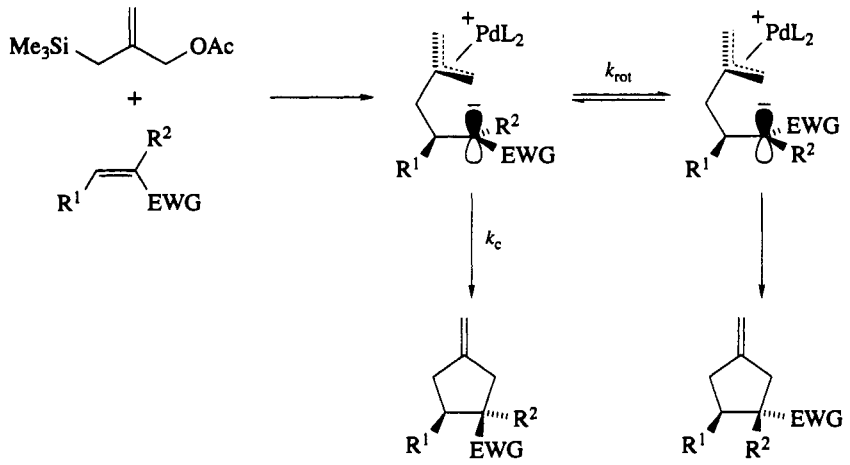
>99:1 *de*



(7)

4:1 *de*

A nonconcerted mechanism, involving a least-hindered approach of the cycloaddends and a stepwise addition of the palladium complex to the β-carbon of the α,β-unsaturated alkene, followed by cyclization without loss of alkene geometry and/or competitive rotation about the C_α–C_β bond prior to cyclization with loss of stereochemistry, provides a reasonable account of the cycloaddition (Scheme 5).[22]



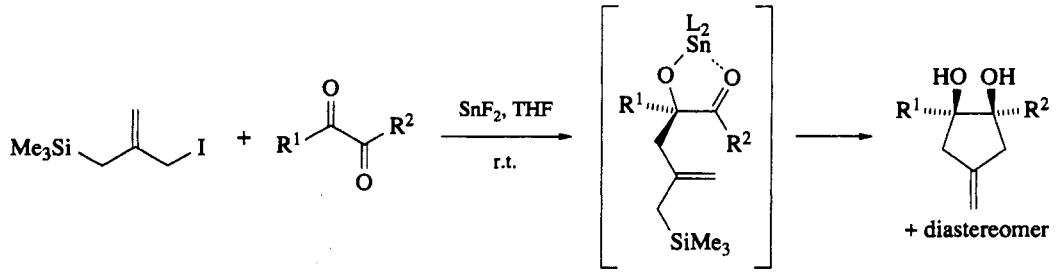
Scheme 5

3.1.3.2 Organo-tin and -zinc Reagents Derived from 3-Iodo-2-[(trimethylsilyl)methyl]propene

Addition of bifunctional conjunctive organometallic reagents derived from 3-iodo-2-[(trimethylsilyl)methyl]propene to 1,2-diones provides a stereoselective pathway to *cis*-4-methylenecyclopentane-1,2-diols.[23] Both zinc and tin(II) fluoride have been used to generate the organometallic. The latter has proven more advantageous, presumably because the Sn^{4+} generated during the reaction serves more effectively than Zn^{2+} to complex with the carbonyl group of the initially formed ketolate, thereby increas-

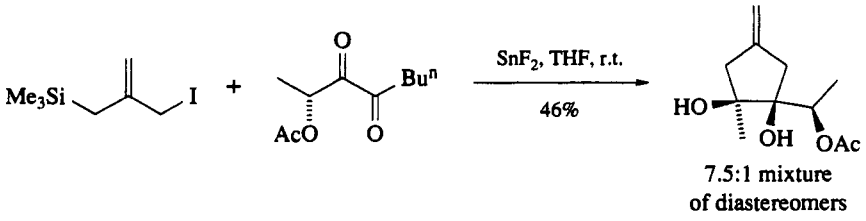
ing the electrophilicity of the carbonyl carbon toward nucleophilic addition. The observed *cis* stereoselectivity is believed to result as a consequence of chelation control, as illustrated in Table 7.[23a]

Table 7 Diastereoselectivity in Cycloaddition to 1,2-Diones



R^1	R^2	*Yield (%)*	*Diastereoselectivity*
Me	Me	72	>75:1
Me	Et	88	>32:1
Me	Ph	72	>28:1
Bu^n	$Cl(CH_2)_4$	73	>50:1

Reasonable diastereofacial selectivity has also been observed in the addition of the allylstannane referred to above to 2-acetoxy-3,4-octanedione (equation 8).[23] Chemoselective Felkin–Anh addition to the more reactive carbonyl carbon located α to the stereocenter is presumed to occur first, followed by an intramolecular chelation-controlled addition of the allylsilane to the second ketone.



(8)

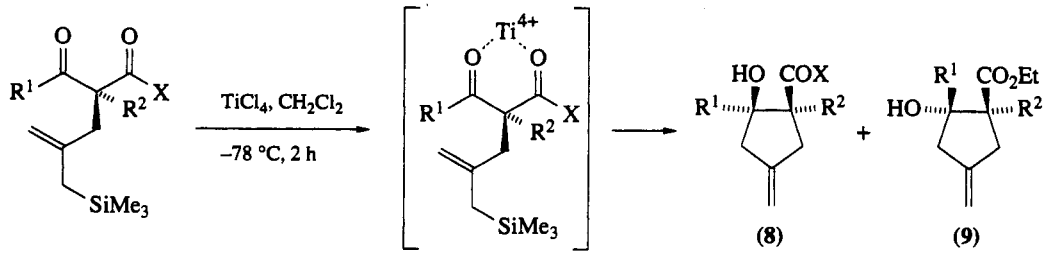
β-Keto esters and β-keto amides, each substituted between the two carbonyl units with a 2-[2-(trimethylsilyl)methyl] group, also undergo Lewis acid catalyzed, chelation-controlled cyclization.[24] When titanium tetrachloride is used, only the product possessing a *cis* relationship between the hydroxy and ester (or amide) groups is produced; yields range from 65 to 88% (Table 8). While loss of stereochemistry in the product and equilibration of diastereomers could have occurred *via* a Lewis acid promoted retro aldol–aldol sequence, none was observed. Consequently, it is assumed that the reactions occur under kinetic, rather than thermodynamic, control. In contrast to the titanium tetrachloride promoted process, fluoride-induced cyclization produces a 2:1 mixture of diastereomeric products, and the nonchelating Lewis acid $BF_3{\cdot}OEt_2$ leads to a 1:4.8 mixture of diastereomers.

3.1.4 1,3-DIPOLAR CYCLOADDITIONS[25]

3.1.4.1 Regioselectivity

The ability to use a given reaction in synthesis depends heavily upon understanding the nature of the factors controlling regiospecificity/regioselectivity. A rationale for the regiochemical outcome of [2 + 3] cycloaddition reactions became available in the early 1970s through the use of frontier molecular orbital (FMO) theory.[26] With it, a further sense of order was established in an area where an understanding of the factors responsible for regiochemical control was absent. Since that time, nearly all practitioners of organic synthesis have developed a fundamental grasp of this matter, and it is commonplace to find predictions couched in terms of FMO arguments.

Table 8 Diastereoselection in Cycloadditions Promoted by Titanium Tetrachloride



R^1	R^2	X	*Yield (%)*	*(8):(9)*
Me	Me	OEt	88	100:1
Pr^i	Me	OEt	66	100:1
Ph	Me	OEt	73	100:1
Me	Pr^i	OEt	65	100:1
Pr^i	H	NMe_2	56	100:1
Bu^t	H	NMe_2	75	100:1
Me	Me	OEt	—	2:1[a]
Me	Me	OEt	—	1:4.8[b]

[a] Bu^n_4NF, THF; [b] $BF_3{\cdot}OEt_2$, CH_2Cl_2.

Dipolar cycloaddition reactions are generally classified into three types, dipole HO controlled, dipole LU controlled or HO,LU controlled, depending upon the relative energies of the dipole and dipolarophile frontier molecular orbitals.[27] If the energy gap separating the dipole HOMO from the dipolarophile LUMO is smaller than that between the dipole LUMO and the dipolarophile HOMO, then the reaction is said to be dipole HO controlled. If the dipole LUMO–dipolarophile HOMO energy gap is smaller, then dipole LU control prevails. If the energy difference between the dipole HOMO and the dipolarophile LUMO is about the same as that between the dipole LUMO and the dipolarophile HOMO, then neither interaction dominates and HO,LU control is operable.

Substituents placed on either the dipole or the dipolarophile affect the energy of the frontier orbitals in a manner which leads to either an acceleration or a deceleration depending upon whether the pertinent FMO energy gap increases or decreases, respectively, as a consequence of the substitution. In general, electron-withdrawing groups lower the level of both the HOMO and the LUMO, electron-donating groups raise the energy of both, and conjugating groups raise the HOMO but lower the LUMO energy.[28]

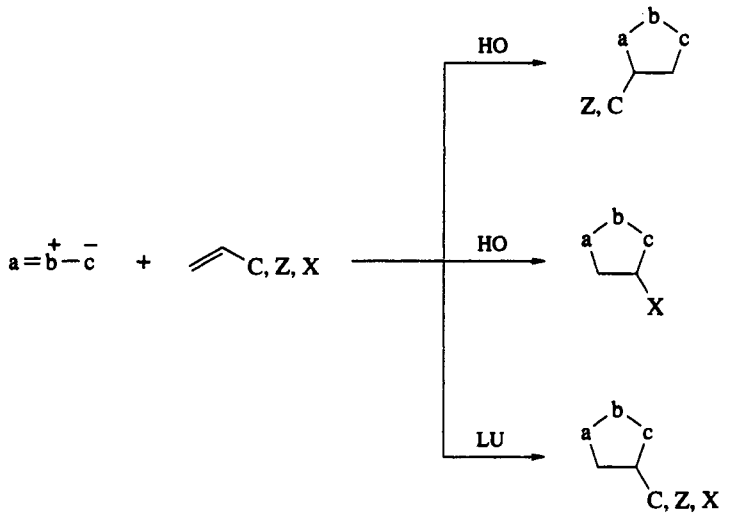
Once the dominant FMO interaction has been identified, then a choice as to which regiochemical outcome is preferred is based upon a comparison of the sizes of the coefficients at the atomic orbital centers involved in the formation of the new bonds. Consequently, at least a qualitative knowledge of the form of the FMOs is useful in assessing the relative merits of one over the other regiochemical outcome. If, as is usually but not always (*vide infra*) the case, the coefficients in both the HOMO and the LUMO differ in size, then the new overlap can occur in either of two ways. It can readily be shown, however, that overlap between the atomic orbitals with the larger coefficients (and, by default, the two centers with the smaller atomic orbital coefficients overlap at the other site of bond formation) is preferred over the alternative.[28,29]

Table 9 illustrates the direction of polarization of the HOMO and the LUMO of simple monosubstituted alkenes ($CH_2{=}CHC,Z,X$) and dipoles ($a{=}^+b{-}^-c$); the atom with the larger coefficient is marked with a star.[26a] Except in cases where C_2 symmetry exists (*e.g.* the azomethine ylide,

Table 9 Direction of Polarization of Dipole and Dipolarophile FMO's

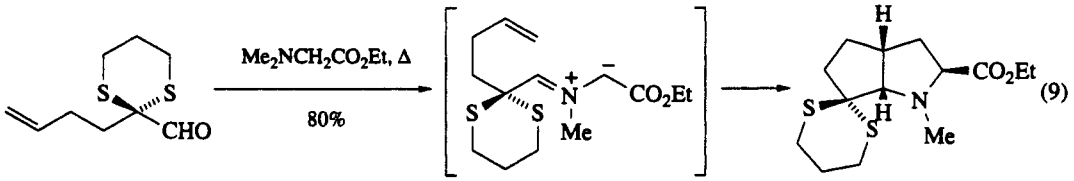
Dipolarophile		*Dipole*	
HOMO	*LUMO*	*HOMO*	*LUMO*
*Z	*Z		
*X	X*	a=b−c*	*a=b−c
*C	*C		

$CH_2{=}{}^{+}NH{-}{}^{-}CH_2$), or for the parent nitrone, $CH_2{=}{}^{+}NH{-}{}^{-}O$, where the coefficients are nearly the same at both termini, dipole HOMOs are polarized toward the 'anionic' terminus c, the LUMO toward a. Use of this information, in accord with the principles put forth above, allows one to make the predictions illustrated in Scheme 6.[26a]

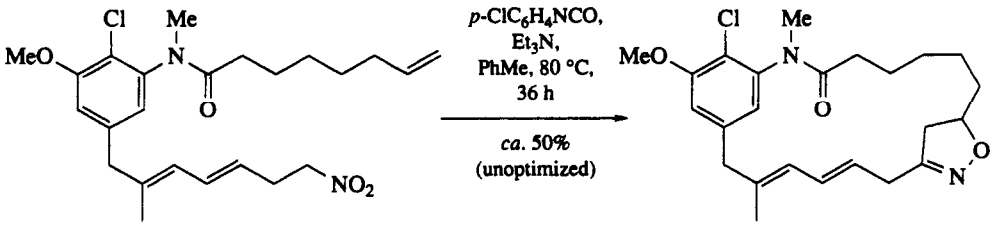


Scheme 6

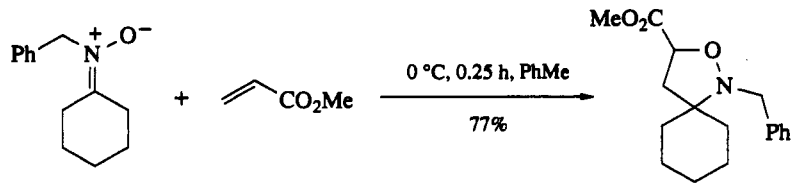
These generalizations are applicable to a large number of cycloadditions, particularly to the intermolecular variety. The examples in equations (9)–(13)[30–34] and Schemes 7–9[31,35,36] illustrate these points and also highlight the tremendous power of [2 + 3] dipolar cycloaddition reactions in the rapid and selective construction of a rich array of both carbo- and hetero-cyclic ring systems.



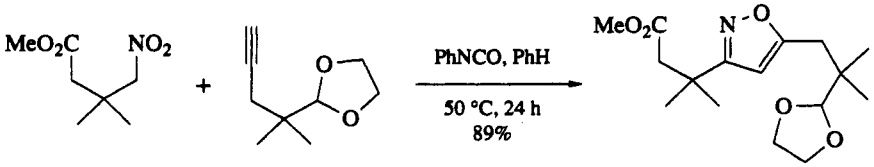
(9)



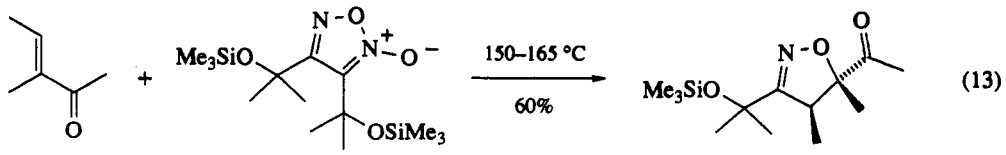
(10)



(11)



(12)

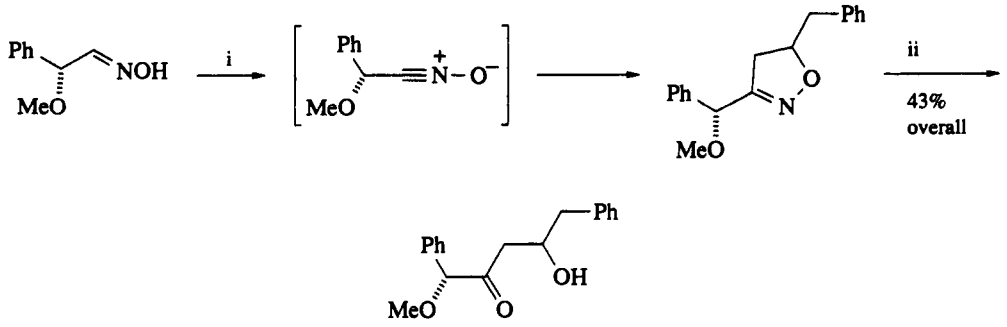


(13)

Exceptions do exist, however, and one must be particularly alert to substituent-induced changes in the direction of polarization, as well as to their affect upon the energy of the frontier molecular orbitals.[37] For example, nitrone cycloaddition regiochemistry is generally LU controlled,[37,38] leading to the production of C-5 substituted isoxazolines in excellent yield. However, as the ionization potential of the nitrone decreases or the electron affinity of the dipolarophile increases, there exists an increased propensity for formation of the C-4 regioisomer. Eventually, a switch from LU to HO control occurs and substantial amounts of the C-4 isomer are produced (equation 14).

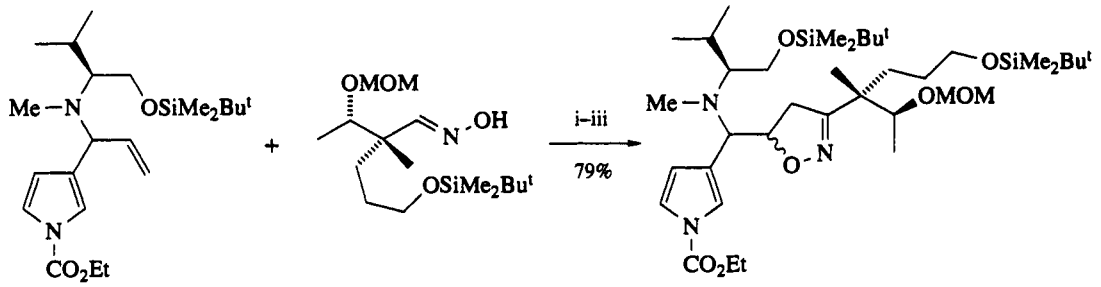
A substituent-induced change in the direction of polarization of one of the FMOs can also lead to a change in regiochemistry. Thus, in contrast to acrylates, crotonates undergo nitrone cycloaddition to afford the regioisomer where the alkyl, rather than the ester, unit is attached to the carbon linked to the nitrone oxygen atom (Scheme 10). While the coefficient at the β-carbon in the HOMO of an acrylate is larger than at the α, the reverse is apparently true for crotonates.[39] This result has been put to exceptionally elegant use in the construction of a number of alkaloids.[39a]

As indicated above, the parent azomethine ylide possesses C_2 symmetry. When the symmetry is reduced by placing a substituent at either end of the dipole, the FMOs polarize. Assuming HO control, the example in Scheme 11 suggests that the largest coefficient of the dipole HOMO resides on the unsubstituted carbon to which the silyl group was attached.[40]



i, Chlorox, , Et_3N, CH_2Cl_2, r.t., 1 h: ii, H_2, Raney Ni, MeOH/H_2O/AcOH, r.t., 16 h

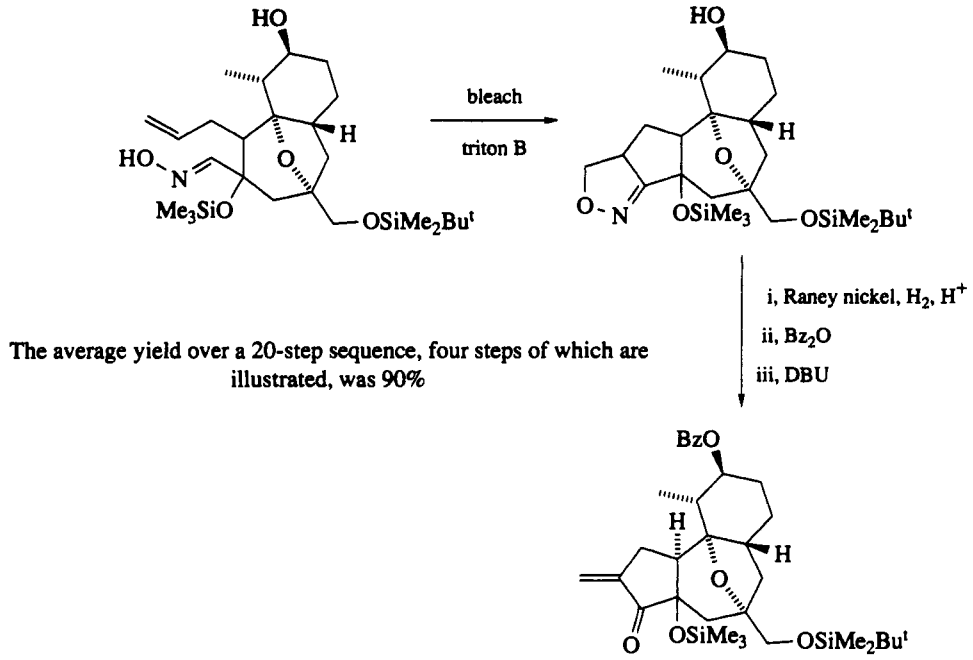
Scheme 7



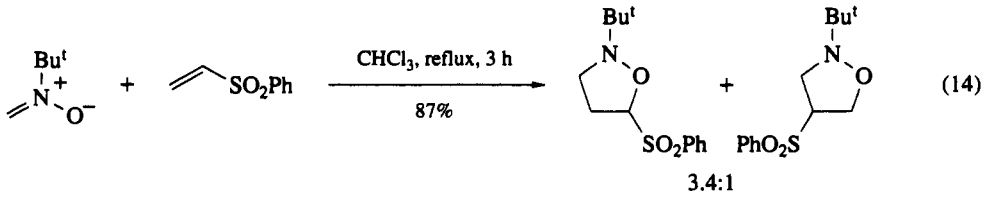
2.5:1 mixture of diastereoisomers

i, Bu^tOCl, –78 °C; ii, Et_3N, –78 °C to r.t.; iii, PhH, 80 °C, 20 h

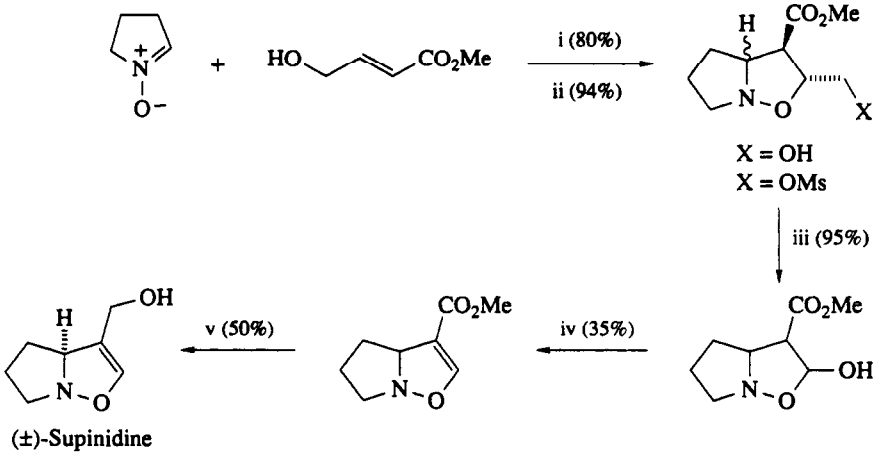
Scheme 8



Scheme 9

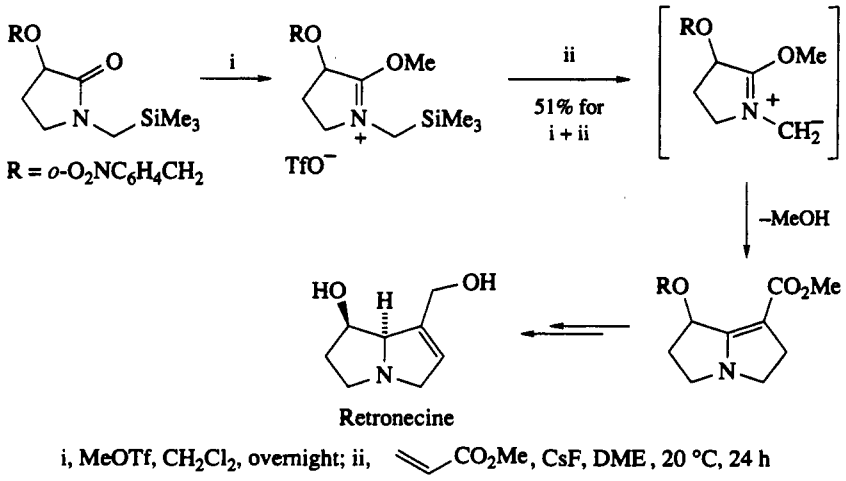


Highly regioselective cycloaddition to monosubstituted 1,3-dienes has been observed, the preferred product corresponding to one formed *via* addition to the less-substituted double bond (equations 15, 16).[39a] Here again, the regiochemical outcome is in accord with simple FMO arguments.



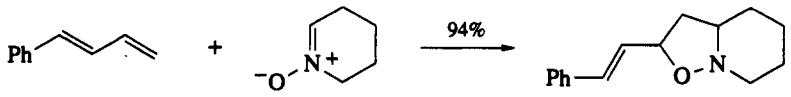
i, $CHCl_3$, 4 h, 25 °C, then reflux, 12 h; ii, MsCl, C_5H_5N, 0 °C, 3 h; iii, H_2, 10% Pd/C, MeOH, 24 h; iv, $POCl_3$, C_5H_5N, 0 °C, 12 min; v, $LiAlH_4$, Et_2O, r.t., 15 min

Scheme 10

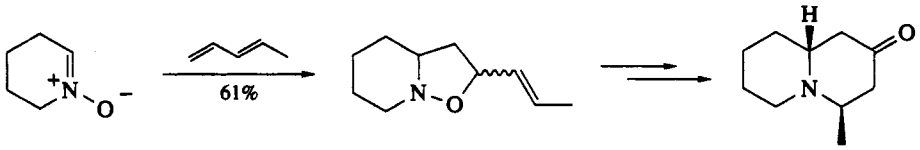


i, MeOTf, CH_2Cl_2, overnight; ii, , CsF, DME, 20 °C, 24 h

Scheme 11



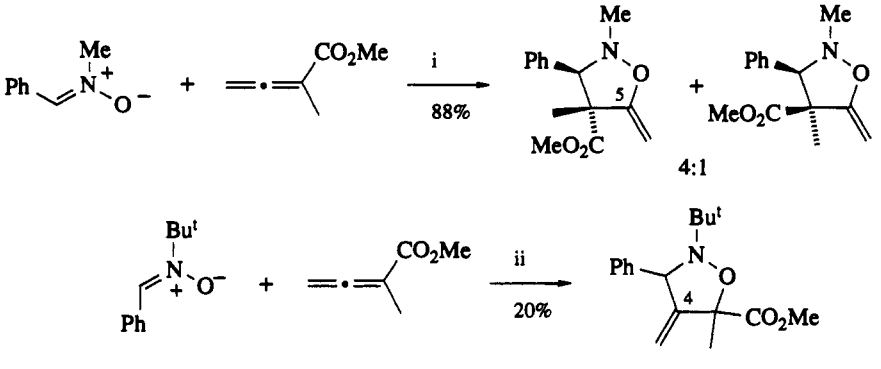
(15)



(16)

(±)-Myrtine

Occasionally, molecular mechanics calculations provide a rationale when FMO theory fails to account for a given regiochemical outcome.[37,41–45] For example, cycloaddition of *C*-phenyl-*N*-methyl nitrone to methyl 2-methyl-2,3-butadienoate leads exclusively to the 5-*exo*-methylene cycloadduct, as one would expect based upon FMO theory. In contrast, *C*-phenyl-*N*-*t*-butyl nitrone affords only the 4-*exo*-methylene isoxazolidine, a result which clearly cannot be in accord with the same principles (Scheme 12). Molecular mechanics calculations, carried out under the assumption that the relative energy differences between the products parallel the energy differences between transition states, were in accord with the experimental results, suggesting that the difference in behavior between the two nitrones may have a steric rather than an electronic origin (Table 10).[37]

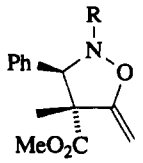
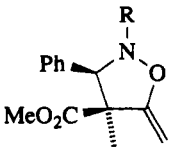
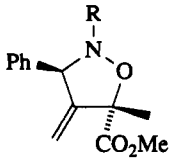
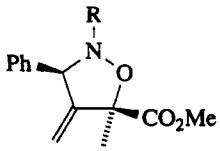


only regioisomer isolated

i, PhH, 45 °C, 10 h; ii, PhH, 80 °C, 8 h, sealed tube

Scheme 12

Table 10 Results of Molecular Mechanics Calculations[a]

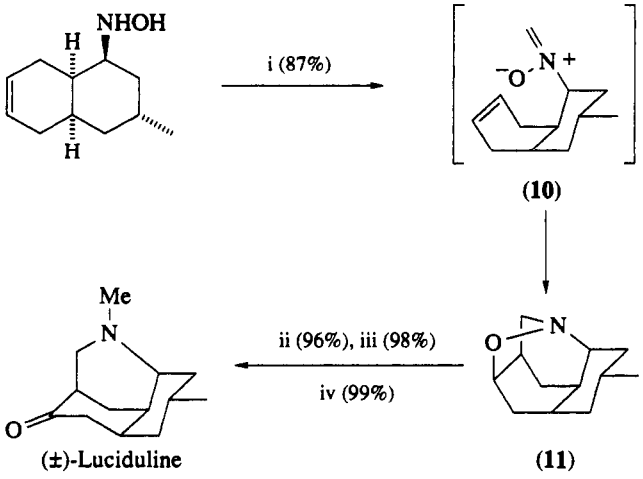
			
R = Me, 24.48 R = Bu^t, 28.96	R = Me, 25.40 R = Bu^t, 29.05	R = Me, 26.67 R = Bu^t, 27.73	R = Me, 27.65 R = Bu^t, 27.84

[a] Energy in kcal mol^{-1}.

While the cycloadditions illustrated thus far involve polarized dipolarophiles, regiospecificity can also occur in instances where the alkene is unpolarized. For example, the *N*-alkenyl nitrone (**10**), an important intermediate in an elegant synthesis of the lycopodium alkaloid (+)-luciduline,[46] undergoes intramolecular cycloaddition to afford only the tetracyclic heterocycle (**11**; Scheme 13). Nitrones (**12a**; $n = 2$) and (**12b**; $n = 3$), two compounds which differ only by the length of the chain linking dipole to dipolarophile, also undergo regiospecific cycloaddition, but do so to produce precisely opposite regiochemical outcomes (Scheme 14). The next higher homolog, nitrone (**12c**; $n = 4$), affords a 3:1 mixture of regioisomeric products, as shown.

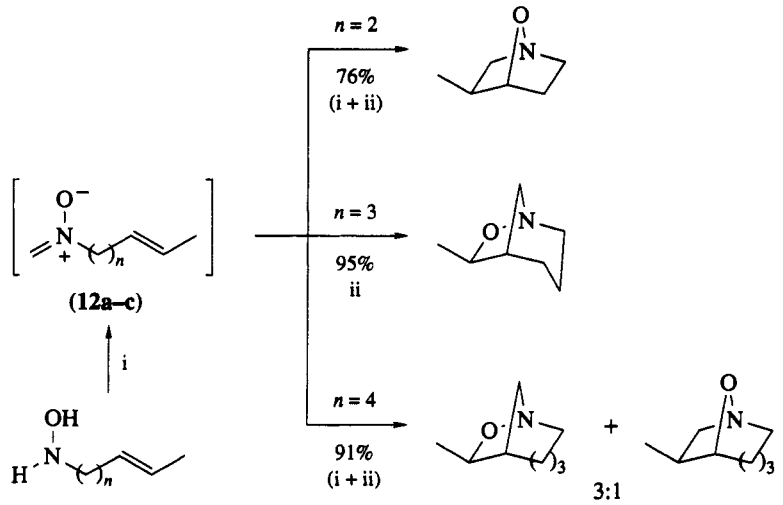
Clearly, FMO arguments do not assist in understanding the nature of the preferences expressed above. Instead, attention has been directed toward differences in the geometry of the presumed transition-state structures for each mode of cycloaddition.[46c,d] In each case it was assumed that the C—C bond is more fully developed than the C—O bond in the transition state. From models it is clear that when two methylene units separate dipole from dipolarophile, the preferred transition state is the one suffering least from angle strain. When the length of the chain link is three, the preferred product arises *via* formation of the entropically favored six-membered ring, instead of the alternative seven-membered ring.

Interestingly, the balance can be tipped toward formation of the seven-membered ring by simply placing an electron-withdrawing group on the terminal carbon of the dipolarophile (Scheme 15). This leads to polarization of the alkene and to an FMO-controlled process. Incidentally, the reaction shown proved critical in a total synthesis of anatoxin *a*, the so-called 'very fast death factor'.[47]



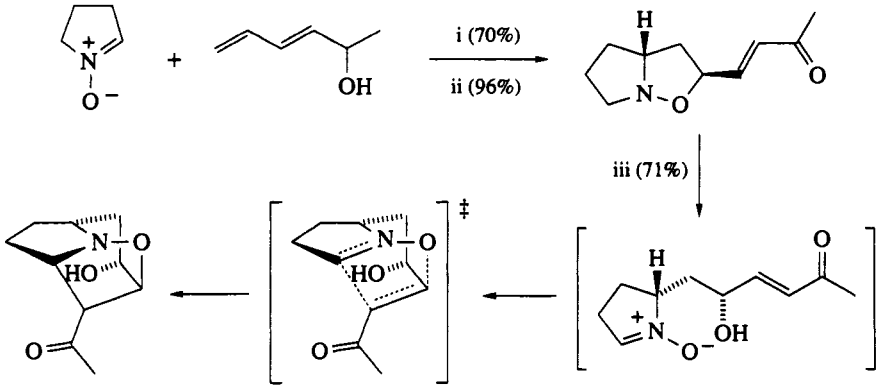
i, $(CH_2O)_n$, 4 Å molecular sieves, PhMe, sealed tube, 115 °C, 4 h; ii, $MeOSO_2F$, Et_2O, 0 °C, 30 min; iii, $LiAlH_4$, THF, 25 °C, 4.5 h; iv, Jones reagent, Me_2CO, 0 to 25 °C, 1 h

Scheme 13



n = 2: i, CH_2O, PhMe, 10 °C, 12 h; ii, PhMe, reflux, 6 h; n = 3: i, CH_2O, PhMe, –20 °C, 15 min, quant; ii, PhMe, reflux, 3 h; n = 4: i, CH_2O, PhMe; ii, PhMe, reflux

Scheme 14



i, HgO, PhH, reflux, 3 h; ii, MnO_2, Celite, CH_2Cl_2, r.t., 24 h; iii, MCPBA, 0 °C, 20 min; K_2CO_3, H_2O; reflux, 18.5 h (in the dark), CH_2Cl_2

Scheme 15

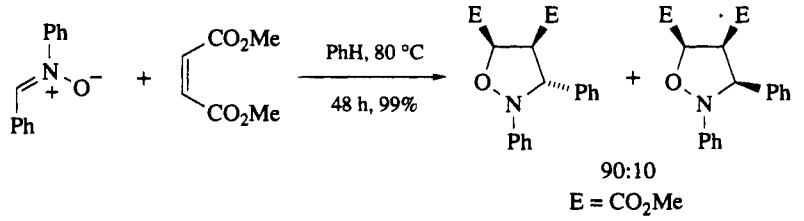
3.1.4.2 Stereoselectivity

3.1.4.2.1 Relative stereoselection

Dipolar cycloaddition reactions proceed with preservation of dipolarophile stereochemistry,[29b] a result which is obviously of synthetic utility. The dipole and dipolarophile approach one another in parallel planes with the substituents attached to the dipolarophile oriented in either an *endo* or an *exo* relationship with respect to the dipole in the transition state. Depending upon which orientation is of lower energy, varying degrees of diastereoselectivity result (*vide infra*).[29b] The consequences of these generalizations are expressed repeatedly in the chemistry described below.

Synthetically useful amounts of *endo* selectivity have been observed in the intermolecular cycloaddition reactions of some acyclic nitrones. For example, the reaction between *C*,*N*-diphenyl nitrone and dimethyl maleate leads to a 9:1 mixture of products, the major arising *via* the (*Z*)-nitrone and *endo* transition state (equation 17).[48] The *endo* but not the *exo* transition state experiences an energy-lowering

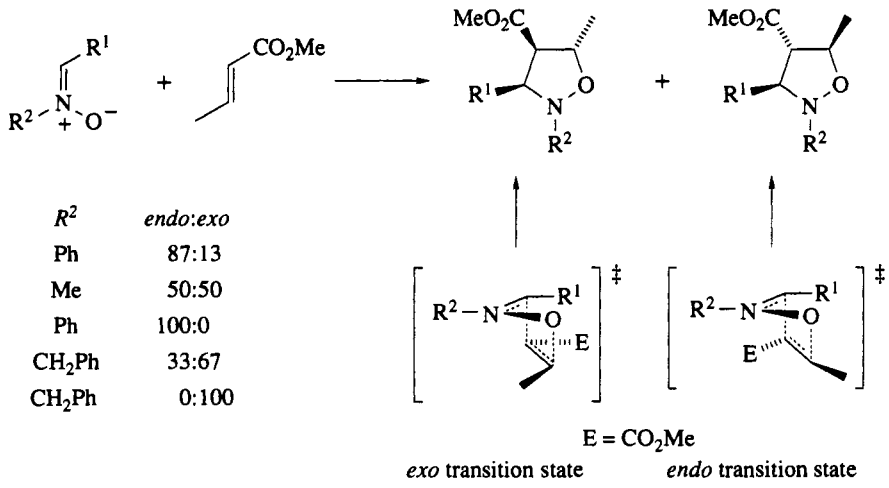
secondary orbital interaction between the coefficient on nitrogen in the LUMO of the nitrone and the coefficient on the carbonyl carbon in the HOMO of the dipolarophile, thereby making it the kinetically preferred product.



(17)

The possible existence of such an interaction by no means ensures that *endo* selectivity will be observed. Table 11 makes this point abundantly clear.[49] Notice particularly how changes in substituents on the carbon and nitrogen of the nitrone can lead to a complete reversal of *endo*/*exo* selectivity.

Table 11 Influence of Nitrone Substitution Upon *endo*/*exo* Stereoselectivity



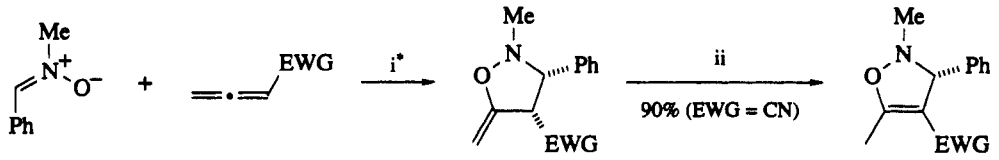
R^1	R^2	*endo*:*exo*
Ph	Ph	87:13
Ph	Me	50:50
Pr^i	Ph	100:0
Pr^i	CH_2Ph	33:67
Me	CH_2Ph	0:100

Nitrones are known to undergo (*E*/*Z*) isomerization;[50] both forms may therefore be available for reaction. For example, the heats of formation for the (*E*)- and (*Z*)-forms of *N*-methyl-*C*-phenyl nitrone place the latter 1.46 kcal mol^{-1} lower in energy than the former.[37,50] This implies that approximately 10% of the (*E*)-form is present in solution even at room temperature. On the other hand, the (*E*)-form of *N*-*t*-butyl-*C*-phenyl nitrone is 6.3 kcal mol^{-1} less stable and only the (*Z*)-isomer exists in solution.[37] For steric reasons the (*E*)-isomer has been proposed to undergo cycloaddition at a faster rate than the (*Z*).[37] Interestingly, cycloaddition of the (*E*)-isomer *via* an *exo* transition state leads to the same product as that from the (*Z*)-isomer through an *endo* transition state. This factor must obviously be considered when interpreting experimental results.

The reaction of methyl 1,2-butadienoate with *C*-methyl-*N*-phenyl nitrone (Scheme 16) leads to a single diastereoisomer and is believed to take place through a transition state (**13**) which places the methoxycarbonyl and phenyl groups above one another,[37,51] thereby allowing maximal π-overlap (attractive van der Waals interaction). To do so requires that the (*E*)-form of the nitrone exist in solution and that it react faster than the (*Z*), both being reasonable suggestions (*vide supra*).

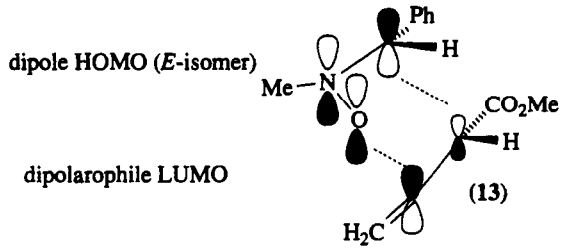
Vinyl ethers and esters display a marked preference for undergoing cycloaddition through an *endo* rather than an *exo* transition state. The sole product isolated from the reaction of nitrone (**14**) with ethyl vinyl ether and vinylene carbonate arises in this manner (equation 18).[52] This selectivity has been attributed to stabilization of the *endo* transition state by developing anomeric and *gauche* interactions which are absent in the *exo* transition state.[53] Thus, it is assumed that the transition-state structure resembles the product in its lowest-energy conformation, one which places both the dipolarophile OR unit and the alkyl group attached to nitrogen in pseudoaxial orientations. In this manner, a stabilizing anomeric interaction between OR and the nitrone oxygen develops, as does a *gauche* interaction between the latter

and the developing lone-pair electrons on nitrogen. By assuming the *gauche* relationship, the system avoids the alternative energy-raising *anti*- and *syn*-periplanar arrangement of lone pairs shown in (**15**).

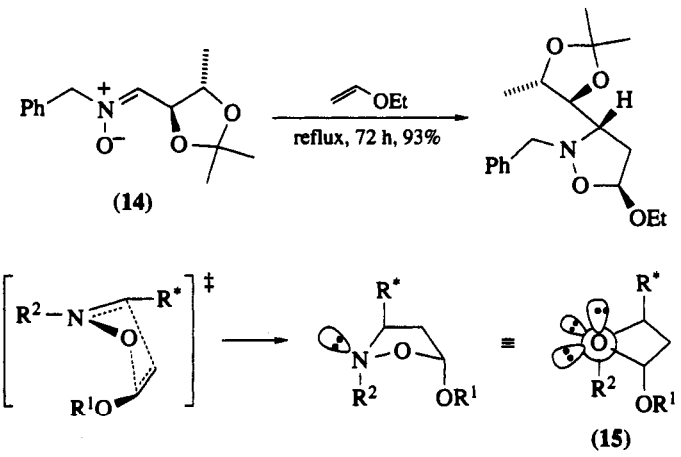


* 50% (A+B) when EWG = CO_2Me; 99% (A) when EWG = CN

i, EWG = CO_2Me, 45 °C, 20 h (silica gel chromatography converts A to B); EWG = CN, PhH, 40 °C, 3 h; ii, Bu^nLi, THF, −78 to 0 °C



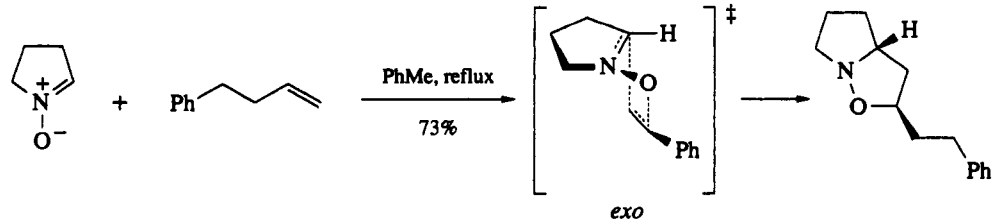
Scheme 16



(18)

With cyclic nitrones, where (*E*/*Z*) isomerization is not possible, the *exo* transition state is usually sterically preferred (equation 19–21).[54–56] When steric factors in the *endo* and *exo* transition states are nearly the same, however, the existence of bonding secondary orbital interactions in the *endo* transition state can tip the balance in its favor; this appears to be the case for the reaction of methyl crotonate and 1-pyrroline 1-oxide (equation 22).[57]

Nitrone cycloaddition reactions are reversible,[58] thereby offering the opportunity to change stereoselection from that of kinetic to thermodynamic control, should the selectivities associated with these path-



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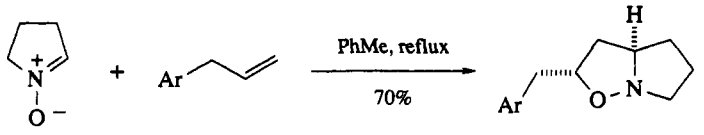

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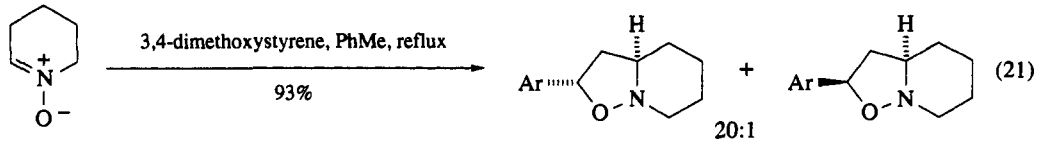
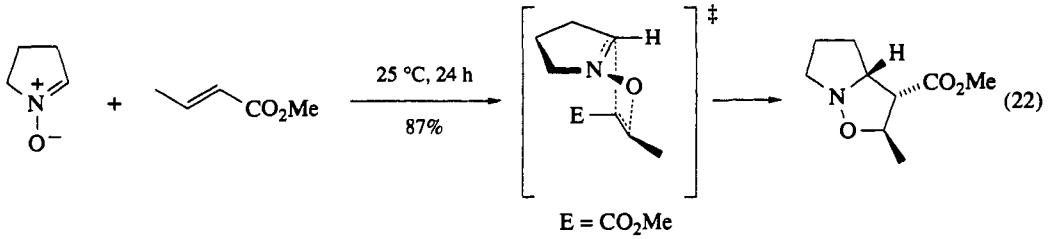


(21)



(22)

ways differ. To illustrate, consider the cycloaddition portrayed in Table 12; it served as a key step *en route* to 1α,25*S*,26-trihydroxycholecalciferol.[58b] Unfortunately, a 36:45:7:12 ratio of four diastereomeric isoxazolidines was produced when the reaction was conducted at room temperature, albeit with complete regiochemical control and in high yield. The required 23*S*,25*S*-isomer was separated from the other three and the latter were heated overnight (refluxing xylene) in the presence of an excess of methyl methacrylate to effect cycloreversion and equilibration. After four cycles, the total yield of the 23*S*,25*S*-isomer reached 71%.

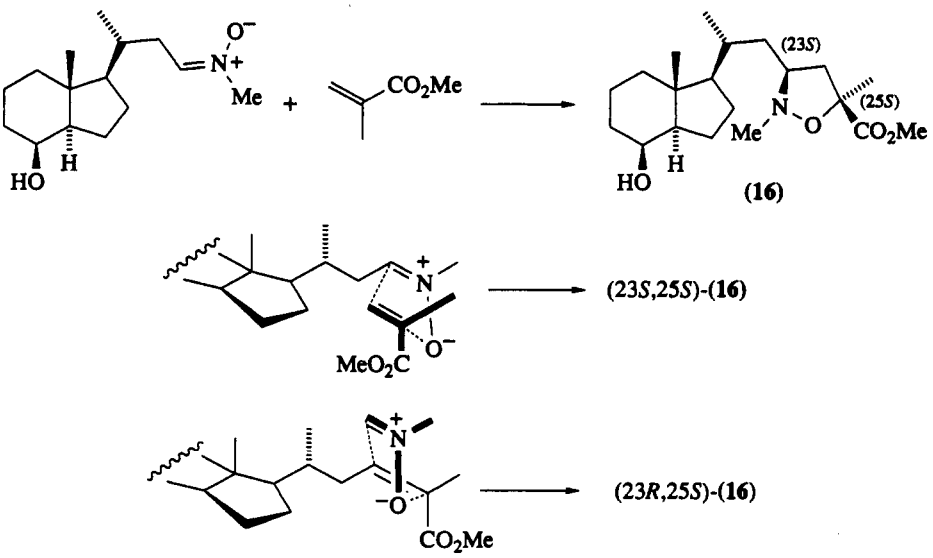
The two major products, the 23*S*,25*S*- and the 23*R*,25*S*-isomers, arise *via* the sterically less encumbered *exo* transition state, the minor products (23*S*,25*R* and 23*R*,25*S*) from an *endo* transition state. The analogous *N*-benzyl and *t*-butyl nitrones, on the other hand, display high *endo* selectivity, further attesting to how the group attached to nitrogen can play an important role in determining stereoselectivity (*vide supra*). In this case, the larger the group on nitrogen, the larger the *endo*/*exo* ratio (Scheme 17).

Molecular mechanics calculations have recently been used to assist in explaining the stereochemical course of several intramolecular cycloaddition reactions.[43,59] In one case,[59a] calculations were carried out to determine the relative energies of four diastereomeric products which could have been produced in the intramolecular azomethine cycloaddition reaction displayed (equation 23). A single product was isolated, though in only 25% yield. The assumption was made that the calculated differences in product stability were reflected by similar, but smaller, energy differences in the transition states.

Both ground state and transition state molecular mechanics calculations have been used to account for the stereochemical outcome of intramolecular nitrile oxide cycloadditions involving a series of vinylazetidinones and azetidines (Scheme 18).[43] Qualitative accord with the experimental results was observed once again (Table 13). Given the good agreement between theory and experiment, and the ease with which these calculations can be carried out, one is certainly tempted to use them (cautiously) in a predictive sense.

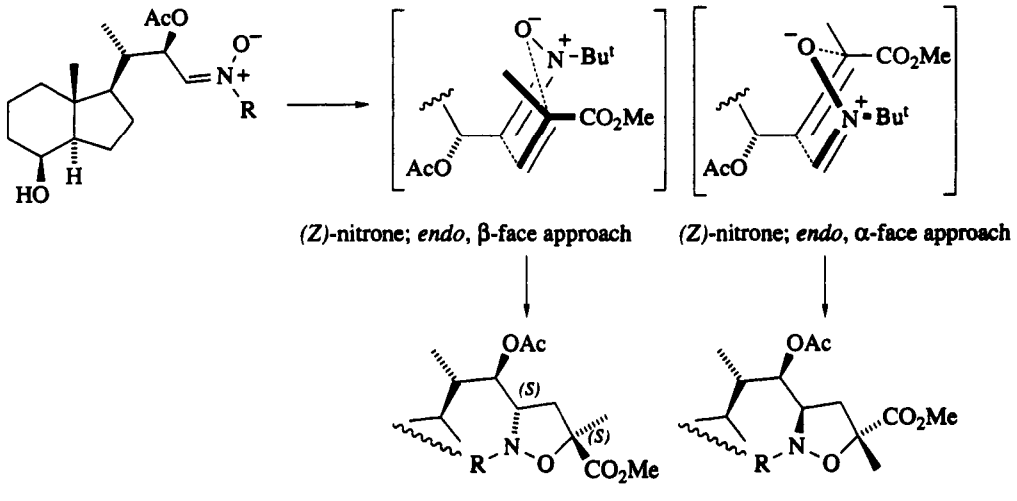
The preferred mode of addition to *cis*-3,4-disubstituted cyclobutenes varies from one where the dipole adds exclusively *anti* to the substituents, to instances where exclusive *syn* cycloaddition is observed (Table 14).[60] The latter observation is true particularly when the substituents are electron donating (*e.g.* Cl, OR), and is intriguing in that it is clearly opposite to that predicted solely on steric grounds. Several theories have been put forth to explain the results and the reader is directed to the original literature for a detailed account.[61] The tendency for the π-bond of these systems to distort toward a pyramidal geometry in the ground state, even by as little as *ca.* 1–5°, is generally believed to be associated with the selectivity; distortion reduces the torsional interaction between vicinal substituents.[61c] Thus the trigonal hydrogens move out-of-plane, away from the electron-donating substituents[61a] and, as the reaction progresses, away from the dipole. The movement is toward a geometry which allows attainment of a staggered

Table 12 Influence of Reaction Conditions Upon Product Composition



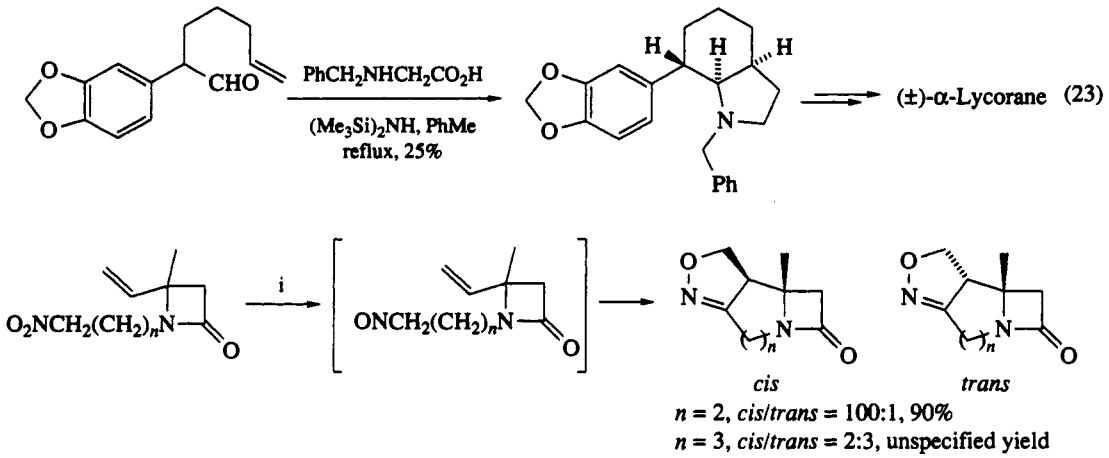
Solvent, temp. (°C)	*Product composition* 23*S*,25*S* : 23*R*,25*S* : 23*S*,25*R* : 23*R*,25*S*
CH_2Cl_2, 22	35 : 45 : 7 : 12
PhMe, 90	34 : 38 : 11 : 16
Xylenes, 140	31 : 22 : 26 : 20

arrangement between the trigonal C—H bonds as well as the bonds which are being formed to the dipole, and the C—X and C—H bonds at the allylic carbon. It has been suggested that 'the tendency for staggering of vicinal bonds with respect to partially formed bonds is greater than for fully formed bonds'.[61b] Perhaps the *syn*-facial selectivity observed in these cycloadditions reactions is an expression of this idea.



		endo:exo	*yield* (%) *SS-isomer*
Methyl methacrylate, r.t., 15 h	R = CH_2Ph	83:17	72
Methyl methacrylate, 50 °C, 42 h	R = Bu^t	>99:<1	81

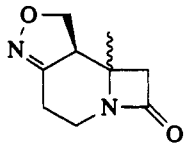
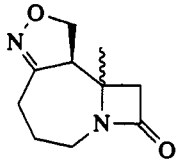
Scheme 17



i, $n = 2$: PhNCO, Et_3N, $CHCl_3$, r.t., 10 h; $n = 3$: PhNCO, Et_3N, $CHCl_3$, r.t., 6 h

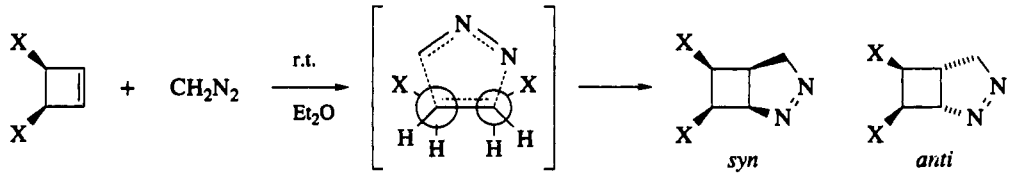
Scheme 18

Table 13 Results of Molecular Mechanics Calculations for Nitrile Oxide Cycloaddition

		Total energy (kcal mol^{-1})			
		Cis	*Trans*	*Energy difference*	*Cis:trans*[a]
	Ground state	53.93	56.94	3.01	100:1
	Transition state	43.13	44.67	1.54	
	Ground state	64.82	65.43	0.61	2:3
	Transition state	53.81	54.04	0.23	

[a] Experimental ratio determined by NMR.

Table 14 Diastereofacial Selectivity in Additions to 3,4-Disubstituted Cyclobutenes



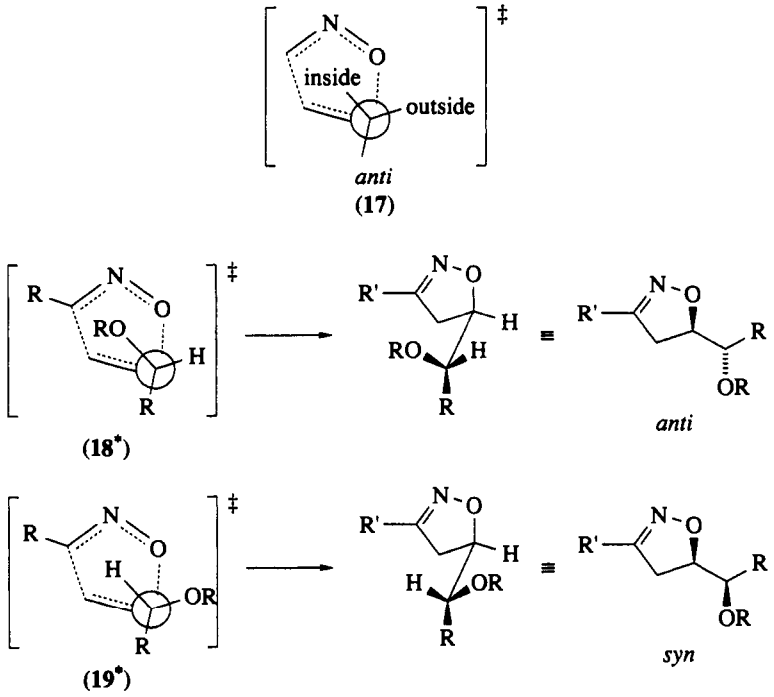
X	*θ* (°)[a]	*Yield (%)*	*Product(s)*
—$(CH_2)_3$—	5.1 (toward X)	70	*anti* only
—O(C═O)O—	nearly coplanar	82	1.8:1 *anti/syn*
—OC≡CMe	3.1 (away from X)	95	*syn* only

[a] Deviation of trigonal C—H bonds from planarity based on STO-3G calculations.

3.1.4.2.2 Absolute stereoselection

There is no doubt that the field of asymmetric induction occupies a very important place in modern synthetic methodology. Elegant protocols designed to carry out dipolar cycloadditions have been developed and important advances in the theoretical description of these processes have taken place as a consequence (*vide infra*).[25] Diastereoselective cycloadditions have been carried out between optically active nitrile oxides,[62] nitrones,[52,63a–d] azomethine ylides[64] and achiral dipolarophiles, and between optically active dipolarophiles and achiral nitrile oxides[65–70] and achiral nitrones.[71] The products have been put to good use, either by 'translating' the cycloaddition diastereoselectivity to the construction of useful optically active acyclic intermediates, or in the total synthesis of natural products (*vide infra*).[25,39a,66,69b]

The 'inside alkoxy effect' is useful for predicting the stereoselectivity of nitrile oxide cycloaddition reactions with chiral allylic ethers.[65] The hypothesis states that 'allylic ethers adopt the inside position and alkyl substituents prefer the sterically less-crowded *anti* conformation in transition states for these electrophilic cycloadditions'. The terms 'inside' and 'outside' are defined in (**17**) for a hypothetical nitrile oxide cycloaddition transition state. Both *ab initio* (Gaussian 80 with 3-21G basis set) and molecular mechanics calculations agree, each predicting the lowest-energy transition state to be the one described, *i.e.* (**18***; H outside); just above it lies one where the alkyl group is *anti*, OR outside and H inside (**19***).[65] As illustrated, the former leads to a product wherein OR and the nitrile oxide oxygen are *anti*, the latter to one with them *syn* (Scheme 19).

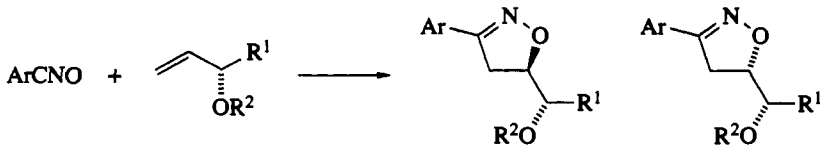


Scheme 19

It is argued that if the OR unit occupied the *anti* position, then the electron withdrawal by the σ^*_{CO}-orbital from the π-orbital of the dipolarophile would destabilize the electrophilic transition state.[65] By assuming the inside (or outside) position, σ^*_{CO}–π interaction is minimized and overlap of the electron-donating σ_{CH} and σ_{CR} orbitals with the *p*-orbital is maximized.

The model correctly predicts (rationalizes) the observed preference for formation of the *anti* rather than the *syn* product in the cycloaddition reactions of a wide variety of chiral allylic ethers, thus successfully laying to rest years of frustrated discussion.[65,66] It also correctly predicts that as the size of R increases (Me ~ Ph < Et < Pr^i < Bu^t), the preference for transition state structure (**18***) should increase leading to enhanced *anti* stereoselectivity (Table 15).[65] At first, this prediction seems strange. However, once it is realized that, like the Felkin-Anh model for nucleophilic addition to a carbonyl,[72] the outside position is actually more sterically demanding than the inside, then the prediction is sensible on purely steric grounds. Thus, the angle of approach of the nitrile oxide oxygen to the alkene actually places it nearer the outside than the inside substituent located at the allylic carbon.[67]

Table 15 *Anti/syn* Stereoselectivity in Nitrile Oxide Cycloadditions to Chiral Allylic Ethers[a]

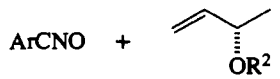


Ar	R^1	R^2	*Anti:syn*
p-$O_2NC_6H_4$	Me	OMe	64:36
p-$O_2NC_6H_4$	Ph	OMe	67:33
p-$O_2NC_6H_4$	Bu^t	OMe	>95:5
Ph	Me	OTMS	71:29
p-$O_2NC_6H_4$	Ph	OTMS	69:31
p-$O_2NC_6H_4$	Bu^t	OTMS	>95:5
p-$O_2NC_6H_4$	Me	$OSiMe_2Ph$	65:35
p-$O_2NC_6H_4$	Et	$OSiMe_2Ph$	80:20
p-$O_2NC_6H_4$	Pr^i	$OSiMe_2Ph$	91:9

[a]Conditions: CH_2Cl_2, 25 °C when Ar = p-$O_2NC_6H_4$; Et_2O, 20 °C when Ar = Ph.

On the other hand, the ratio varies little with changes in electronic or steric demands of either the nitrile oxide substituent or the alkyl group attached to the oxygen of the allyl ether (Table 16).[65,66,68,69] Similar observations have been made when R^2 = Me, THP, OAc and SiR_3.[65,66]

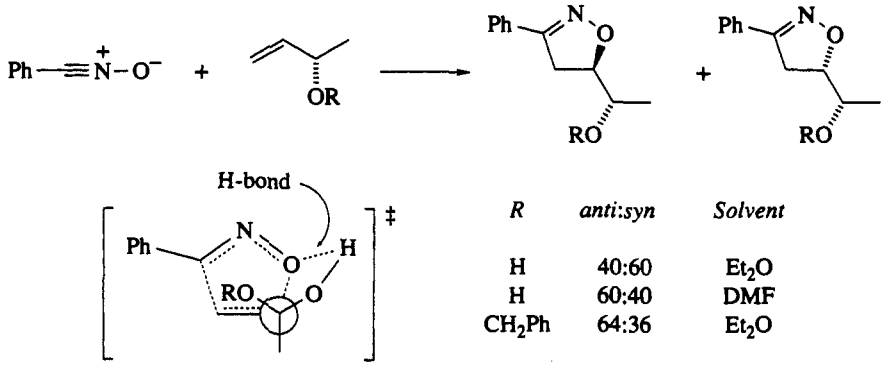
Table 16 Insensitivity of Cycloaddition Stereoselectivity to Ether Substituent[a]

	R^2	*Yield (%)*	*Anti:syn*
	Me	63	64:36
	C_6H_4OMe-p	89	66:34
Ar = p-$NO_2C_6H_4$	Ph	93	60:40
	$C_6H_4NO_2$-p	91	60:40

[a]CH_2Cl_2, 25 °C.

In contrast to allylic ethers, chiral allylic alcohols give rise to a modest preference for the *syn* product, presumably a reflection of stabilization through hydrogen bonding between the incoming nitrile oxide oxygen and the allylic alcohol.[67] *Ab initio* calculations agree that the outside OH position is favored over the inside. Additional support for this idea comes from the fact that in good hydrogen-bonding acceptor solvents like DMF, the 40:60 *anti/syn* ratio observed in diethyl ether becomes 60:40, nearly the same value as that found for the corresponding allyl ether (Table 17).[67]

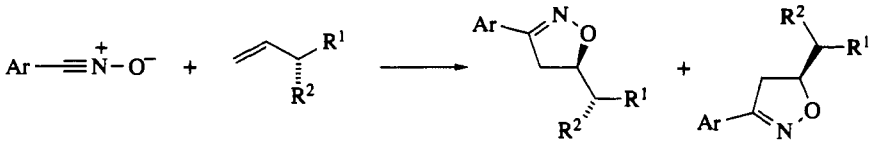
Table 17 Influence of Hydrogen Bonding and Solvent Upon Stereoselectivity

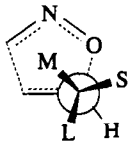


R	*anti:syn*	*Solvent*
H	40:60	Et_2O
H	60:40	DMF
CH_2Ph	64:36	Et_2O

Studies dealing with the general case where the groups attached to the stereogenic center of the allylic framework differ in size have only recently been performed. Remarkably good agreement between the results of MM2 calculations and experiment were evident and are summarized in Table 18.[68] The major product arises from a staggered transition state (**20**) similar to those shown above, with the largest group (L) *anti*, the medium-sized group (M) inside, and the small group (S) outside.

Table 18 Comparison of Calculated and Experimentally Determined Diastereoselectivity

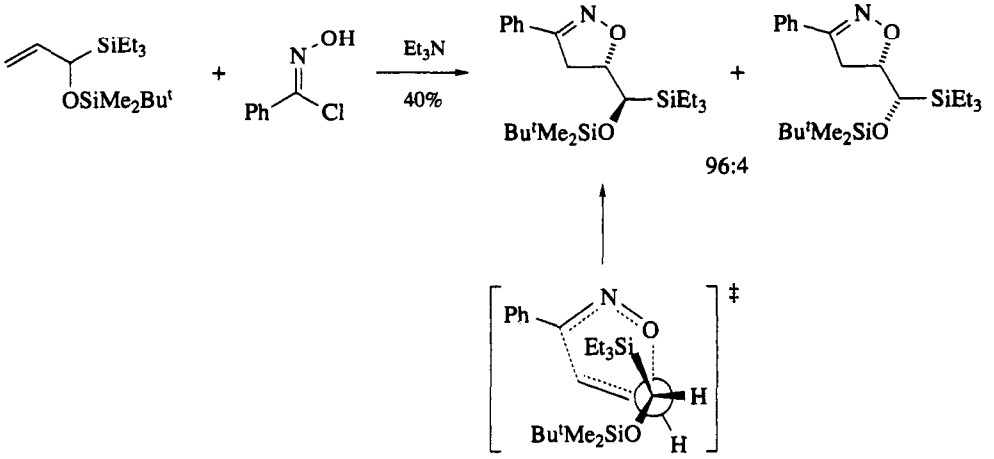




(20)

R^1	R^2	*Total yield (%)*	*Experimental (±3%)*	*Calculated*
Et	Me	72	50:50	50:50
Ph	Me	70	59:41	53:47
Pr^i	Me	50	65:35	72:28
C(OMe)Me$_2$	Me	93	80:20	87:13
Bu^t	Me	82	77:23	97:3
Me	OMe	63	64:26	68:32
Bu^t	OMe	64	>97:3	96:4

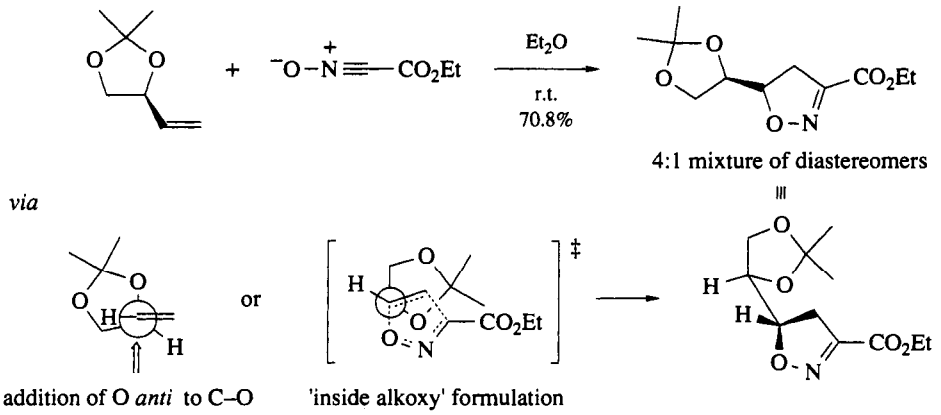
Interestingly, the transition states are calculated to be relatively early in terms of bond making and breaking, but are product-like in terms of conformational preferences about the bonds to the alkene.[67] For example, the X-ray crystal structure for the product of the reaction between *p*-nitrobenzonitrile oxide and 3,4,4-trimethyl-1-pentene resembles the transition-state model. Similarly, comparison of the ORTEP plot resulting from a single-crystal X-ray analysis of the major product resulting from the reaction of benzonitrile oxide with a chiral (α-oxyallyl)silane, CH_2=CHCH(OTBDMS)$SiEt_3$, closely resembles the predicted, preferred transition-state model, one which places the large trialkylsilyl group *anti*, the medium-size alkyl or oxy group inside, and the small hydrogen outside. The minor product apparently arises from a transition state where the location of the medium and small groups is reversed (Scheme 20).



Scheme 20

The addition of (ethoxycarbonyl)formonitrile oxide to (+)-(*S*)-isopropylidene-3-butene-1,2-diol led to an 80:20 mixture (60% diastereomeric excess) of diastereomers in *ca.* 70% yield (Scheme 21); the major

product was converted to 2-deoxy-D-ribose to illustrate the utility of the process.[69] The observed diastereoselectivity was explained using a different transition-state model than the one discussed thus far. In particular, it was assumed that cycloaddition occurred preferentially *via* a transition state where the nitrile oxide oxygen adds *anti* to the C—O bond in the dipolarophile as shown.[72] This approach does appear to minimize steric interactions. However, it maximizes σ^*_{CO} electron withdrawal from the alkene in a process which is, like most other nitrile oxide cycloadditions, LU controlled. The 'inside alkoxy' transition-state model invoked previously also accounts for the observed diastereoselectivity *via* a transition state which minimizes the σ^*_{CO}–π interaction.

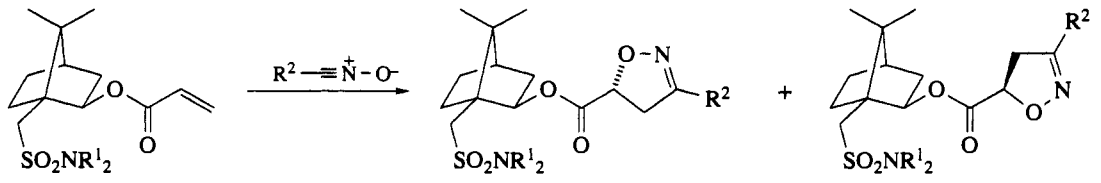


Scheme 21

Poor (<4% *de*) to modest (56% *de*) amounts of diastereofacial selection is observed in the cycloaddition of nitrile oxides to optically active acrylates.[70] The plan in each case, of course, was to use a chiral auxiliary which would preferentially shield one of the two π-faces of the dipolarophile. Of the auxiliaries used, the sulfonamide esters derived from (+)-camphorsulfonyl chloride worked best, the menthyl esters derived from (–)-menthol the poorest (<4% *de*). As illustrated in Table 19, changes in both temperature and solvent had either no or little affect on the product ratios. Unlike Diels–Alder reactions, the addition of Lewis acids, specifically Et_2AlCl, $EtAlCl_2$ and $TiCl_4$, resulted in significant decreases in both the rate of cycloaddition and isolated yield, without an appreciable change in diastereomer ratio.[70]

Examination of the structure of the major diastereomer suggests that it is derived from a cycloaddition between the nitrile oxide and the *s-cis* conformer of the acrylate. Calculations performed on simple transition-state models for the process do indeed place the formulation involving the *s-cis* conformer at lower energy than the alternative *s-trans* form.[70]

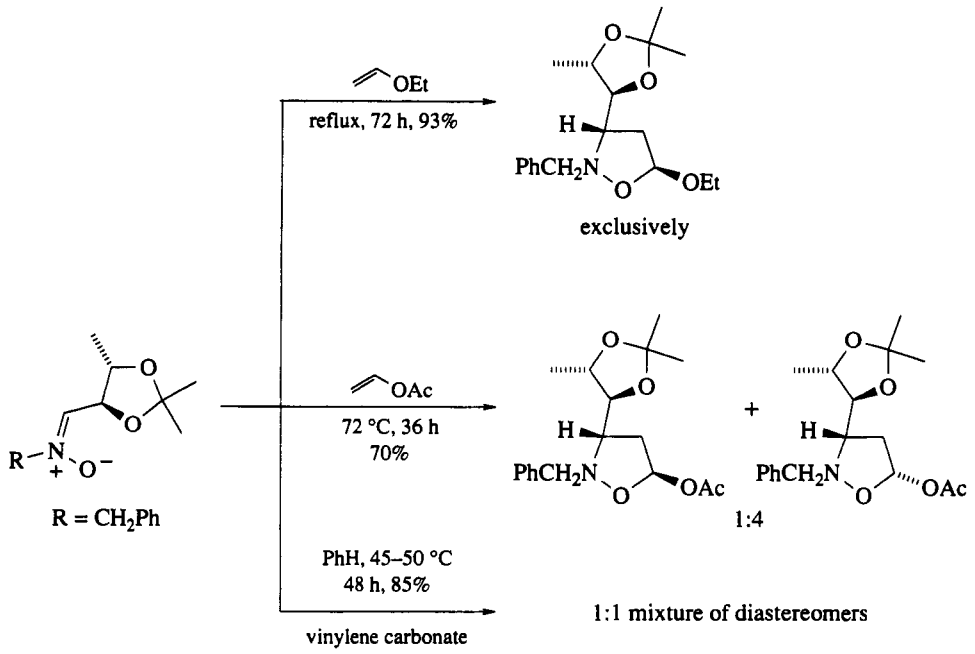
Table 19 Influence of Conditions Upon Diastereoselectivity in Cycloadditions to Chiral Acrylates



R^2	*Solvent*	*Temp. (°C)*	*Diastereomer ratio (% de; 21:22)*
Ph	PhH or PhMe	Ambient	77:23 (54)
Ph	a	0	b
Ph	a	–20	b
Ph	Hexane	Ambient	76:24 (52)
Ph	Et_2O	Ambient	72:28 (44)
Ph	CH_2Cl_2	Ambient	70:30 (40)
Bu^t	PhMe	Ambient	77:23 (54)
Bu^t	a	185	66:34 (32)

[a]Not specified. [b]No detectable change.

A variety of elegant experiments serve to highlight the nature of the subtle factors which control diastereofacial selectivity in dipolar cycloaddition reactions between optically active nitrones, of the type illustrated, and electron-rich dipolarophiles.[52,53,63b] In general, facial selectivity is found to be influenced by the nature of the substituent on nitrogen and by the presence of a second stereogenic center. As illustrated, selectivities ranging from zero to 'complete' have been observed (Scheme 22). Notice also the preference for formation of the *endo* transition state derived product.

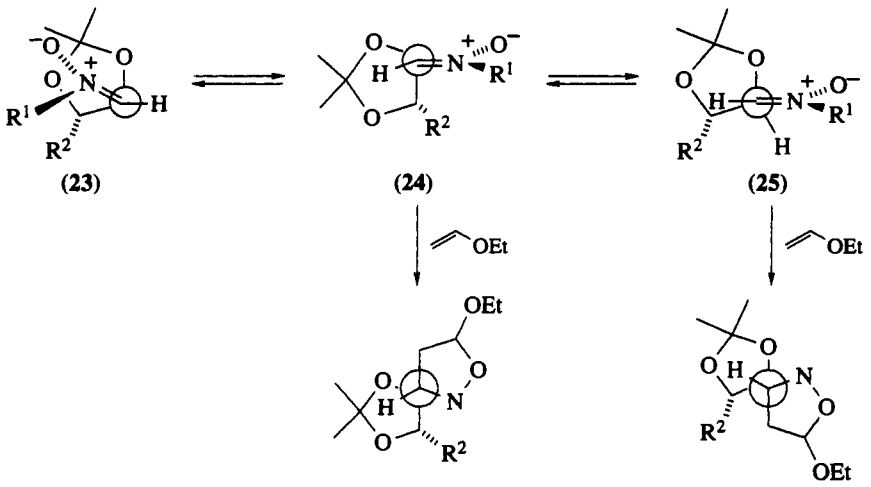


Scheme 22

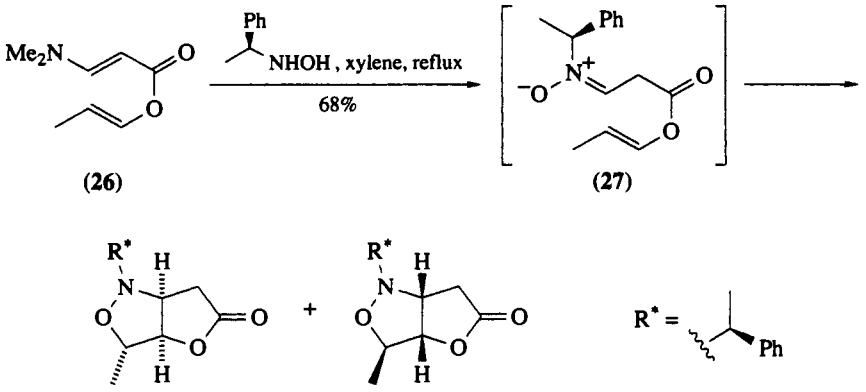
To rationalize the stereochemical outcome of the reactions illustrated as well as a host of other examples, the following arguments have been put forth.[53] Firstly, since the cycloaddition reactions are exothermic and have an early, reactant-like transition state, those factors which influence the relative energy of the equilibrating rotamers (**23**)–(**25**) also influence the transition-state energies. Examination of (**23**)–(**25**) reveals that (**23**) is sterically most congested, suggesting that the equilibrium should lie toward (**24**) and (**25**). Yet (**23**) could be the highest-energy and most reactive form of the nitrone. However, molecular mechanics calculations place it 8–10 kcal mol^{-1} higher in energy than (**24**), making it only a minor contributor to the conformational equilibrium during cycloaddition. Of (**24**) and (**25**), rotamer (**25**) finds one of the ketal CO bonds located *anti* to the π framework of the nitrone, thereby stabilizing it through an energy-lowering σ^*_{CO}–π_{CC} interaction. Secondly, attack of the dipolarophile is assumed to occur on to the face of the nitrone indicated by the double arrow. One concludes that cycloaddition should occur to give the major diastereomer *via* (**24**) and the minor diastereomer *via* (**25**), as observed (Scheme 23).

Diastereofacial selectivity is also expressed in the cycloaddition reactions of optically active nitrones bearing stereogenic centers on nitrogen, rather than on carbon.[50b,63c,63d,73] For example,[63d] formylation of *trans*-propenyl acetate with Brederick's reagent led to acrylate (**26**) in 91% yield. The latter was converted to nitrone (**27**) by heating it with the oxalate salt of (*S*)-(–)-*N*-hydroxy-α-methylbenzenemethanamine. Under these conditions the nitrone undergoes intramolecular cycloaddition leading to a 68% yield of an 82:18 mixture of diastereomers (Scheme 24). While the dipolarophile stereochemistry is preserved in the usual manner, this example is the first recorded instance of preferential addition of the nitrone oxygen to the non-oxygen bearing carbon of an enol ether.[74] In contrast, intermolecular nitrone cycloadditions with enol ethers and esters shows a marked preference for the opposite regiochemical outcome (*vide supra*).

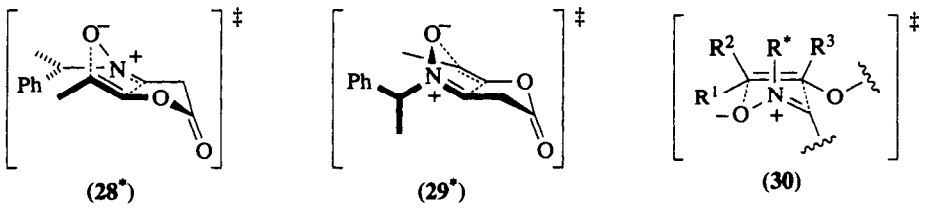
A working model, which may account for the results, proposes that transition state (**28***) leads to the major and (**29***) to the minor diastereomer. Notice that, in each, the α-methylbenzyl group is oriented with the small hydrogen atom directed toward the dipolarophile.[63d] As anticipated from this model, the degree of diastereoselection is dependent upon the substituents R^2 and R^3 located on the dipolarophile



Scheme 23



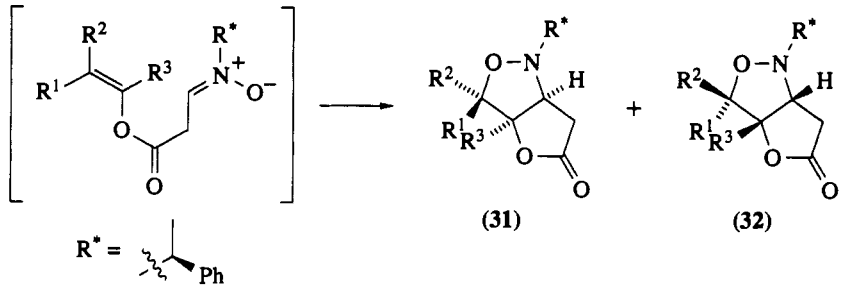
Scheme 24



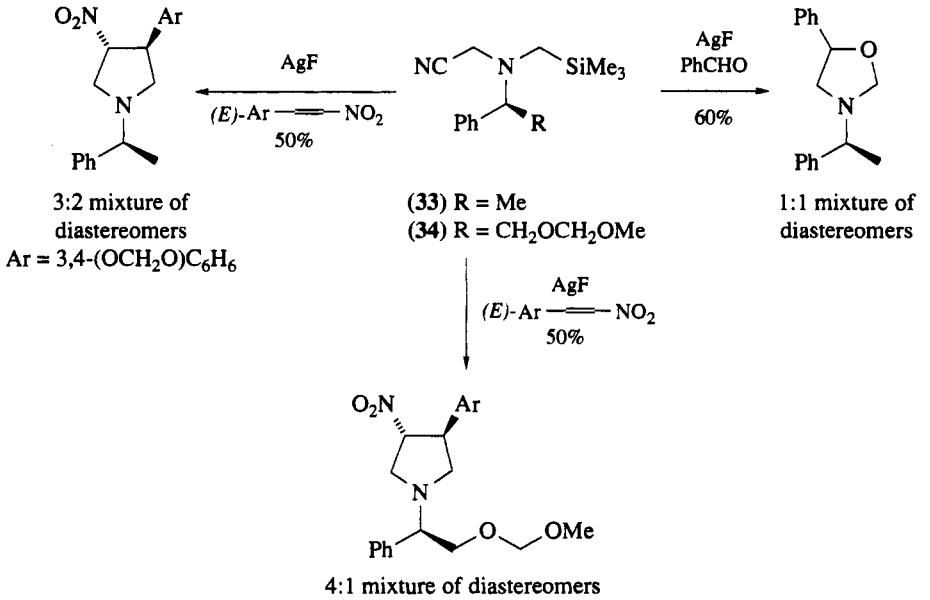
since each is in position to interact with the other and with R* in the transition state (**30**). The largest selectivity is observed when R^2 or R^3 = Me, the smallest when both are hydrogen (Table 20).[63d]

The same chiral auxiliary has been used in the cycloaddition of an optically active azomethine ylide to benzaldehyde and to 1-nitro-2-(3,4-methylenedioxyphenyl)ethylene; the ylide was generated *in situ* by treating (*R*)-(+)-*N*-(1-phenylethyl)-*N*-cyanomethyl-*N*-trimethylsilylmethylamine (**33**) with silver fluoride.[64] Unfortunately, no selectivity was observed in the first case and only a 3:2 preference was expressed in the second. Use of the azomethine ylide derived in the same manner from (*R*)-(−)-*N*-(1-phenyl-2-methoxyethyl)-*N*-cyanomethyl-*N*-trimethylsilylmethylamine (**34**) displayed a modest, but potentially useful, 4:1 diastereofacial selectivity in its reaction with 1-nitro-2-(3,4-methylenedioxyphenyl)ethylene. The precise structure of the major and minor product was not determined (Scheme 25).

Table 20 Diastereoselectivity in Intramolecular Nitrone Cycloaddition Using a Chiral Nitrone



	(31):(32)
$R^1 = R^3 = H$, $R^2 = Me$	82:18
$R^1 = Me$, $R^2 = R^3 = H$	53:47
$R^1 = R^2 = R^3 = H$	60:40
$R^1 = R^2 = H$, $R^3 = Me$	73:27
$R^1 = R^2 = Me$, $R^3 = H$	73:27



Scheme 25

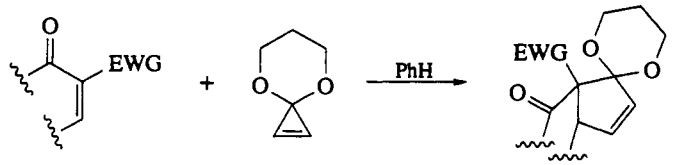
3.1.5 1,3-DIPOLAR SYNTHETIC EQUIVALENTS[75]

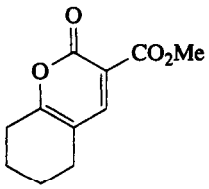
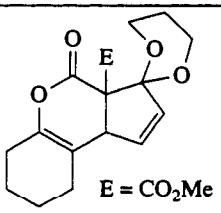
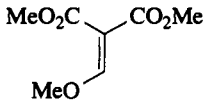
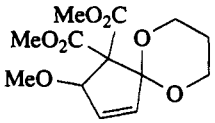
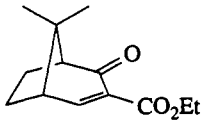
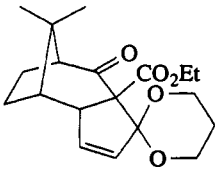
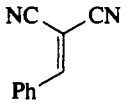
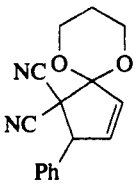
3.1.5.1 Polarized Cyclopropanes

3.1.5.1.1 Cyclopropenone ketals

In 1984, the facile [3 + 2] cycloaddition of cyclopropenone ketals to alkenes bearing geminal electron-withdrawing groups was reported.[76] The reaction proceeds regiospecifically, always placing the ketal adjacent to the carbon bearing the electron-withdrawing group. The reactions are typically run at temperatures of 70–80 °C in benzene or acetonitrile. Isolated yields range from *ca.* 40 to 80%. Representative examples of this mechanistically interesting and synthetically useful process are shown in Table 21.[75]

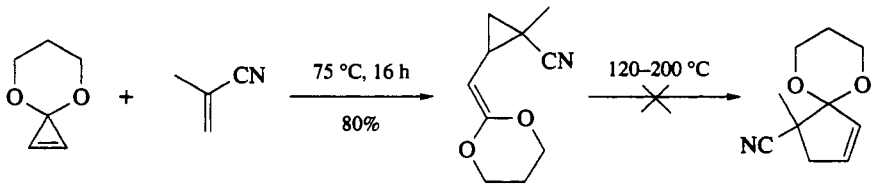
Table 21 Reaction of Cyclopropenone Ketal With Electron Deficient Alkenes



Substrate	*Equiv. of ketal*	*Conditions*	*Product*	*Yield (%)*
	1.0–2.0	80 °C, 12 h		42
	2.0	80 °C, 5 h		84
	1.0	75 °C, 13 h		45
	2.0	80 °C, 4 h		86

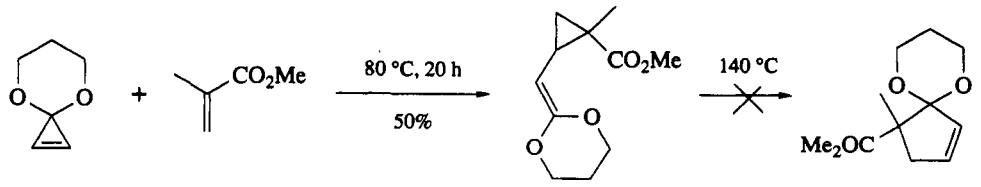
The synthetic utility is restricted somewhat by the failure of alkenes activated by only one electron-withdrawing group to undergo the cycloaddition. Instead, vinylcyclopropanes, corresponding to [1 + 2] cycloadducts, are formed. Unfortunately, attempts to affect a vinylcyclopropane–cyclopentane rearrangement were unsuccessful. 2-Acetoxyacrylonitrile fails to participate in either [1 + 2] or [2 + 3] cycloaddition (Schemes 26, 27).[76b]

The cyclopropenone ketal behaves as the 1,3-dipolar equivalent (**35**; Scheme 28). Yet attempts to detect it, or to affect the rate of the process by varying solvent polarity, indicate that little discernible dipolar character is associated with the intermediate involved in the rate-determining step.[76] Detailed



9:1 *cis:trans*

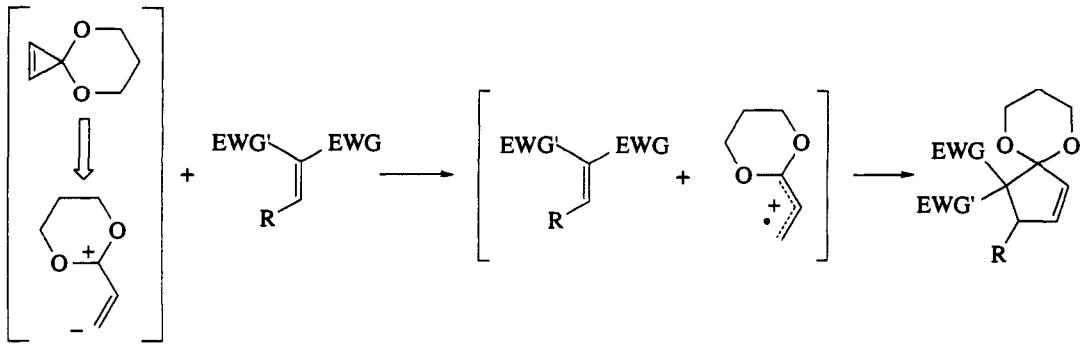
Scheme 26



1:1 *cis:trans*

Scheme 27

mechanistic studies have ruled out several potentially viable mechanisms. It has been suggested that a π-delocalized singlet vinylcarbene is formed *via* a reversible, thermal process and is followed by single electron transfer from it to the electron-deficient doubly activated alkene to generate a π-delocalized cation radical–radical anion pair; their combination leads to the product.[76]

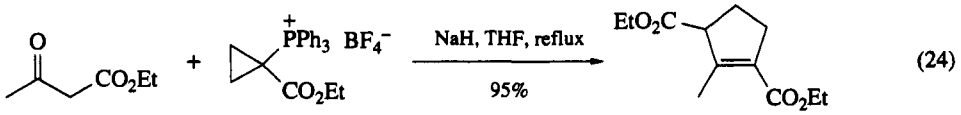


(35)

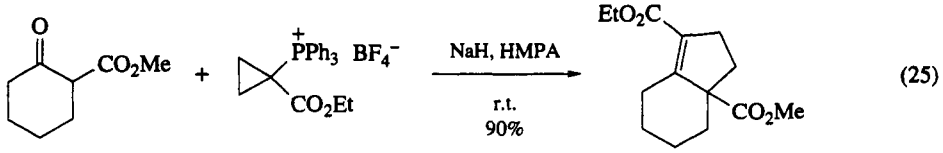
Scheme 28

3.1.5.1.2 Cyclopropylphosphonium salts

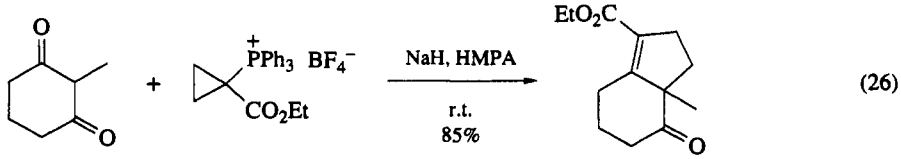
It is well known that cyclopropane rings, activated toward reaction by the existence of geminal electron-withdrawing groups, can be opened by nucleophiles.[77] One such system is ethoxycarbonylcyclopropyltriphenylphosphonium tetrafluoroborate.[75,78] When allowed to react with an enolate derived from a β-keto ester or a 1,3-diketone, the salt suffers ring opening to generate an ylide which subsequently undergoes an intramolecular Wittig cyclization on to the ketone, leading to the creation of a five-membered ring.[78] In so doing the phosphonium salt clearly behaves as a synthon for a 1,3-dipolar reagent.[75] Equations (24)–(26) provide an indication of the scope of the reaction.



(24)



(25)



(26)

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3.2
Transition Metal Mediated Cycloadditions

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3.2.1 GENERAL INTRODUCTION

Five-membered ring systems are rapidly emerging as important structural features in a large number of natural products and theoretically interesting molecules. The development of methodologies for the construction of these systems has thus become a subject of great interest and intense effort for synthetic chemists. In recent years, one has seen a number of C_5 annulation procedures, with the majority focusing on multistep sequences based on 1,4-dicarbonyl compounds or their functional equivalents.

One particularly attractive and logical approach to a five-membered ring is the [3 + 2] cycloaddition. This reaction couples a three-carbon 4π unit directly with a two-carbon 2π unit, forming two C—C bonds in one operation. The net result is rapid and efficient construction of complex cyclic structures from simple building blocks. This direct method is analogous to the highly effective and popular [4 + 2]

Diels–Alder reaction. The [3 + 2] methodology has the promise and the potential to achieve similar success if one can likewise control the chemo-, regio- and diastereo-selectivity of these reactions.

The ready availability of starting materials, such as dienes and alkenes, has contributed to the popularity of the Diels–Alder reaction. Unfortunately, this is not true in [3 + 2] cycloadditions. While the C_2 unit is well represented by simple unsaturated molecules as in the Diels–Alder reactions, the source of the odd-numbered 4π fragment is less obvious because it is not a common stable entity. Hence, the success of using the [3 + 2] methodology in a synthetic sequence depends critically on the effective generation, reactivity and selectivity of this C_3 synthon.

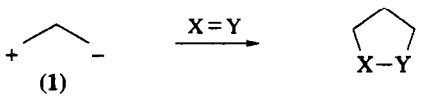
Thermal [3 + 2] cycloadditions have been discussed in the previous chapter. Transition metals also play a critical role in mediating such reactions.[1] Reaction of a commercially available or readily synthesized organic substrate with an appropriate transition metal reagent or catalyst can generate a reactive intermediate which can function as the three-carbon synthon. One can view this as the stabilization of the C_3 fragment by ligation to the transition metal center. One unique advantage of these transition metal mediated reactions is the ability to modulate the selectivity of the cycloaddition by the judicious selection of the metal and its ancillary ligands. The opportunity to use chiral ligands to effect enantioselective synthesis is another useful feature. In addition, the properties of this three-carbon unit can be so markedly altered by the metal that the resulting complex may undergo completely different types of reaction from those of the thermally generated systems. This may open up new synthetic avenues not available before. The transition metal complexes described in this section are not esoteric, but are either commercially available or readily prepared. In most cases, these transition metal-mediated reactions require only routine oxygen- and moisture-free laboratory techniques.

3.2.2 CLASSIFICATION OF REACTIONS

The main research efforts in transition metal mediated [3 + 2] cycloaddition can be categorized into the development of three important types of C_3 synthon: dimethylenemethane, 2-oxyallyl, and trimethylenemethane. This review summarizes some recent achievements up to the first quarter of 1989, and centers around these three synthons. Emphasis will be placed on the chemo-, regio- and stereo-selectivity of these reactions, their preparative aspects, and their synthetic potential.

3.2.3 THE DIMETHYLENEMETHANE SYNTHONS

A [3 + 2] cycloaddition involving a dimethylenemethane (**1**) and an unsaturated receptor is depicted in equation (1). A number of these three-carbon synthons has been developed. They include stable and easily prepared organometallic species, as well as the activation of an organic precursor with a transition metal reagent or catalyst. The discussion on the generation and reactions of this three-carbon synthon will be organized according to precursor types: allylic, alkynyl, allenylic, cyclopropyl and others.

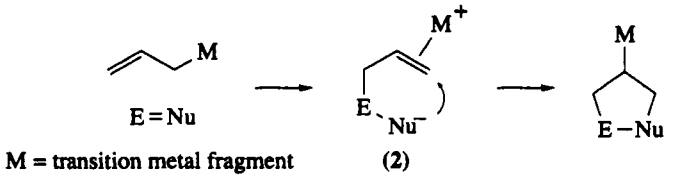


(**1**) (1)

3.2.3.1 Allylic Precursors

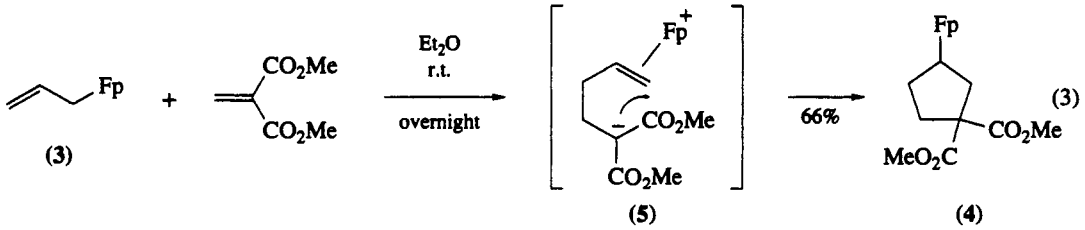
Cycloaddition reactions of 18-electron transition metal η^1-allyl complexes with unsaturated electrophiles to form five-membered rings have been extensively investigated. These transformations constituted a family of metal-assisted cycloaddition reactions in which the metal functions as an electron-donor center. These are typically two-step processes that involve the initial formation of a dipolar metal η^2-alkene intermediate (**2**) and subsequent internal cyclization (equation 2).[2–4] The most extensively investigated application of this methodology has been with dicarbonyl-η^5-cyclopentadienyliron (Fp) complexes from the laboratory of Rosenblum.[3,4] These (η^1-allyl)Fp complexes are available either by metallation of allyl halides or tosylates with a Fp anion, or by deprotonation of (alkene)Fp cations.[4,5]

The parent (η^1-allyl)Fp (**3**) reacts readily with a highly activated electron-deficient alkene such as dimethyl methylenemalonate at room temperature to give the Fp-cyclopentane (**4**) (equation 3).[4] As discussed previously, the mechanism apparently involves the initial Michael addition of (**3**) to the



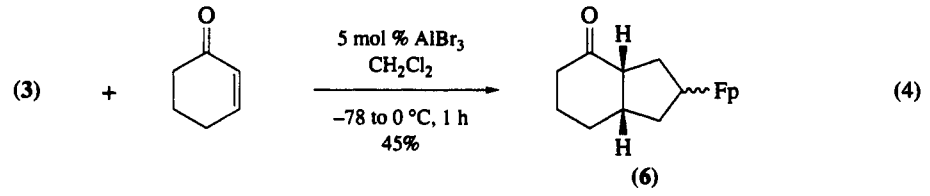
(2)

electron-deficient alkene to produce the intermediate complex (**5**). Ring closure is achieved *via* the attack of the stabilized anion on the Fp-coordinated (and thus activated) alkene.

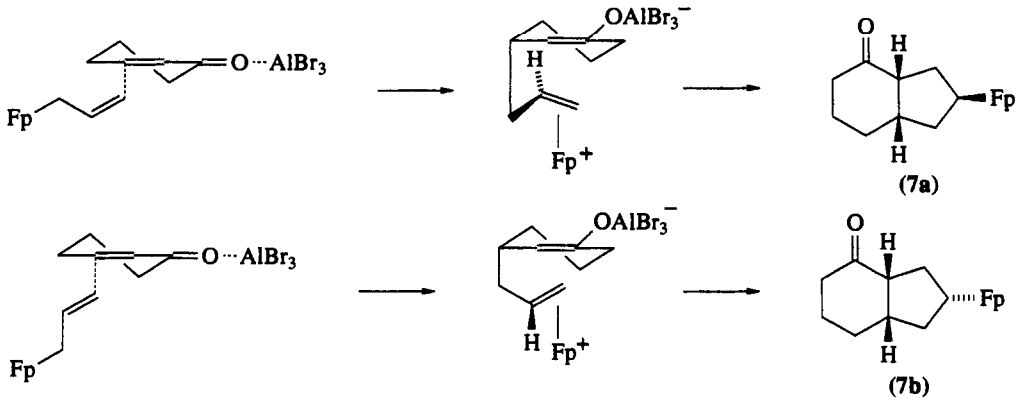


(3)

The cycloadditions of (η^1-allyl)Fp complexes to alkenes proceed with high chemoselectivity. Only highly activated alkenes such as methylenemalonates, benzylidenemalononitrile,[6] TCNE[4] or 1,2-dicyano-4,5-dichloroquinone[4] will participate in the reaction. With the less electrophilic α,β-unsaturated systems, cycloaddition can only be effected with Lewis acid activation. Thus the cycloadduct (**6**) is formed in reasonable yield (as a mixture of stereoisomers) from (**3**) and cyclohexenone using freshly sublimed $AlBr_3$ (equation 4). The same reaction gives only a 8% yield with $AlCl_3$. The exclusive formation of a *cis*-hydrindanone system can be explained by suprafacial attack of the enone on the allyl unit, which is then followed by another suprafacial ring closure of the dipolar intermediate, affording the thermodynamically preferred cyclic system (**7a**) and (**7b**).[6]

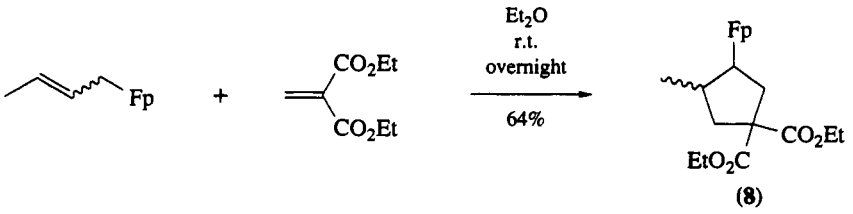


(4)

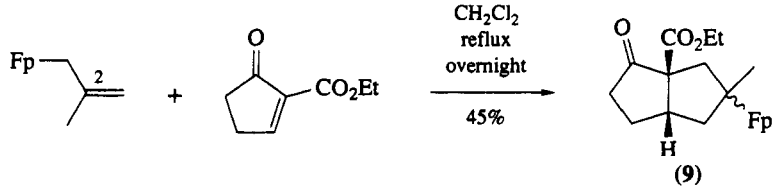


The more sterically demanding (η^1-2-butenyl)Fp cycloadds to diethyl methylenemalonate to give adduct (**8**) as a mixture of stereoisomers (equation 5).[6] In this case the poor stereoselectivity may be due to the fact that the starting butenyl complex is a mixture of *cis* and *trans* isomers. Formation of the bicyclic ketone (**9**) from the reaction of (η^1-2-methallyl)Fp and 2-ethoxycarbonylcyclopentenone suggests that alkyl substituents can also be tolerated at C-2 of the (allyl)Fp unit (equation 6).[6] The corresponding (η^1-2-methoxyallyl)Fp fails to produce any cycloadduct with 2-ethoxycarbonylcyclohexenone or 2-cyclo-

hexenone in the presence of $AlBr_3$. In this case it appears that closure of the zwitterionic intermediate is impeded by the electron-donating methoxy group.

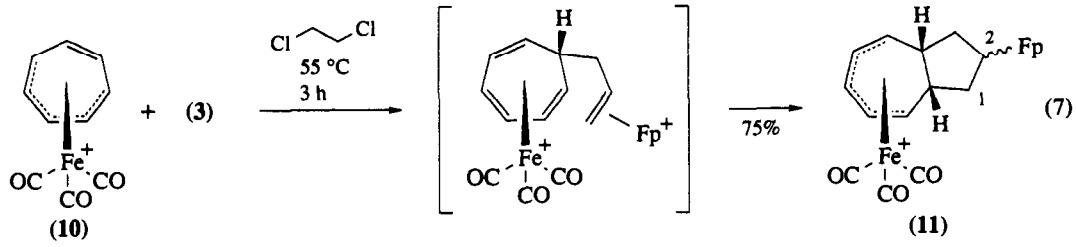


(8) (5)

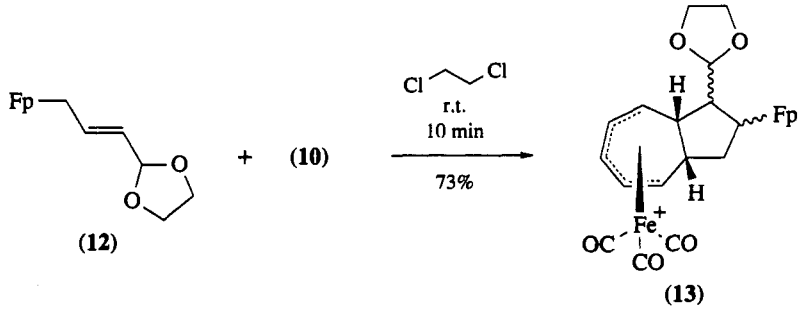


(9) (6)

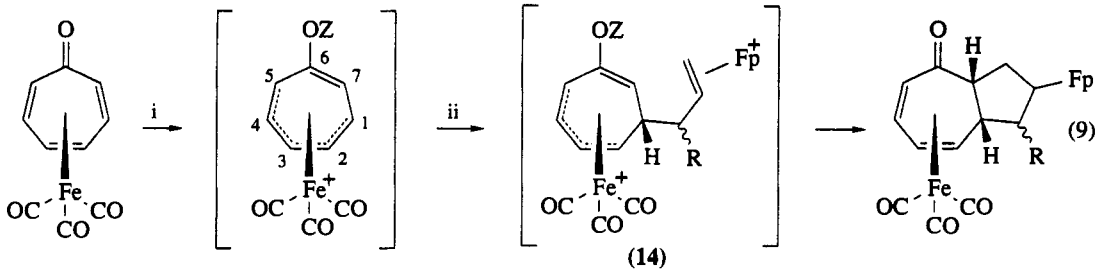
The construction of hydroazulenes using (allyl)Fp chemistry exemplifies a synthetic application of this [3 + 2] cycloaddition and illustrates some rather interesting regioselectivity of these reagents. The tropyliumiron tricarbonyl (**10**) reacts with (η^1-allyl)Fp (**3**) to give the dinuclear *cis*-hydroazulene complex (**11**) as a mixture of C-2 epimers (equation 7).[7] With 1-substituted (allyl)Fp complexes such as ketal (**12**), reaction with (**10**) affords exclusively the 1-substituted hydroazulene complexes (**13**) in good yield (equation 8).[7] Another remarkable regioselectivity of the (allyl)Fp cycloaddition is manifested in the reaction with substituted tropyliumiron tricarbonyls. The readily available troponeiron tricarbonyl can be activated for the [3 + 2] cycloaddition by trimethylsilyl or di-*n*-butylboryl triflate at low temperature. Treatment of the resulting trimethylsilyloxy- or di-*n*-butylboryloxy-tropylium salt with a number of (allyl)Fp complexes yields the *cis*-4-ketohydroazulene as the sole product (equation 9).[8] These reactions are likely to proceed *via* intermediate (**14**), which is derived from attack of the allyl organometallic nucleophile at the least sterically hindered position of the pentadienyl ligand, *i.e.* on the opposite side of the $Fe(CO)_3$ moiety. The formation of a single regioisomer is remarkable in view of the known dynamic equilibrium of structural isomers of a substituted tropyliumiron tricarbonyl. The oxygen substituents (Z = TMS or BBu_2) on the tropylium unit appear to exert the regiocontrol. Reaction of the corresponding 2-methyltropone system with the parent (η^1-allyl)Fp (**3**) also results in a single regioisomer (equation 10).[9] Likewise, the hydroazulene complex (**15**) is formed in the reaction of 4-methyltroponeiron tricarbonyl and (**3**) (equation 11).[9]



(10) (11) (7)



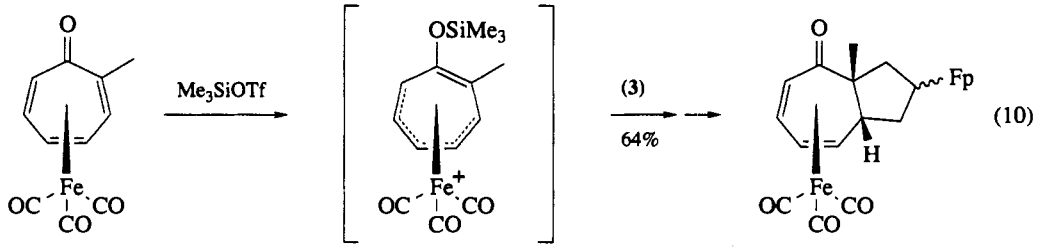
(12) (13) (8)

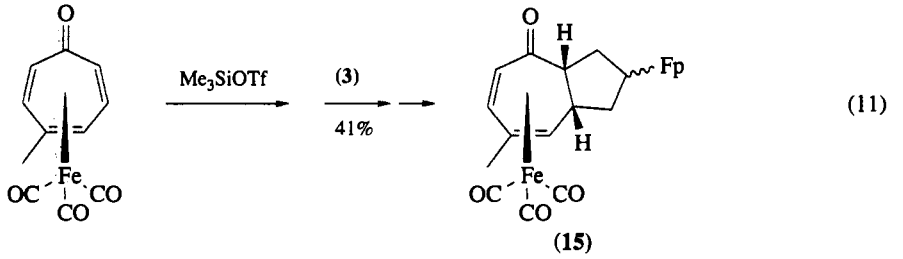


(14)

Nucleophile	*R*	*Activator*	*Z*	*Yield*
Fp—⟋⟍R	H	Me_3SiOTf	Me_3Si	58%
	H	Bu^n_2BOTf	Bu^n_2B	60%
	Me	Bu^n_2BOTf	Bu^n_2B	62%

i, 1 equiv. of activator added at –78 °C, CH_2Cl_2, 3 h;
ii, nucleophile at –78 °C, 2 h, then reflux 2 h, then EtOH, K_2CO_3





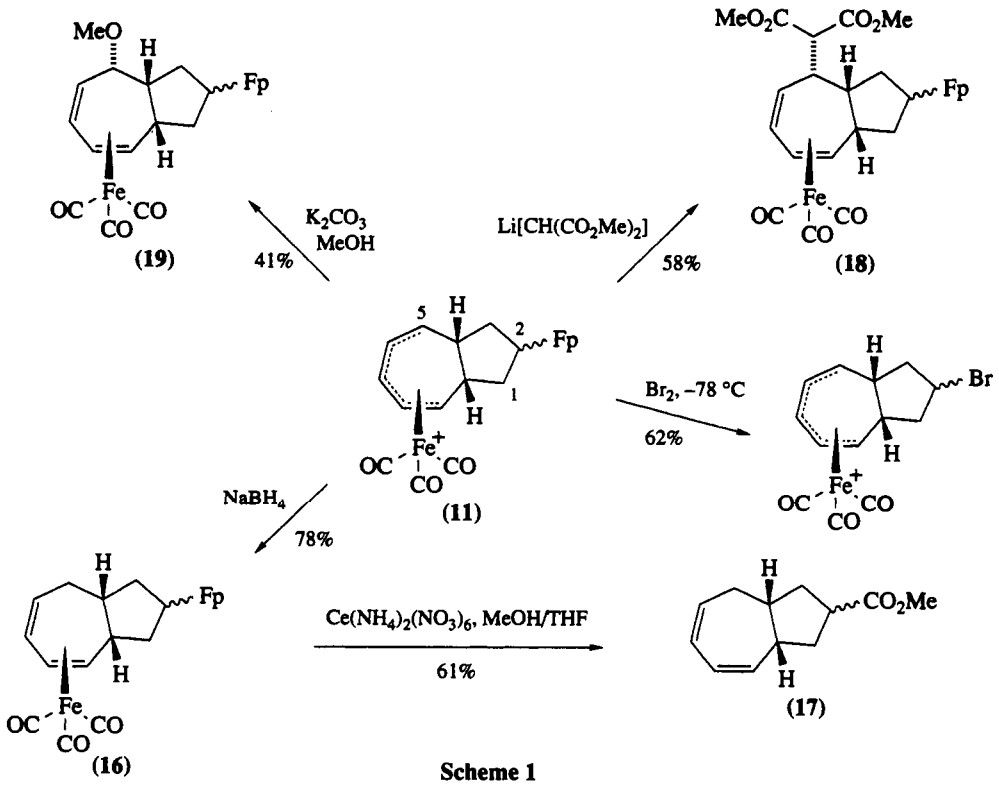
(15)

The subsequent transformation of these cycloadducts further illustrates the versatility of this approach in the construction of guaianolide sesquiterpenes (Scheme 1).[7] The Fp moiety incorporated in the adduct allows for the introduction of diverse functionalities at C-5 and C-2. For example, reduction of the cycloadduct (**11**) with sodium borohydride produces a good yield of the iron complex (**16**). Oxidation of this complex with cerium ammonium nitrate gives methyl ester (**17**). In addition, (**11**) reacts with nucleophiles such as lithium dimethylmalonate and methanol to give the alkylated complex (**18**) and the methoxylated complex (**19**), respectively. Oxidative demetallation of (**11**) with bromine leads to selective replacement of the Fp moiety at C-2 by bromide.[7]

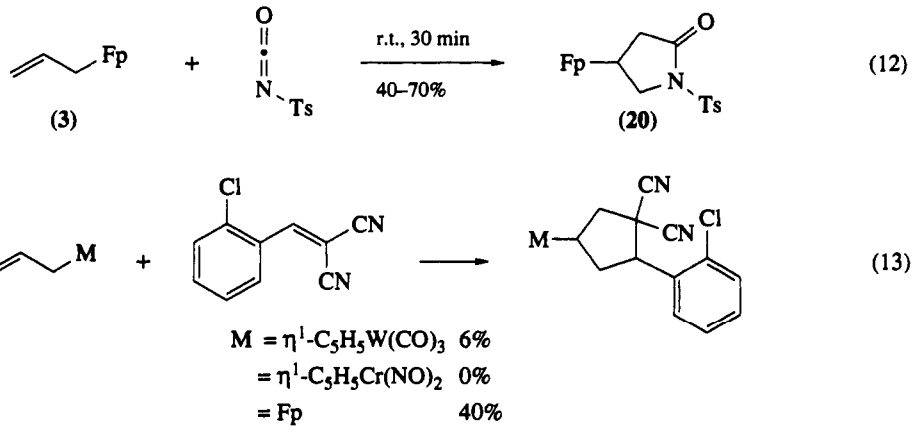
This [3 + 2] strategy can also be extended to include other heteroatom substrates. The (η^1-allyl)Fp (**3**) reacts smoothly with toluenesulfonyl isocyanate to afford butyrolactam (**20**) (equation 12).[10]

Other η^1-allyl transition metal complexes have also been investigated, but mostly they are less effective than the corresponding Fp system. For example, the tungsten, cobalt, chromium and molybdenum analogs of (**3**) cycloadd with the highly electron deficient TCNE at indistinguishable rates;[4] however, with the less reactive *o*-chlorodicyanostyrene there is a distinct difference in their reactivity. The tungsten η^1-allyl complex affords only 6% of the adduct after 4 h in refluxing THF, whereas the chromium complex fails to react even after prolonged heating. For comparison, the iron complex (**3**) cyclizes smoothly with the same styrene in only 3 h at room temperature (equation 13).[4]

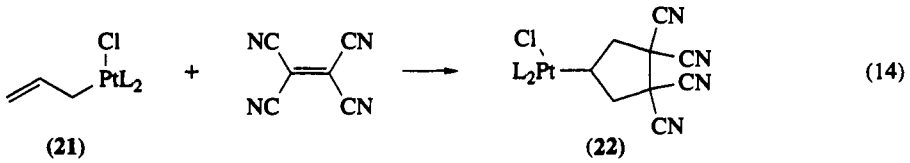
Cycloaddition of the analogous 16-electron (η^1-allyl)Pt^{II} complexes (**21**) with TCNE proceeds at –78 °C for three days to give the adduct (**22**) (equation 14).[2] The reaction of η^1-allylpalladium complexes (**23**) with maleic anhydride has also been reported (equation 15).[11] This reaction is sensitive to the nature



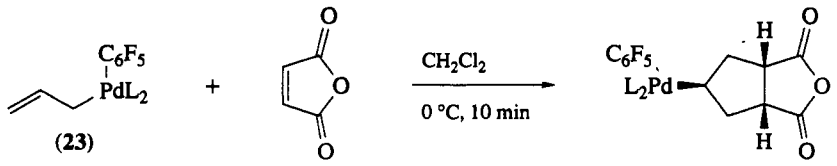
Scheme 1



of the aryl ligand on the metal. Replacing the pentafluorophenyl ligand with a 2,3,5,6-tetrachlorophenyl group gives propene as the main product. No reaction is observed with (**23**) and dimethyl fumarate or maleate.



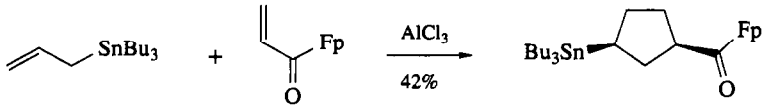
L	*Yield*
Ph_3P	70%
Ph_2PMe	54%
$Ph_2PCH{=}CHPPh_2$	64%



(15)

L_2	*Yield*
$Ph_2PCH_2CH_2PPh_2$	60%
$Ph_2PCH{=}CHPPh_2$	30%

A novel [3 + 2] cycloaddition of allylstannanes to α,β-unsaturated (acyl)Fp complexes in the presence of a Lewis acid has been reported. Allyltributyltin reacts smoothly with an (acryloyl)Fp complex at low temperature with a stoichiometric amount of $AlCl_3$ to give the bimetallic cyclopentane (equation 16).[12] It should be noted that allyltrimethylsilane fails to produce any cycloadduct under similar conditions.



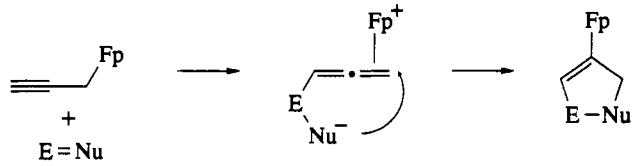
(16)

3.2.3.2 Alkynyl Precursors

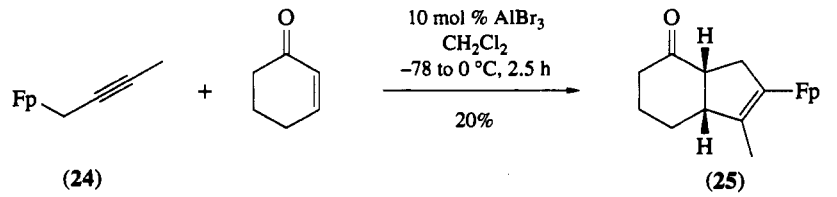
Alkynyl organometallic reagents based on the Fp system have also been used in [3 + 2] cycloadditions to give cyclopentene systems. The mechanism is similar to the allyl case (equation 17). Reaction of (η^1-butynyl)Fp (**24**) with cyclohexenone activated with aluminum bromide generates the bicyclic adduct (**25**) in moderate yield (equation 18).[6] The same butynyl complex cycloadds to the tropyliumiron tricarbonyl (**10**) and its oxo derivative to give good yields of iron carbonyl adducts (equation 19).[7,8] The Fp group in adduct (**26**) is readily removed by exposure to dilute sulfuric acid. The cycloadditions of $FpCH_2C{\equiv}CR$ (R = Me, Ph, CH_2Fp) with unsaturated substrates such as toluenesulfonyl isocyanate, sulfonylurethane, diarylketene and *N*-sulfinylaniline in variable yields have been reported.[13] The butynyl complex (**24**) reacts with diphenylketene and *N*-sulfinylaniline to give cyclopentanone (**27**)[13] and γ-sultam (**28**),[10] respectively (equation 20).

3.2.3.3 Allenylic Precursors

A novel nucleophilic cyclopentene annulation with (trimethylsilyl)allene mediated by titanium tetrachloride has been developed by Danheiser and coworkers.[14–17] One powerful feature of this one-step cycloaddition is its capability to generate substituted five-membered rings regiospecifically. As illustrated in equation (21), the reaction proceeds with high stereoselectivity *via* effective suprafacial addition of the allenylic unit to the electron-deficient alkene. This [3 + 2] annulation methodology is most effective with 1-substituted TMS-allenes, which are available from propargyl alcohols (equation 22).[14,15] Methyl vinyl ketone reacts smoothly with 1-methyl-1-(trimethylsilyl)allene (**29**) at –78 °C to give a good yield of the

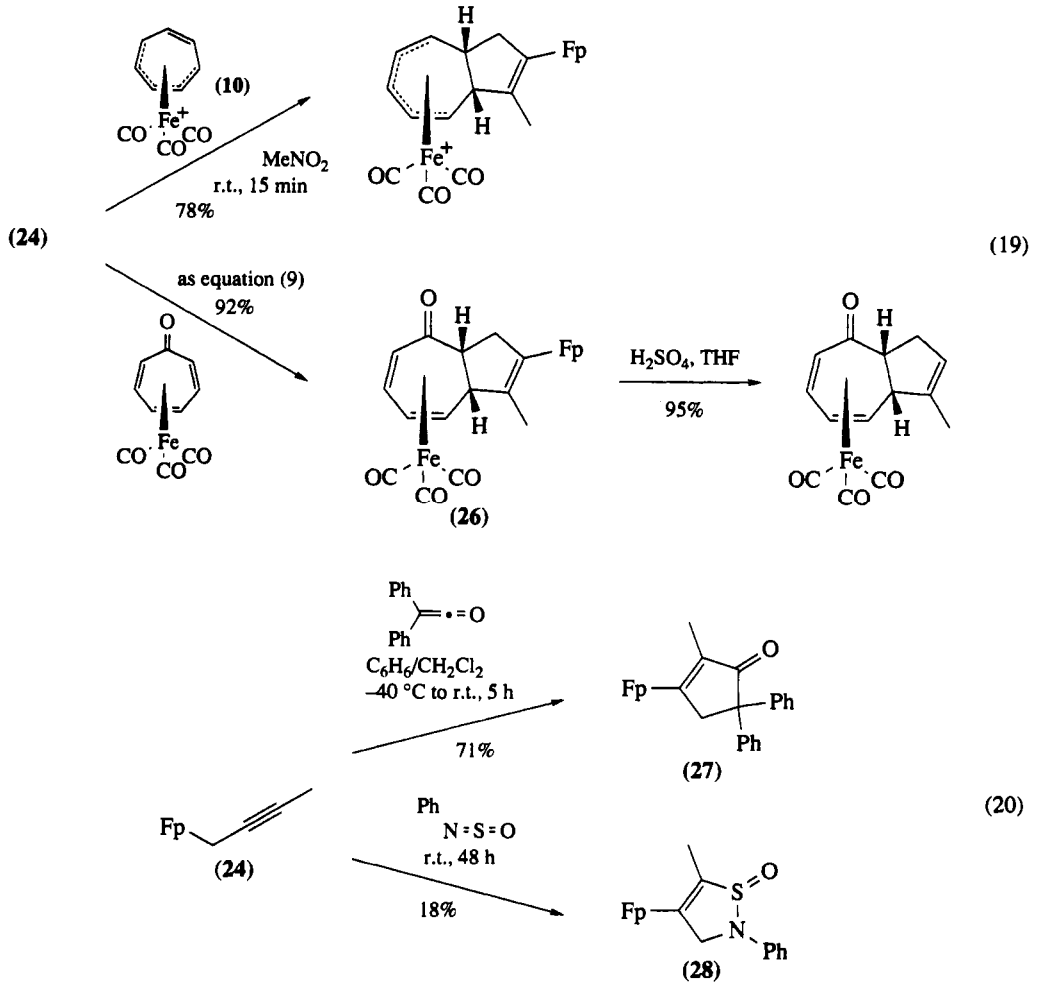


(17)



(18)

(**24**) (**25**)

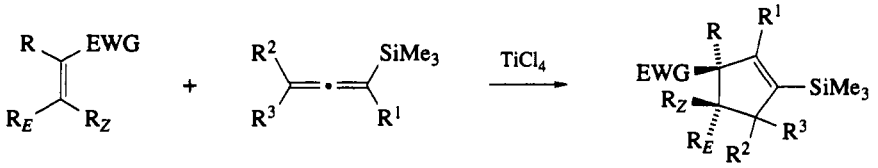


(19)

(20)

annulation product (**32**) (equation 23).[15] The reaction is likely to involve initial complexation of the enone with $TiCl_4$. Regiospecific electrophilic substitution at the least-hindered end of the allene by the activated enone produces a stabilized vinyl cation (**30**). A 1,2-shift of the TMS group isomerizes (**30**) to cation (**31**), which is then intercepted internally by the titanium enolate to produce the cyclic product. Alkynoic ketones, such as 3-butyn-2-one, also undergo smooth annulation to generate a cyclopentadiene system (equation 24).[15] Isopropylidenecyclohexanone gives the spiro adduct with the silyl allene (**29**) only at room temperature (equation 25).[15] The low yield formation of the highly sterically congested cyclopentene adduct (**33**) (equation 26), and the failure of annulation with the more hindered isophorone,[14] demarcates the steric limit of this cycloaddition.

The reactions of (*E*) and (*Z*)-3-methyl-3-penten-2-one demonstrate the high stereoselectivity of this cycloaddition. From the (E)-isomer a single cyclopentene (**34**) is observed. The reaction of the correspond-



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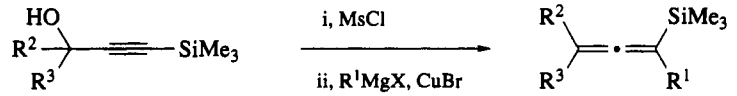

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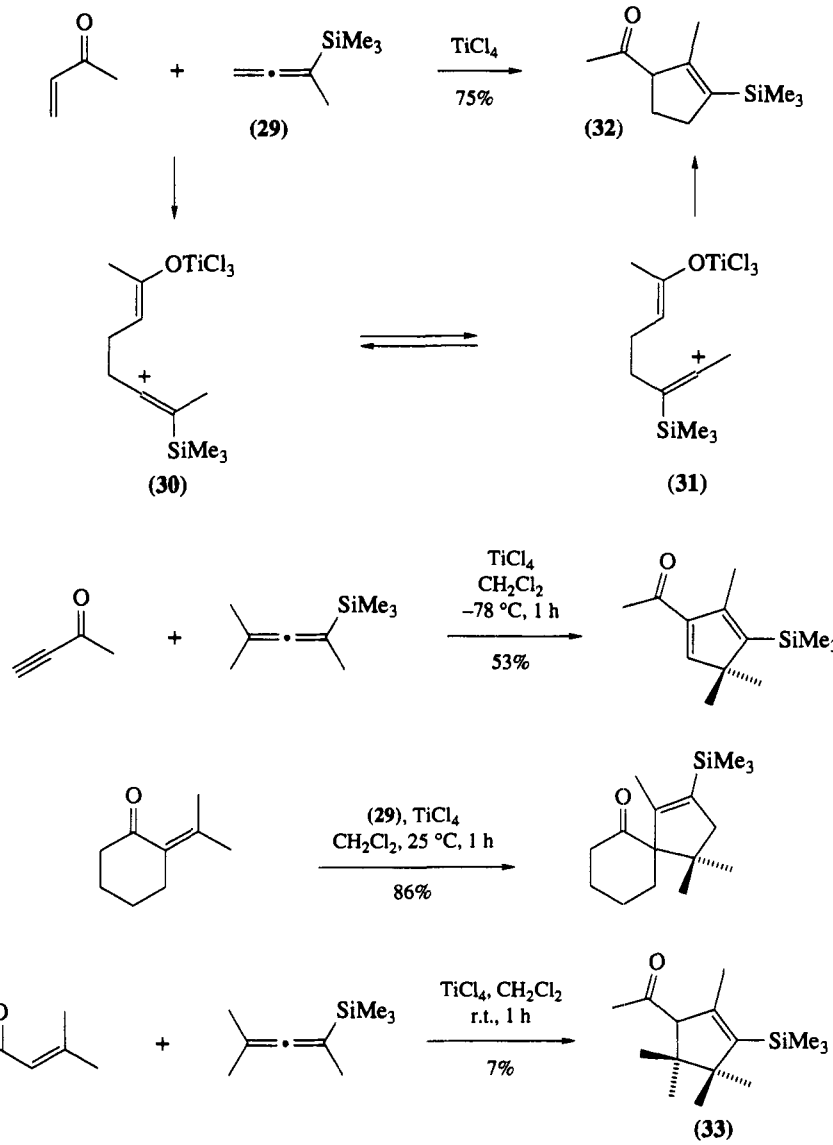
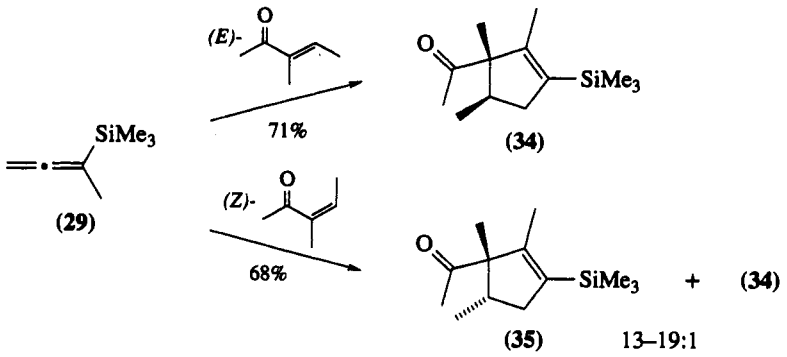


ing (*Z*)-isomer generates mainly the other diastereomer (**35**) (equation 27).[15] Cyclopentenone and cyclohexenone yield exclusively *cis*-fused adducts with (**29**). Cycloheptenone also gives predominantly the *cis*-fused bicyclic system (equation 28).[15] The stereoselectivity of this [3 + 2] annulation is further shown in the formation of a single stereoisomer (**36**) from the reaction of carvone (**37**) with (**29**) (equation 29).[15] The vinylsilane moiety incorporated in these cyclic products can serve as the basis for a variety of useful transformations. Regiospecific electrophilic substitution reactions of vinylsilanes are well documented. For example, TMS-cyclopentene (**32**) can be readily converted to the diacetyl derivative (**38**) in high yield under mild conditions (equation 30).[15]

This $TiCl_4$-promoted allene cycloaddition has also been extended to the synthesis of five-membered ring heterocycles.[16] In this case, increasing the steric shielding about the silicon atom seems to improve the cyclization process by suppressing the unproductive desilylative alkylation. For example, 1,3-dimethyl(*t*-butyldimethylsilyl)allene (**39**) reacts smoothly with cyclohexanecarbaldehyde to give in high yield the dihydrofuran predominantly as one stereoisomer (equation 31). Similar reaction with an *N*-acyliminium ion precursor (**40**) produces the pyrrolizidine system as a mixture of bicyclic isomers (equation 32).[16]

(Allenyl)Fp complexes have also been used successfully in cycloaddition reactions. Thus (η^1-allenyl)Fp cycloadds to tropyliumiron tricarbonyl (**10**) to give the hydroazulene complex (**41**) (equation 33).[7] However, reaction of the same allenyl organometallic species with cyclohexenone generates only the four-membered ring cycloadduct (**42**) (equation 34).[6] In the latter case it is likely that the (η^1-alle-



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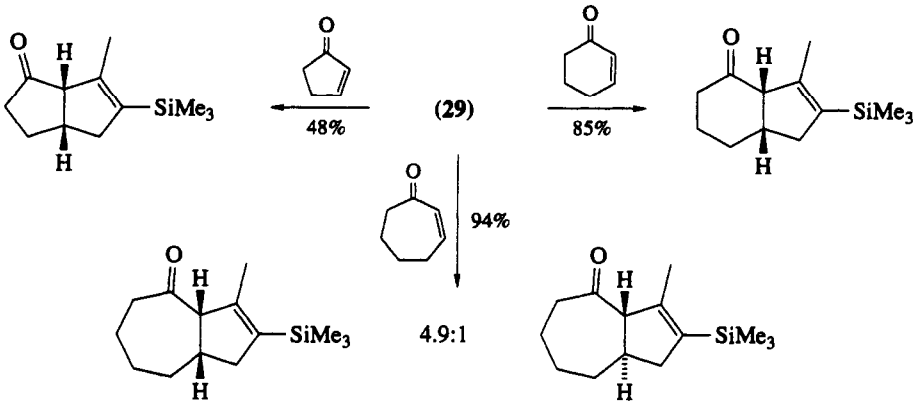

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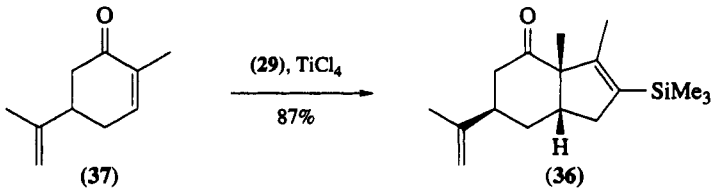

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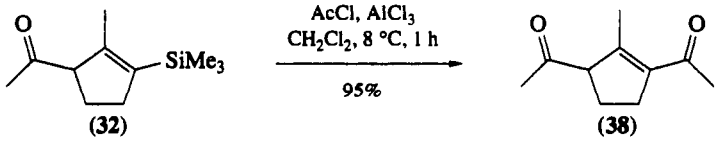
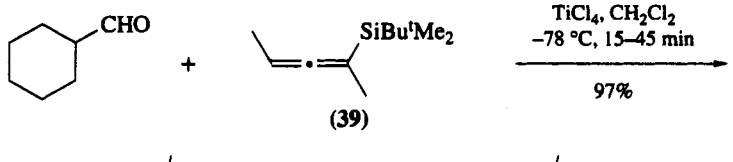
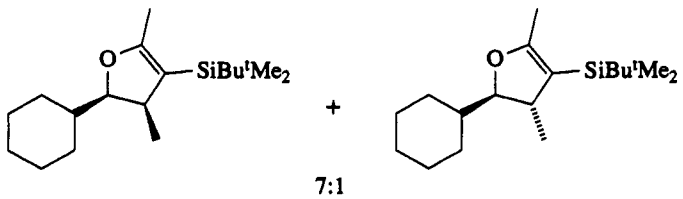


(30)

nyl)Fp complex is initially isomerized by traces of acid to (η^1-1-propynyl)Fp, which is then responsible for the observed product.





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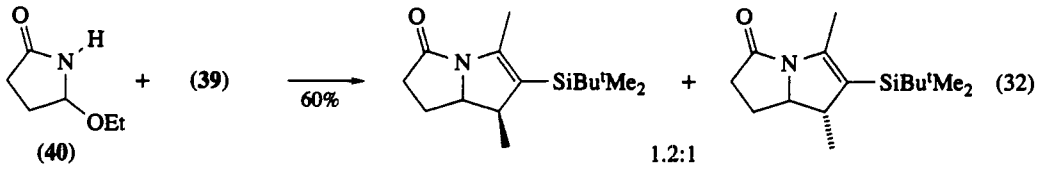
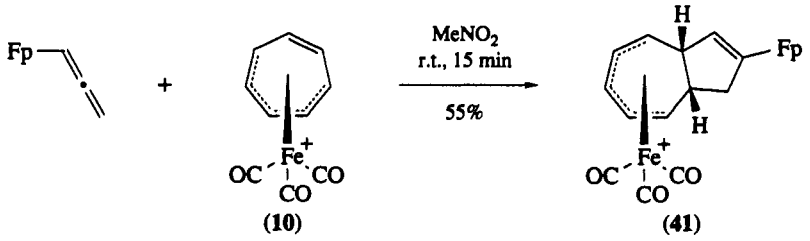
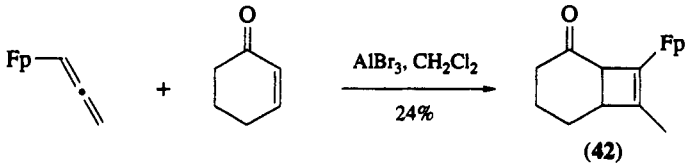
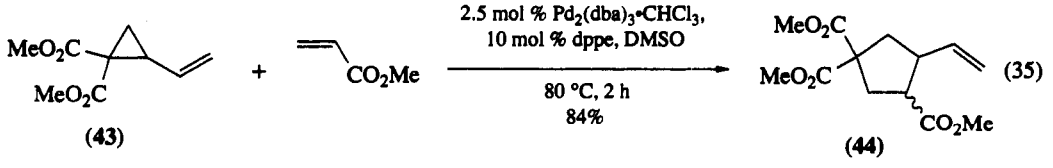


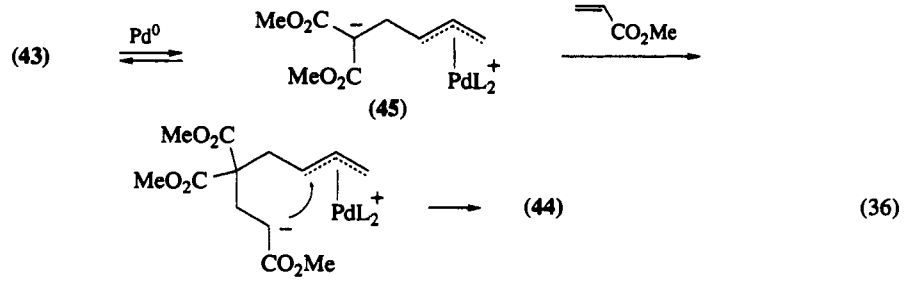


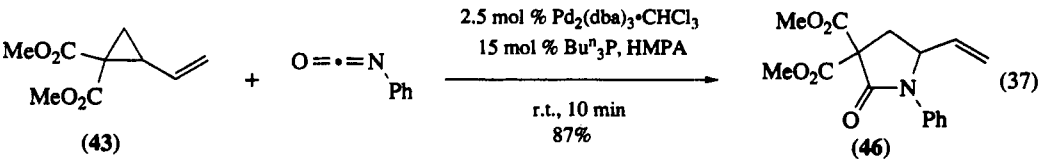


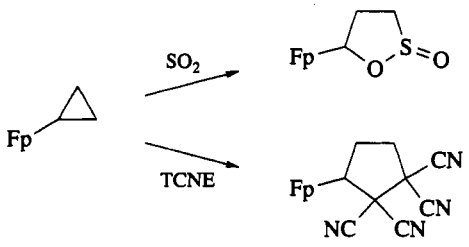
3.2.3.4 Cyclopropyl Precursors

While simple unactivated cyclopropanes have yet to be used for [3 + 2] cycloaddition, Tsuji and coworkers have developed a palladium-catalyzed cycloaddition reaction using electron-deficient vinylcyclopropanes.[18,19] Thus, vinylcyclopropane (**43**) undergoes smooth cyclization with methyl acrylate in the presence of a palladium catalyst to give vinylcyclopentane (**44**) as a mixture of diasteroisomers (equation 35).[18] The cycloaddition probably proceeds through the zwitterionic (π-allyl)palladium intermediate (**45**) and its stepwise reaction with the acrylate (equation 36). Enones such as cyclopentenone and methyl vinyl ketone will also react. Reaction of the same vinylcyclopropane with phenyl isocyanate produces vinyllactam (**46**) (equation 37).[19] Some cycloaddition reactions with (cyclopropyl)Fp complexes have also been reported. However, the substrates are limited to SO_2 and TCNE and the yields have not been disclosed (equation 38).[20]





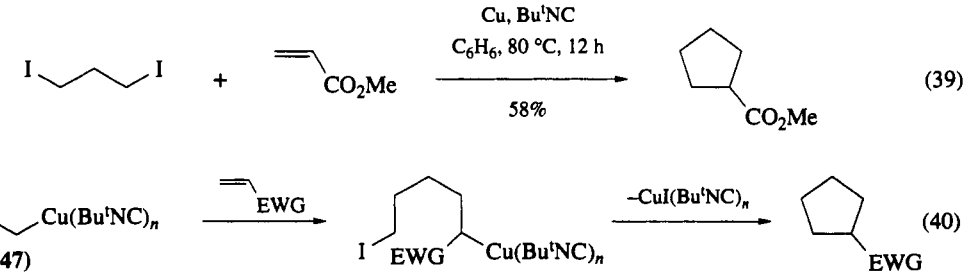




(38)

3.2.3.5 Other Precursors

The isolation of cyclopentanecarboxylates from 1,3-diiodopropane and an acrylate in the presence of metallic copper and an alkyl isonitrile has been reported by Saegusa and coworkers (equation 39).[21,22] The reaction is proposed to involve formation of a transient 3-iodopropylcopper–isonitrile complex (**47**) from the diiodopropane, which then adds to the unsaturated ester in a Michael fashion (equation 40). The nonconcertedness of this reaction results in stereoselective cycloaddition. For example, both diethyl maleate and fumarate produce the same cyclopentane adduct in identical yields (equation 41). The generality of this cycloaddition has not been explored.



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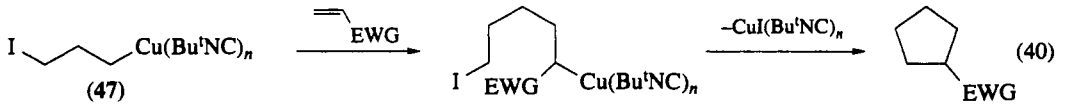

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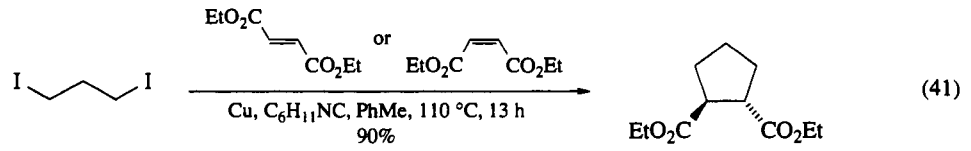
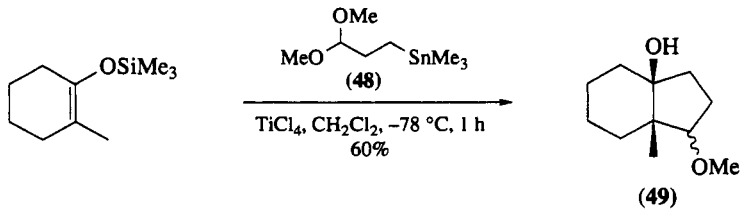


(41)

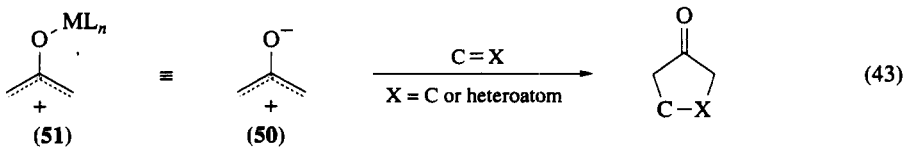
Another $TiCl_4$-mediated electrophilic annulation using acetal stannane (**48**) has also been developed recently.[23] As an example, the silyl enol ether of 2-methylcyclohexanone has been shown to form the *cis*-fused bicyclic alcohol (**49**) in reasonable yield with this tin reagent (equation 42).[24]



(42)

3.2.4 THE 2-OXYALLYL SYNTHONS

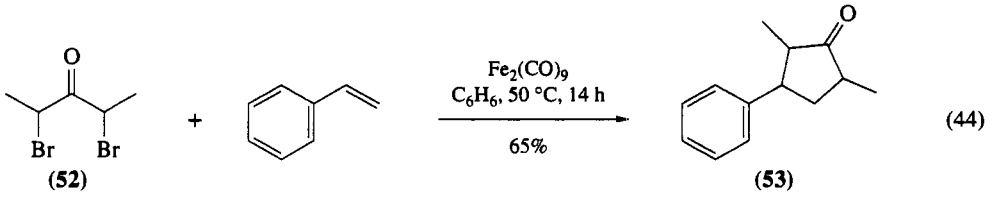
2-Oxyallyl (**50**) is a useful C_3 synthon in [3 + 2] cycloadditions because it generates a five-membered ring containing a carbonyl moiety (equation 43).[24] Although oxyallyl zwitterions can be generated from the ring-opening reaction of cyclopropanones, they have only limited synthetic utility. A transition metal-stabilized system (**51**), which can be generated *in situ* from readily accessible organic precursors, provides an alternative approach. An electrophilic version of the 2-oxyallyl synthon derived from a α,α′-dibromo ketone–diiron nonacarbonyl system has been developed by Noyori and coworkers.[25–33]



(43)

3.2.4.1 Cyclopentanone and Cyclopentenone Syntheses

Reaction of styrene with the commercially available 2,4-dibromopentan-3-one (**52**) in the presence of a stoichiometric amount of $Fe_2(CO)_9$ gives a 65% yield of cyclopentanone (**53**) as a mixture of two diastereoisomers (equation 44).[25] The cycloadduct is formed in a stepwise fashion *via* electrophilic attack of the incipient (oxyallyl)Fe^{II} complex (**54**) on the alkene to form the zwitterionic species (**55**). Ring closure of this intermediate affords the cyclopentanone product (equation 45).[26] In light of this mechanism, it is not surprising that the reaction is highly chemoselective, *i.e.* only electron-rich alkenes will participate in the cycloaddition. One is also limited to alkyl-substituted oxyallyl systems since both α,α′-dibromo- and α,α,α′,α′-tetrabromo-acetone fail to yield any cycloadduct. $Fe_2(CO)_9$ is the most efficient reagent, although $Fe(CO)_5$ can also be used. The dibromo ketones are either commercially available or easily prepared by simple procedures.[30]



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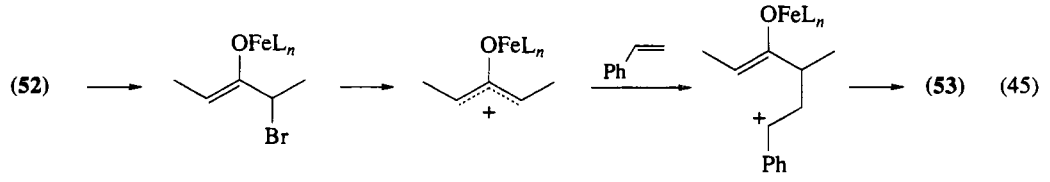
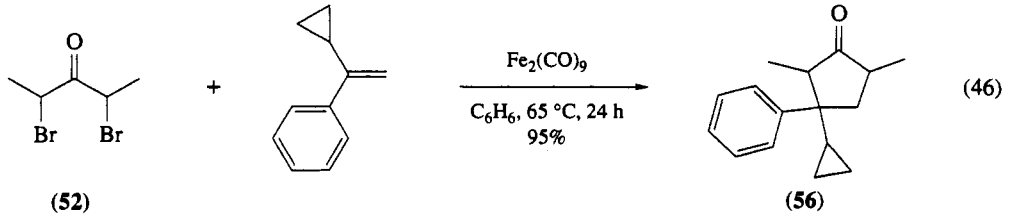


(45)

The yield of this cycloaddition depends primarily on the stability of the intermediary carbocation, such as (**55**).[27] Thus α-cyclopropylstyrene reacts smoothly with (**52**) under similar conditions to produce unrearranged cyclopentanone (**56**) in high yield (equation 46).[25] The facility of this reaction is due to the cation-stabilizing property of the phenyl and cyclopropyl groups. In addition to the electronic effect, the steric environment of the alkenic partner is also important. These two controlling factors can at times counteract each other. In the iron carbonyl-activated cycloaddition involving (**52**), the more electron-rich α-methylstyrene reacts five times faster than styrene, while styrene cycloadds very much faster than *trans*-β-methylstyrene. In the latter case the rate deceleration is presumably due to the sizeable steric hindrance to electrophilic attack in the transition state.[27] Cycloaddition with more sterically hindered oxyallyl systems also gives lower yields and other side products. The iron carbonyl-mediated reaction of tetramethyldibromo ketone (**57**) and α-methylstyrene gives only a poor yield of the expected cyclopentanone (**58**) together with a mixture of other 1:1 adducts (equation 47).[25] The alkylidenetetrahydrofuran (**59**) is formed from the ring closure at the oxygen site of intermediate (**60**), promoted by steric crowding of the carbon terminus. The acyclic products are formed from proton migration within the same intermediate.



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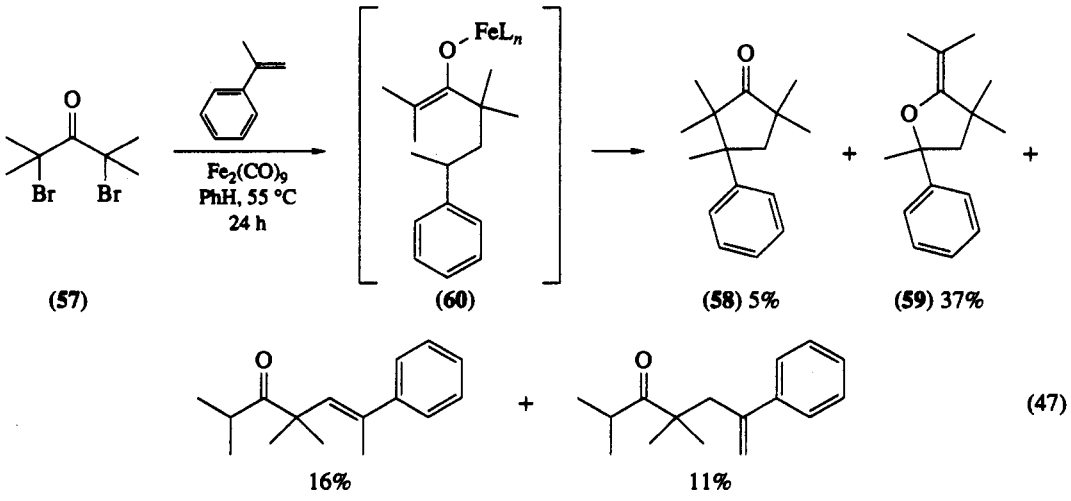
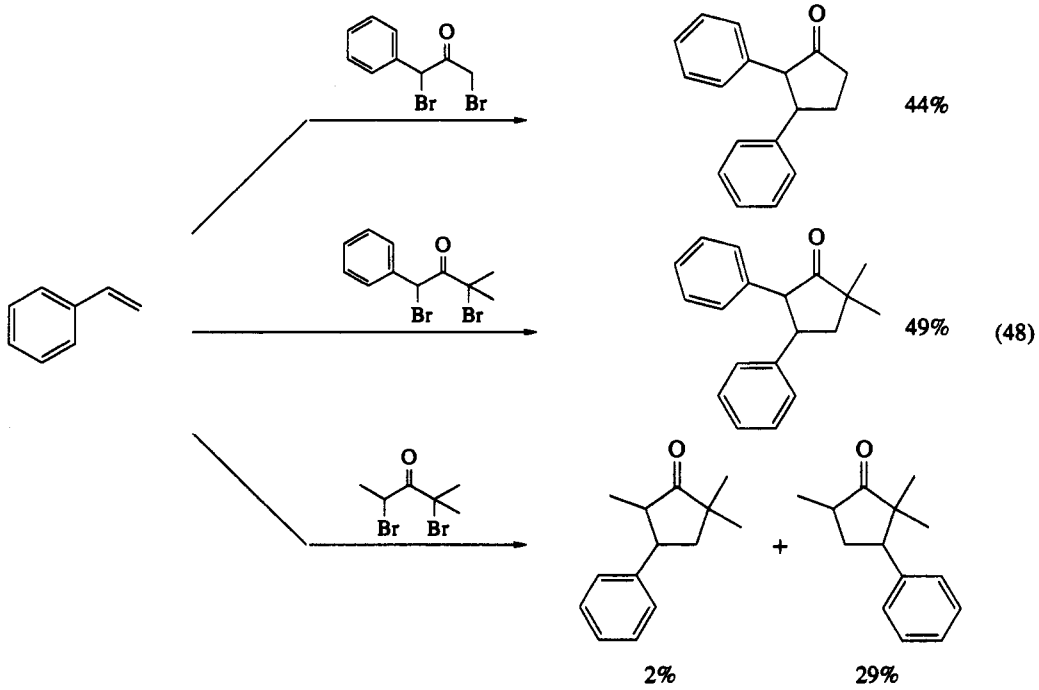


(47)

The high regioselectivity of this [3 + 2] cycloaddition is illustrated in equation (48).[28] The prime controlling factor is the relative stability of the zwitterionic intermediates, which in this case is determined by the number and the type of substituents on the iron enolate moiety. In this case it appears that a phenyl group on the dibromo ketone precursor exerts greater regiocontrol than the combination of two alkyl groups. This regioselective cycloaddition of an unsymmetrically substituted 2-oxyallyl has been utilized in a one-step synthesis of (±)-α-cuparenone (**61**) from dibromo ketone (**62**) and styrene (**63**) (equation 49).[29,30]



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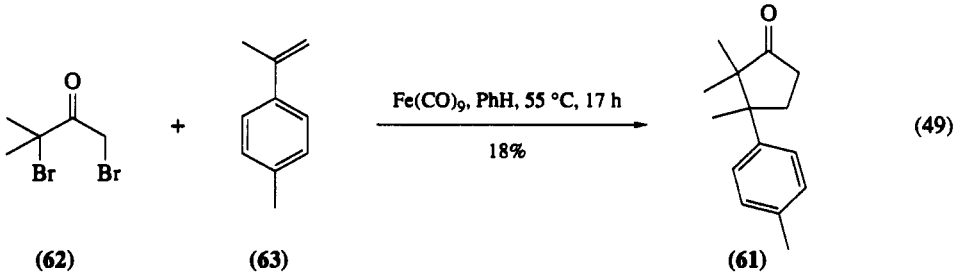
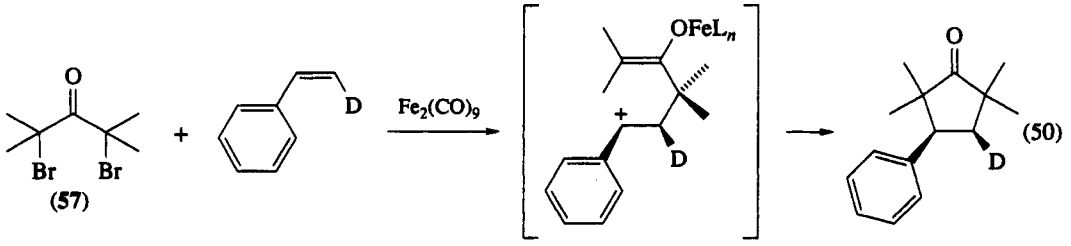
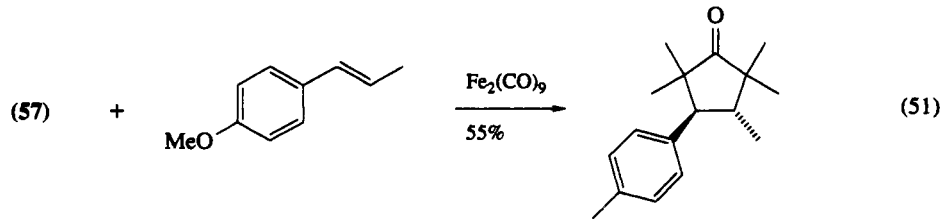


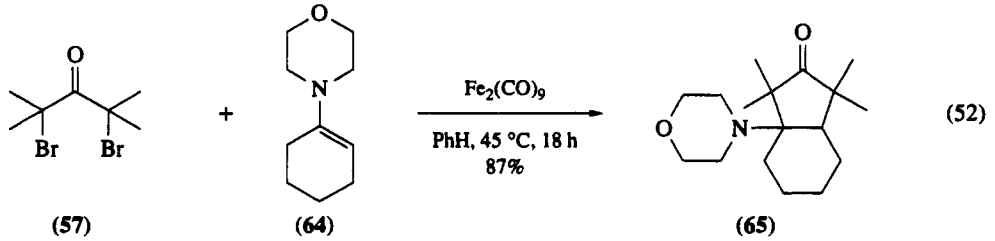
(49)

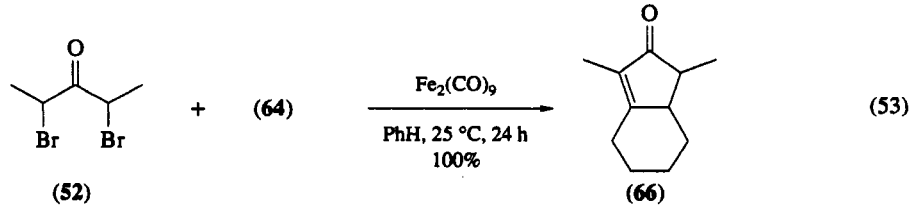
The iron carbonyl-mediated cycloaddition is also highly stereospecific despite a nonconcerted mechanism. In the reaction of dibromo ketone (**57**) with *cis*-β-deuteriostyrene, only the *cis* stereoisomer of the adduct is detected at low conversion (equation 50).[27,31] This stereospecificity is attributed to the formation of a U-shaped intermediate, in which the bonds are fixed rigidly by charge-transfer or coulombic attraction between the iron enolate and the cationic center. The result can also be explained by rapid bond formation between the two termini before bond rotation can occur. *Trans*-anethole also couples stereospecifically with (**57**) (equation 51).[25]

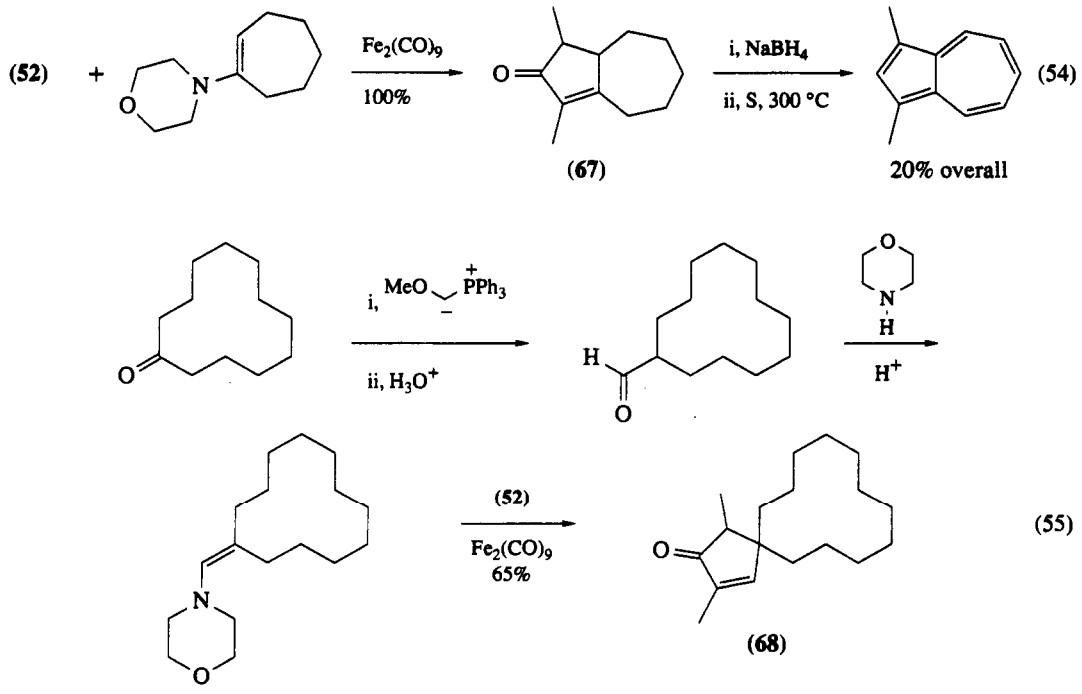




Enamines are excellent substrates for the cycloaddition. The $Fe_2(CO)_9$-activated dibromo ketone (**57**) reacts with the morpholinoenamine of cylcohexanone (**64**) to afford a good yield of bicyclic adduct (**65**) (equation 52).[32] A facile synthesis of cyclopentenones can be achieved using secondary dibromo ketones. For example, dibromo ketone (**52**) reacts with the same enamine (**64**) to give a quantitative yield of bicylic enone (**66**) after chromatography on silica gel (equation 53).[32] For bulky α-substitutents on the oxyallyl unit, *e.g.* an isopropyl group, the elimination of morpholine can be effected by treatment of the initial adduct with NaOH in ethanol. The [5,7] bicyclic enones resulting from [3 + 2] cycloaddition of cycloheptanone enamines are useful intermediates in the synthesis of azulenes, *e.g.* adduct (**67**) can be easily converted to 1,3-dimethylazulene in reasonable yield (equation 54).[32] Another application of this enamine cycloaddition is the construction of spiro[*n*.4]alkenones. A synthesis of spiro[4.11]hexadecenone (**68**) from cyclododecanone is presented in equation (55).[32] The iron carbonyl-promoted cyclocoupling between secondary dibromo ketones and enamines provides a general route to α,α′-dialkyl cyclopentenones. Some attractive features are the availability of the starting materials, high yields, simple procedures, and ease in which α-substituents are incorporated. However, one limitation of this methodology is its inability to produce cyclopentenones without α-alkyl groups.





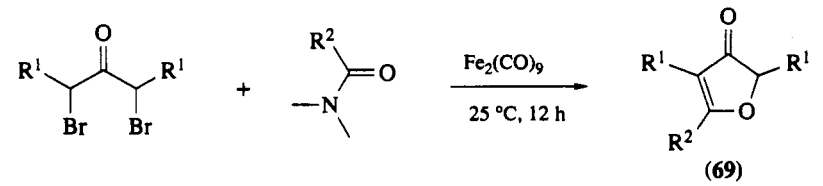


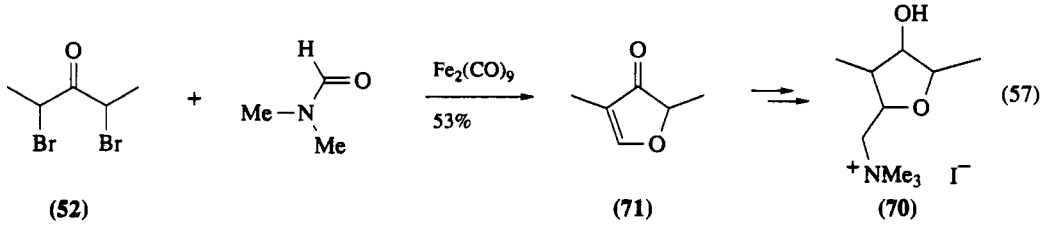
3.2.4.2 Furanone Synthesis

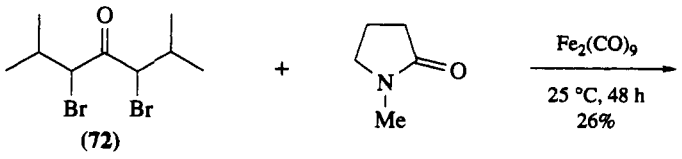
The iron carbonyl-promoted reaction of secondary dibromo ketones and an amide produces 3(2*H*)-furanone derivatives (**69**) (equation 56).[33] This cyclocoupling reaction has some useful applications, such as the synthesis of a muscarine analog (**70**) from furanone (**71**) (equation 57). Reaction of the dibromo ketone (**72**) with *N*-methylpyrrolidinone results in formation of the aminofuranone (**73**) *via* an intramolecular deamination (equation 58).

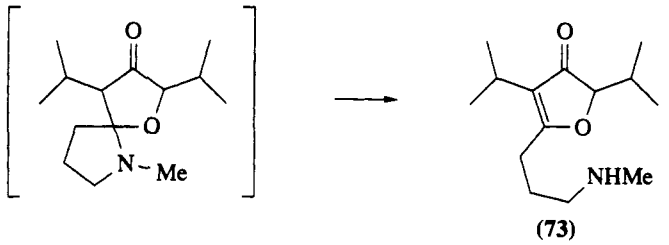
3.2.4.3 Intramolecular Reactions

The intramolecular version of this [3 + 2] process provides an entry into terpenes with a bicyclo[2.2.1]heptane skeleton.[30] Treatment of the C_{10} dibromo ketone (**74**) with $Fe_2(CO)_9$ produces (±)-camphor in reasonable yield (equation 59). The corresponding C_{15} analog (**75**) yields a 2:1 mixture of (±)-campherenone (**76**) and (±)-epicampherenone (**77**) (equation 60). The product ratio is reversed if the (*Z*)-isomer of the dibromo ketone precursor is used.

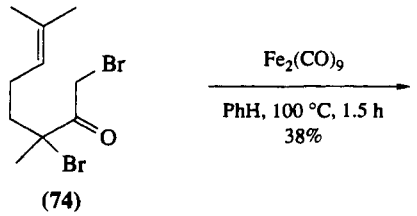




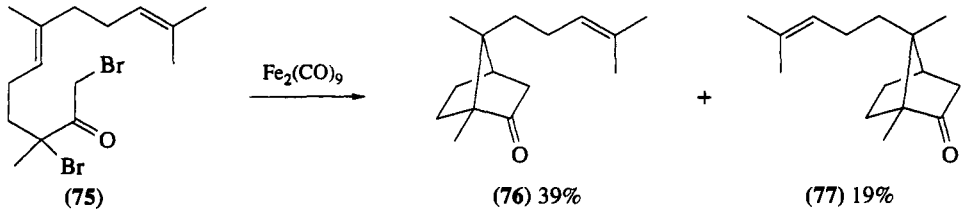




(58)



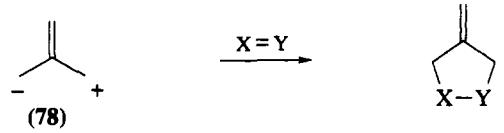
(59)



(60)

3.2.5 THE TRIMETHYLENEMETHANE SYNTHONS

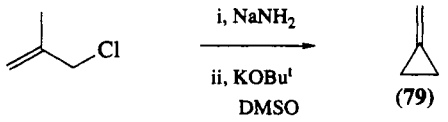
Trimethylenemethane (TMM; **78**) represents a very useful synthon in the [3 + 2] cycloaddition approach to cyclopentanoids. In addition to contributing the three-carbon unit necessary for ring formation, it also generates a methylene moiety useful for further synthetic elaboration (equation 61). For example, the exocyclic alkene can be cleaved to generate a ketone carbonyl, or it can be transformed into a methyl group or a *gem*-dimethyl unit. The effectiveness of this [3 + 2] approach for the construction of methylenecyclopentanes depends critically on finding efficient systems for generating the TMM synthon. As presented in the previous section, the synthetic utility of substituted 2-methylene-1,3-propanediyls from the thermal decomposition of azo precursors has its limitations. A transition metal mediated system can be a practical alternative if suitable reagents can be identified. Stable TMM–metal complexes, although known for a long time, are generally too unreactive to be of any synthetic value. The combination of a stable and readily available organic precursor and a transition metal catalyst is an ideal solution. In recent years, tremendous progress has been made in a number of laboratories in the development of such systems and their chemistry. The two major types of precursors that have been identified are methylenecyclopropanes[34] and bifunctional conjunctive reagents (BCRs).[35] With these new methodologies, a TMM [3 + 2] cycloaddition strategy has become a very powerful tool in the synthesis of cyclopentanoids.



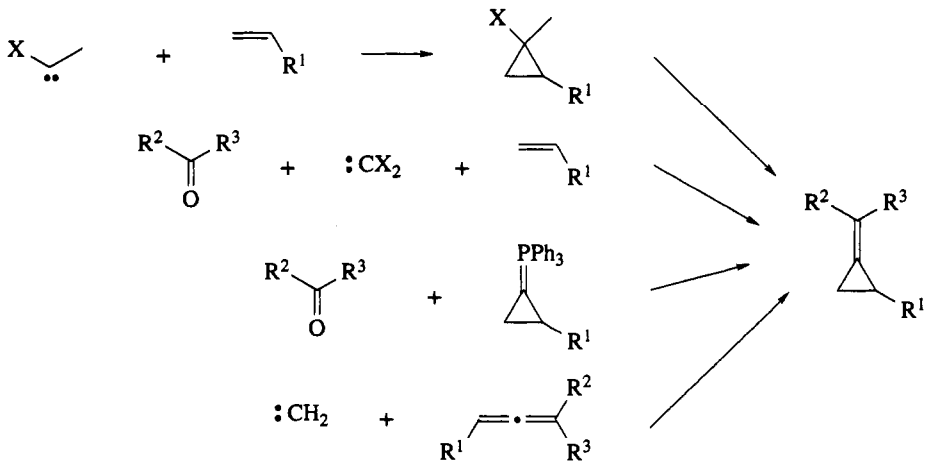
(61)

3.2.5.1 TMM from Methylenecyclopropanes

Methylenecyclopropane (**79**), and its substituted derivatives, have been shown to function as TMM equivalents in the presence of a transition metal catalyst. These cyclic materials are useful synthetic reagents because they are quite stable at ambient temperature and are also readily available. For example, parent compound (**79**) can be prepared from methallyl chloride on a kilogram scale with high yield (equation 62).[36] Other efficient syntheses of various substituted derivative systems are outlined in Scheme 2.[34]

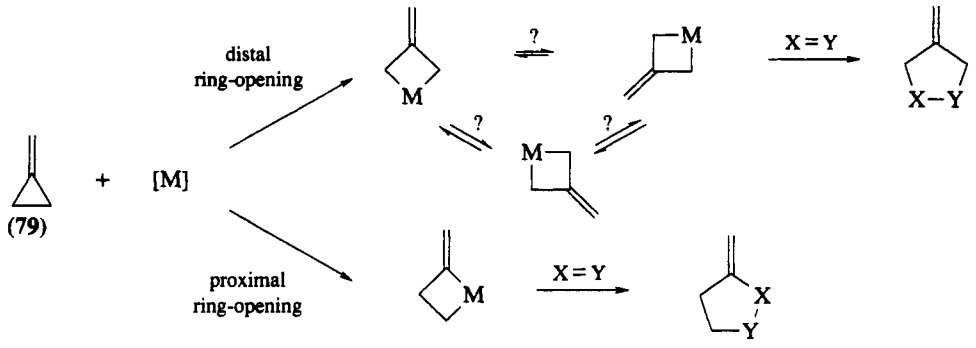


(62)



Scheme 2

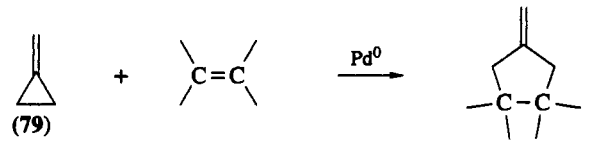
There are two possible modes of methylenecyclopropane cycloaddition: the distal ring-opening and the proximal ring-opening (Scheme 3). The former generates a functional equivalent of a TMM. However, interconversion between isomeric structures may lead to scrambling of the three methylene termini of the synthon. This can present a problem in controlling the regioselectivity of substituted systems since nonsymmetrical TMM synthons are involved. While the proximal ring-opening mode does not formally constitute a TMM cycloaddition, it does however generate a methylenecyclopentane. Zerovalent nickel and palladium species are the two types of catalyst most effective for methylenecyclopropane activation. The choice of the catalyst system can have a profound effect in determining the reaction pathway, *e.g.* distal *vs.* proximal ring-opening, as well as the regioselectivity of substituted systems. The ensuing discussion of [3 + 2] reactions involving methylenecyclopropanes is divided into these two catalyst systems.



Scheme 3

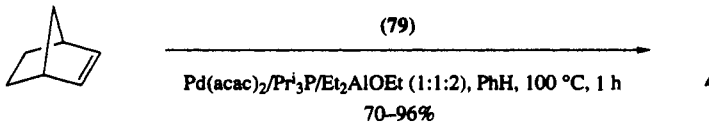
3.2.5.1.1 Cycloaddition with a palladium catalyst: parent system

Palladium(0) catalysts promote exclusive distal ring-opening cycloaddition of (**79**) with alkenes (equation 63). The reaction is normally performed in an autoclave at elevated temperature in benzene or THF. The most effective catalyst system is a 1:1 mixture of a palladium(0) species and a hindered trialkylphosphine ligand, *e.g.* Pr^i_3P.[34] Thermally stable complexes, such as bis(dibenzylideneacetone)palladium, can be employed as a source of Pd^0. The catalyst can also be generated by the *in situ* reduction of Pd^{II} salts, *e.g.* $Pd(acac)_2 + Et_2AlOEt$, although (η^3-allyl)CpPd functions as a catalyst without any external reducing agent. The efficiency of the cycloaddition is sometimes improved by pumping a mixture of the reactants into a preheated catalyst solution.[34]

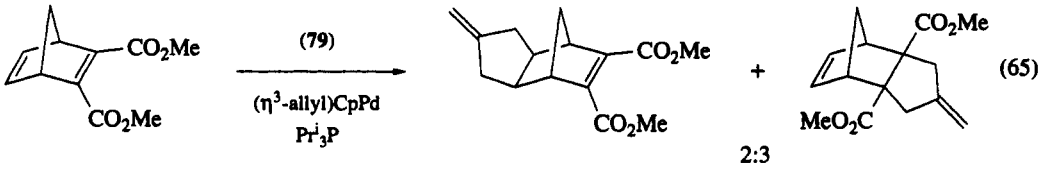


(63)

A variety of alkenes can participate in the cycloaddition. Simple alkenes such as ethylene and allene will react to form methylenecyclopentane adducts. Facile cycloadditions with strained alkenes are also observed.[37,38] For example, norbornene reacts smoothly with (**79**) to give only the *exo* adduct (**80**) in good yield (equation 64).[37] Electron-deficient alkenes, having an ester, ketone or sulfone activating group, are also substrates. However, the methylenecyclopropane cycloaddition does not appear to be very chemoselective. This is demonstrated by the Pd-catalyzed reaction of (**79**) with 2,3-dimethoxycarbonylnorbornadiene, where both double bonds of the norbornadiene react to an almost equal extent (equation 65).[34]

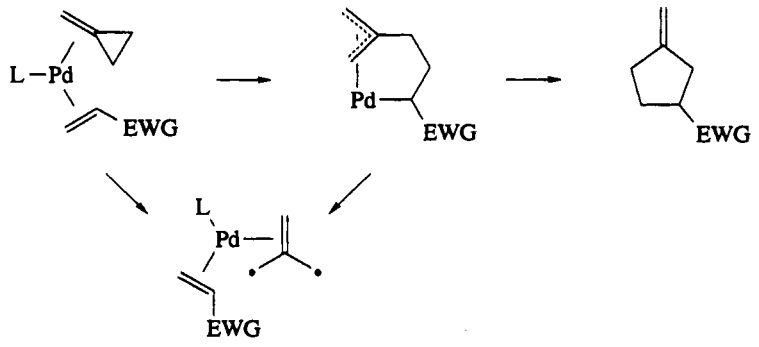


(64)



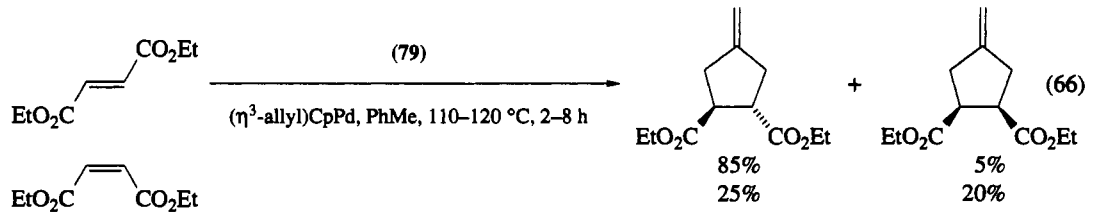
(65)

The mechanism for methylenecyclopentane formation is believed to involve prior coordination of both (**79**) and the reacting alkene to the metal. Subsequent coupling of these two units generates the cycloadduct (Scheme 4). The success of the reaction thus depends critically on the extent of interaction of the alkenic substrate with the palladium center. Weak alkene coordination will not produce efficient cycloaddition. On the other hand, too strong a binding can prevent methylenecyclopropane activation. This may account for the failure to prepare cycloadducts of highly electron-deficient alkenes, such as maleic anhydride, acrolein and acrylonitrile, which are all excellent ligands. While cyclopentenone gives a satisfactory yield (78%) of the adduct, larger-ring analogs such as 2-cyclohexenone give mainly simple alkylation products.[34,40]



Scheme 4

The stereospecificity of this codimerization is only moderate. While diethyl fumarate gives essentially only the *trans* adduct, the alkene geometry is not preserved in the maleate system (equation 66).[39] In the latter case the concomitant isomerization of the starting material may contribute to the loss of alkene geometry. The slow introduction of reactants by the pumping technique can significantly enhance the stereospecificity of the cycloaddition. Dimethyl maleate has been shown to yield up to 90% of the *cis* adduct under these conditions. The diastereoselectivity of the methylenecyclopropane reaction has not been fully explored. In the few cases where a nonsymmetrical alkene such as the norbornene in equation (64) has been used, the exclusive formation of a single product suggests that the cycloaddition of (**79**) is sensitive to steric effects.



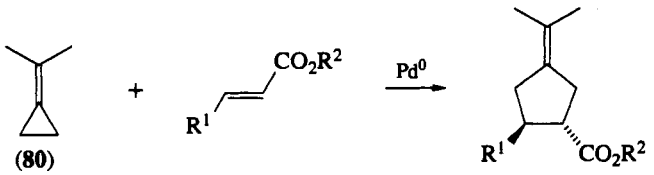
(66)

3.2.5.1.2 *Cycloaddition with a palladium catalyst: substituted systems*

The palladium-catalyzed cycloaddition of substituted methylenecyclopropanes also proceeds *via* distal ring-opening. There is also a propensity to form alkylidenecyclopentane adducts, regardless of the substituent location. This preference is most prominent with precursors having two alkyl or aryl groups on the exocyclic methylene.[34] For example, dimethylidenecyclopropane (**80**) gives exclusively dimethylidenecyclopentanes with a number of alkenes, which include fumarate and norbornene (equations 67, 68). With diethyl maleate, partial loss of alkene stereochemistry is also observed (1:2 *cis/trans* mixture). The diphenyl derivative (**81**) also shows excellent regioselectivity and yields (equations 69, 70).[41] These two cyclopropanes also codimerize smoothly with cyclic alkenones, even with the sluggish 2-cycloheptenone (equation 71). With these enones the enhanced activity of the dialkylidene derivatives is a considerable improvement over that of the parent compound (**79**).[40] An intramolecular [3 + 2] version of the diphenyl system has been utilized in the construction of bicyclo[3.3.0]octanes (equations 72, 73).[42]

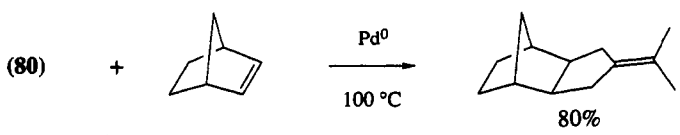
Monosubstituted alkylidenecyclopropanes show lower regioselectivity. While *n*-hexylidenecyclopropane (**82**) and the corresponding phenyl analog (**83**) cycloadd to cyclopentenone, acrylate or crotonate to produce mostly alkylidenecyclopentanes, a mixture of adducts is observed with diethyl fumarate (equations 74–77).[34] Nonetheless, compared to the parent compound (**79**), these mono- and di-substituted alkylidenecyclopropanes often give better cycloaddition reactions with a wider range of alkenes, and are also less susceptible to self-oligomerization.

The regioselectivity associated with ring-substituted methylenecyclopropanes is not as distinct. The 2-methyl derivative (**84**) shows only a small preference for ethylidenecyclopentane formation with diethyl

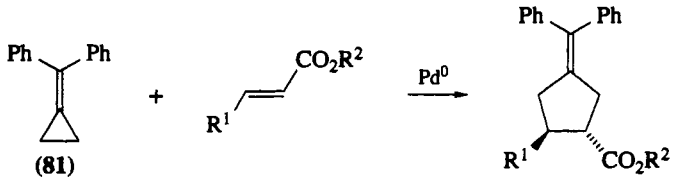


(67)

R^1	R^2	
H	Me	48%
Me	Me	71%
C_5H_{11}	Me	61%
CO_2Et	Et	83%

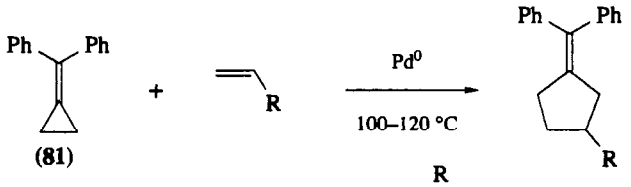


(68)



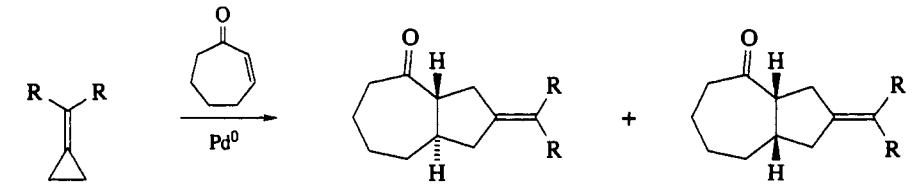
(69)

R^1	R^2	
H	Me	86%
Me	Me	94%
C_6H_{13}	Me	98%
CO_2Et	Et	100%



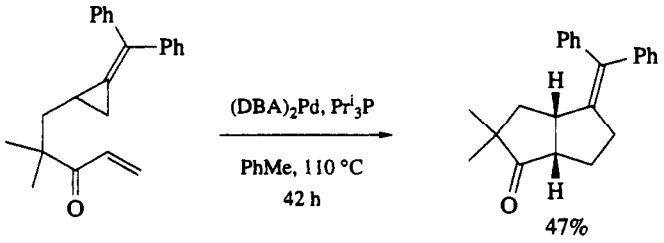
(70)

R	
H	83%
Me	83%
Ph	88%
$(CH_2)_8CO_2Me$	50%
$CH{=}CH_2$	48%

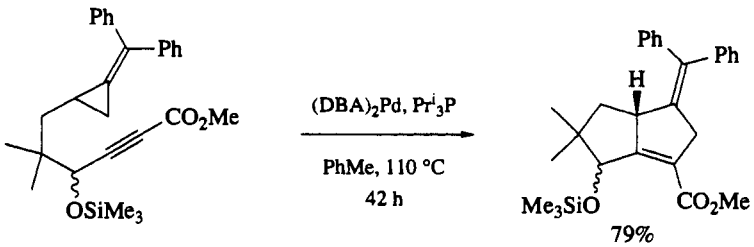


(71)

R = Me (**80**)	45%	5%
R = Ph (**81**)	67%	13%

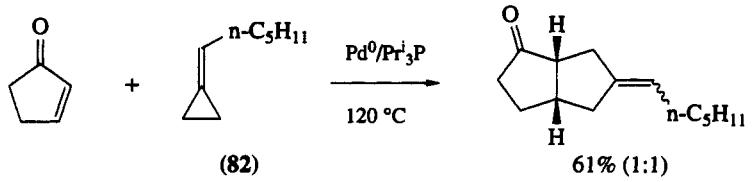


(72)

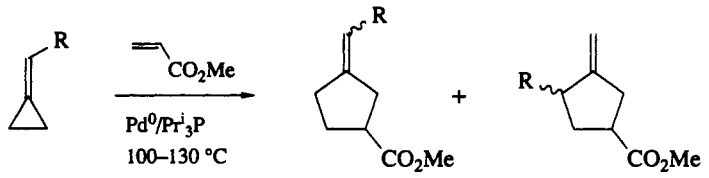


(73)

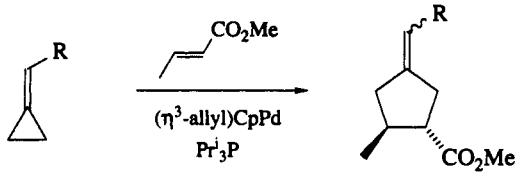
fumarate. The phenyl system (**85**) has a high regioselectivity, but its preference for alkylidenecyclopentane formation is greatly suppressed by increasing the amount of phosphine ligand (equation 78).[34] The alkylidene cycloadduct is also highly favored in the 2-trimethylsilyl system (**86**) (equations 79, 80).[43]



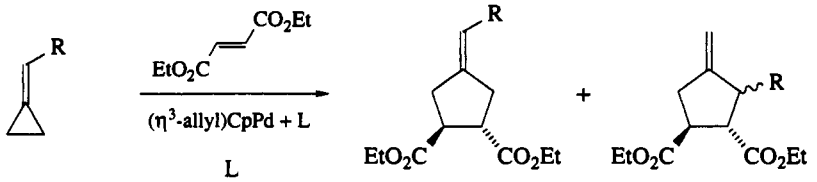
(82) 61% (1:1) (74)



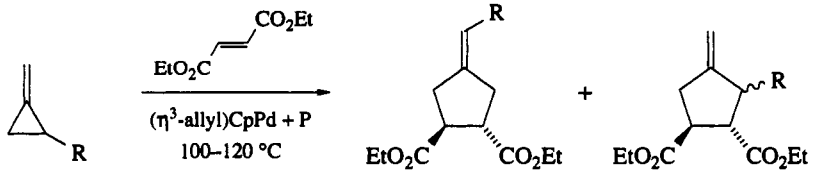
			(75)
R = n-C_5H_{11} (82)	49%	4%	
R = Ph (83)	81%	7%	



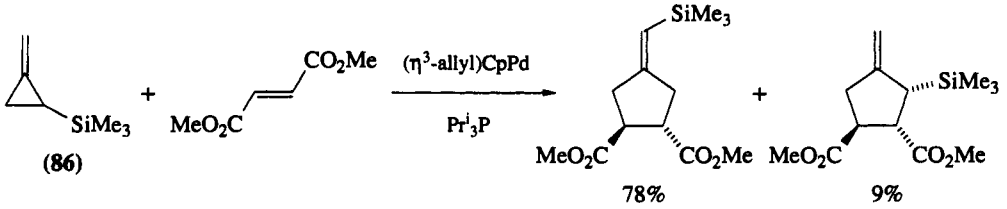
		(76)
R = n-C_5H_{11} (82)	51%	
R = Ph (83)	52%	



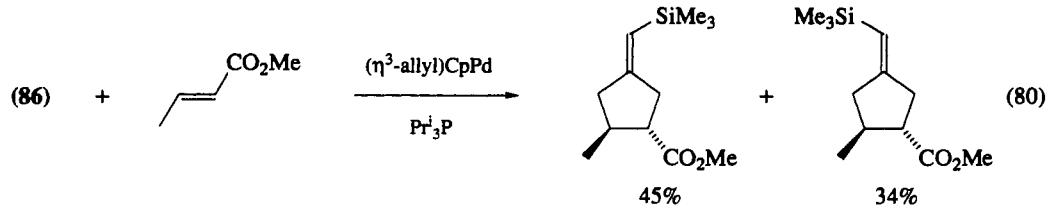
	L			(77)
R = n-C_5H_{11} (82)	Pr^i_3P	31%	27%	
R = Ph (83)	4 Pr^i_3P	37%	30%	



R	P			(78)
Me (84)	Pr_3P	40%	27%	
Ph (85)	Pr_3P	60%	25%	
Ph (85)	4 Pr_3P	10%	76%	



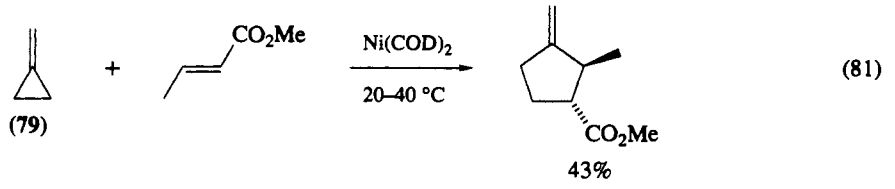
(86) 78% 9% (79)

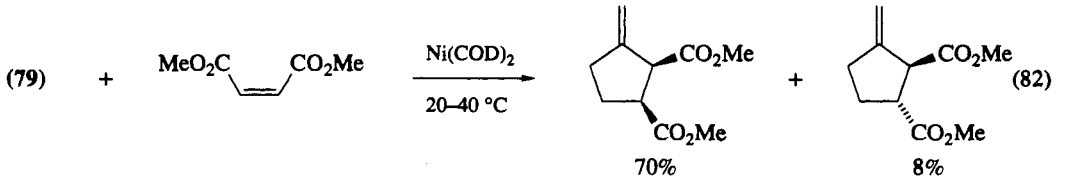


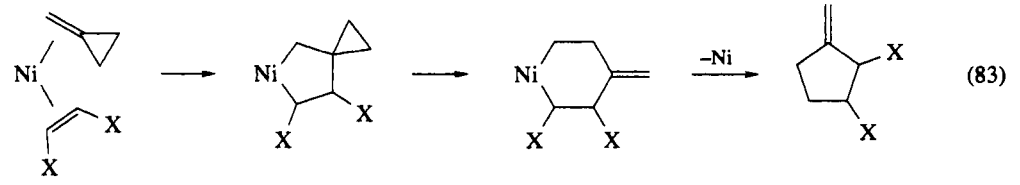
3.2.5.1.3 Cycloaddition with a nickel catalyst: parent system

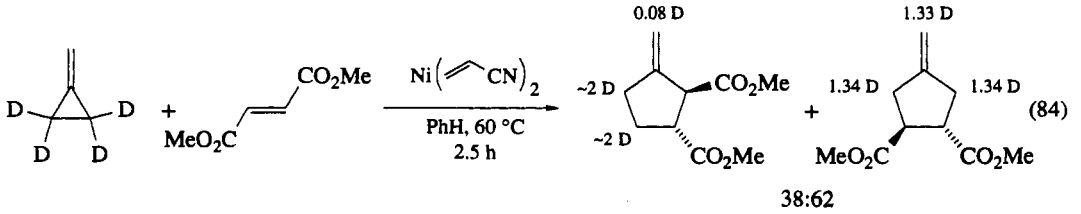
The reactions of (**79**) with a Ni^0 catalyst are very sensitive to the nature of the ancillary ligands and that of the reacting alkene. A 'naked' nickel catalyst, such as $Ni(COD)_2$, produces proximal ring-opening adducts with high stereospecificity (equations 81, 82).[44–46] The proposed mechanism involves nickel-promoted reductive coupling of the methylenecyclopropane and the alkene, which is then followed by a cyclopropylmethyl–3-butenyl rearrangement (equation 83).[46] Dialkyl fumarates and maleic anhydride do not participate in the cycloaddition, but simply function as control ligands to increase dimer formation of (**79**).[47] With bis(acrylonitrile)nickel as the catalyst, both types of ring-opening adducts can be observed with dimethyl fumarate as the alkenic receptor (equation 84). In this case, a deuterium-labelling study at low product conversion suggests that a TMM–Ni intermediate (**87**), or a related rapidly equilibrating σ-complex (**88**), is responsible for the complete scrambling of the label in the distal ring-opening cycloadduct. On the other hand, the proximal ring-opening mode appears to involve a non-equilibrating 2-methylenemetallocyclobutane (**89**), since very little scrambling of the deuterium label is detected.[48]

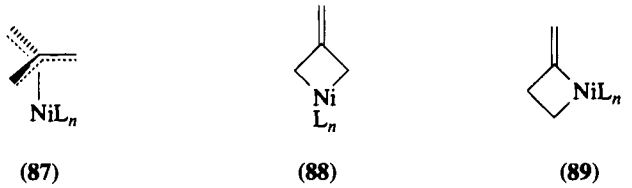
Reactions with phosphine- or phosphite-modified catalysts, *e.g.* $Ni(COD)_2 + PPh_3$, show lower stereospecificity and require higher reaction temperature. In the case of fumarate and maleate this catalyst system promotes only distal ring-opening cycloaddition (equation 85).[49]



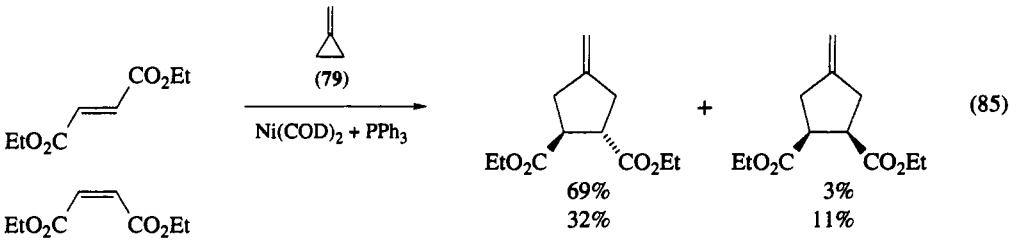








(87) (88) (89)

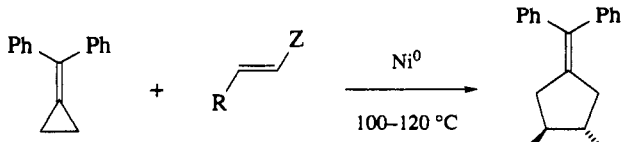


(85)

3.2.5.1.4 *Cycloaddition with a nickel catalyst: substituted system*

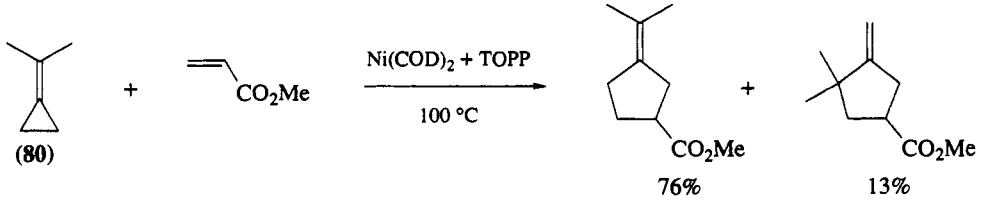
The regiochemistry of Ni^0-catalyzed cyloadditions of substituted methylenecyclopropanes is influenced by many factors. Only diphenylidenecyclopropane (**81**) maintains the strong preference and high yields for alkylidenecyclopentane formation (equation 86).[50] This diphenyl derivative is one of the few TMM precursors that shows this exclusive regioselectivity regardless of reaction conditions. The regiochemistry of dimethyl analog (**80**) is determined by the nature of the ligand as well as that of the reacting alkene (equations 87, 88).[50] The phosphine- and phosphite-modified Ni^0 catalysts also produce a methylenecyclopentane adduct (**90**) with a regiochemistry complementary to that of the corresponding adduct obtained from the Pd^0-catalyzed reactions (see equation 75). This regioisomer has the activating group of the alkene immediately adjacent to the substituents of the methylenecyclopropane precursor. With monoalkylidenecyclopropanes and a nickel phosphite catalyst, this regioisomer can be the only product. Such is the case in the formation of (**91**) from (**82**) and methyl crotonate (equation 89). However, most other reactions generate isomeric mixtures (equations 90, 91).[34]

The highly regioselective Ni^0-catalyzed codimerization of 2,2-dimethylmethylenecyclopropane (**92**) and acrylates is presumed to occur *via* proximal ring-opening of the cyclic precursor.[34,51] In addition, excellent asymmetric induction in the synthesis of a dimethyl(methylene)cyclopentane adduct is achieved using an acrylamide with a chiral auxiliary (equation 92).[52] This strategy to make chiral methylenecyclopentanes also works well with the parent system (**79**). Monoalkyl methylenecyclopropanes, such as (**84**), yield only proximal ring-opening cycloadducts with a Ni^0/PPh_3 catalyst, whereas the corresponding phenyl system (**85**) undergoes both types of ring-opening reactions (equations 93, 94).[34]

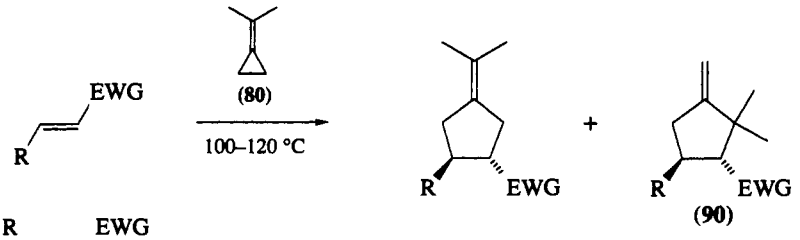


(86)

R	Z	
H	Bu	80%
H	CN	82%
Me	CO_2Me	75%
CO_2Et	CO_2Et	98%

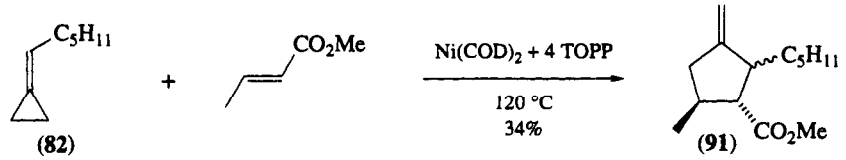


(87)



(88)

R	EWG			
Me	CO_2Me	$Ni(COD)_2 + PPh_3$	31%	17%
Me	CO_2Me	$Ni(COD)_2$ + TOPP	8%	36%
CO_2Et	CO_2Et	$Ni(COD)_2$ + TOPP	31%	52%



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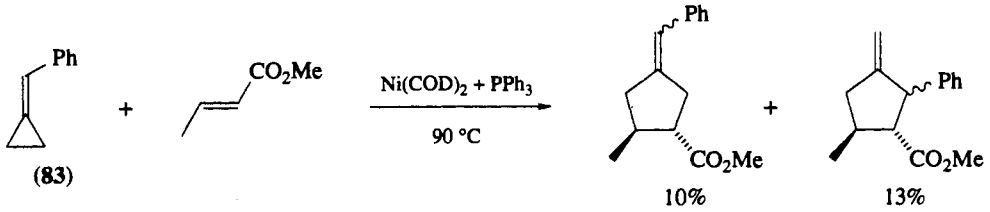

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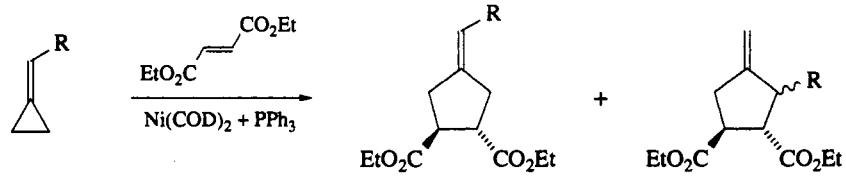
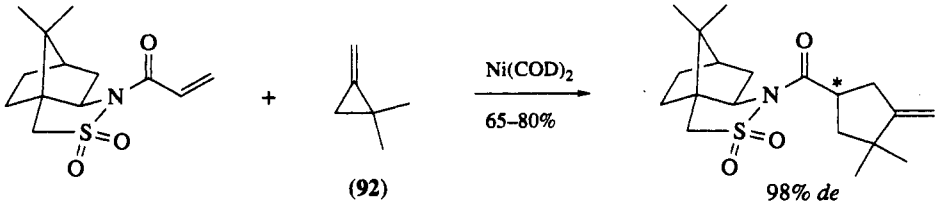
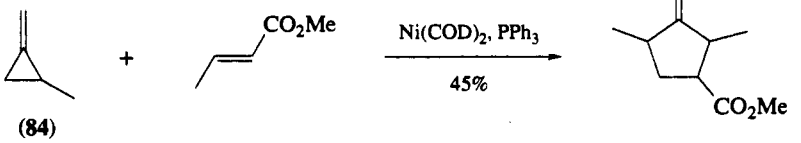


(91)

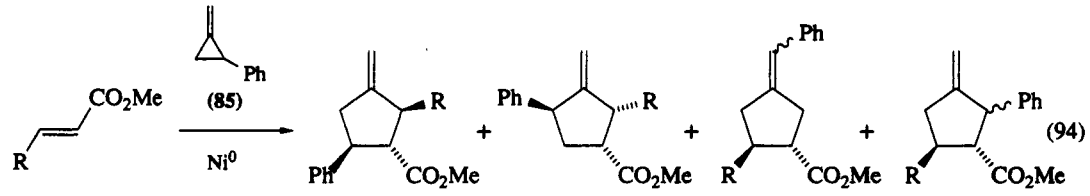
R = n-C_5H_{11} (82)	50%	37%
R = Ph (83)	75%	7%



(92)

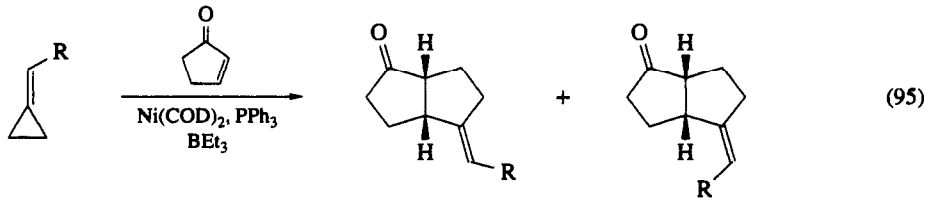


(93)

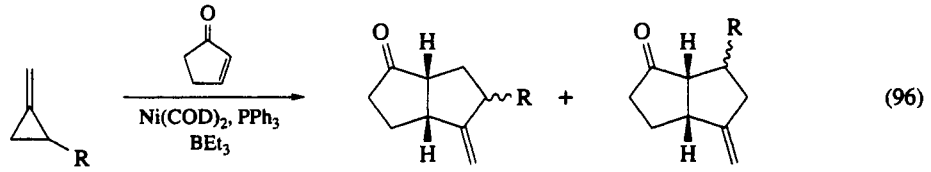


R = H	33%	–	30%	20%
R = Me	26%	8%	5%	5%

The yields and regioselectivity of the reactions of substituted methylenecyclopropanes with 2-cyclopentenone are improved with the use of triethylborane as a Lewis acid co-catalyst (equations 95, 96).[53] No reaction with cyclopentenone is observed in the case of (**82**) without this co-catalyst.[34]

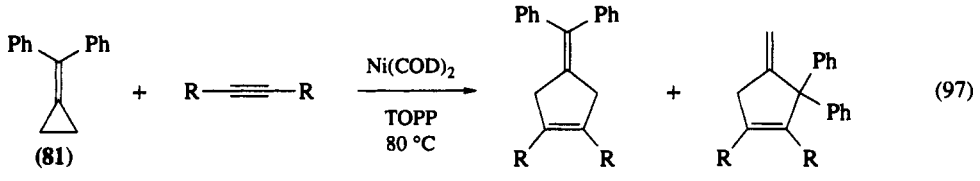


R = n-C_5H_{11} (**82**)	58%	10%
R = Ph (**83**)	72%	–

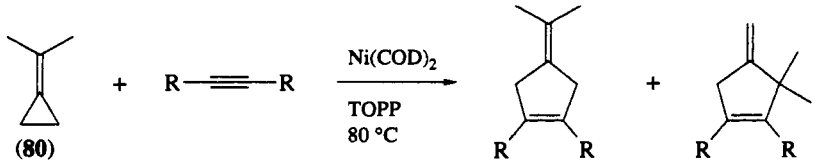


R = Me (**84**)	73%	–
R = Ph (**85**)	–	75%
R = $SiMe_3$ (**86**)	50%	–

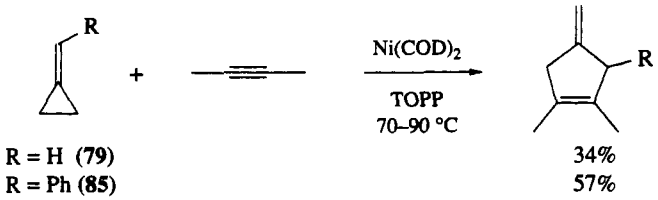
The use of alkynes in transition metal catalyzed reactions is often complicated by their tendency to undergo cyclo-trimerization and -tetramerization. Thus, it is useful to note that a phosphite-modified catalyst, Ni(COD)$_2$/tris(*o*-phenylphenyl) phosphite (TOPP), promotes codimerization of alkynes with methylenecyclopropane and its alkylidene analogs.[34,54] Both electron-rich and electron-poor alkynes participate in cycloaddition with moderate regioselectivity. Opposite regiochemistry is sometimes observed with disubstituted alkylidene systems (equations 97–99).



R = Me	6%	89%	
R = CH_2OSiMe_3	49%	37%	
R = Me_3Si	34%	37%	
R = Me_3Si, CO_2Me	63%	–	



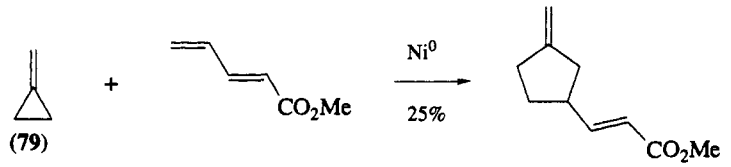
(98)



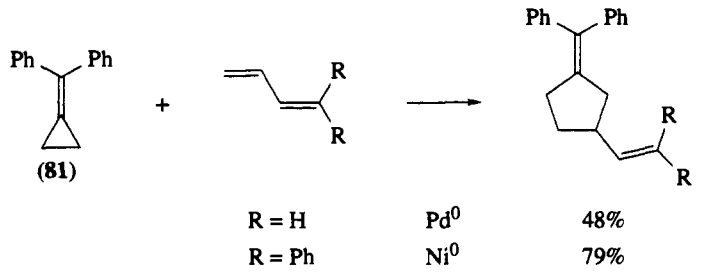
(99)

3.2.5.1.5 Diene, C=O and C=N cycloadditions

Conjugated dienes are a special substrate for the TMM synthon because they can potentially undergo [3 + 2] as well as [4 + 3] cycloaddition. While dimethyl (*E,E*)-muconate gives only seven-membered ring [4 + 3] adducts, methyl 2,4-pentadienoate reacts exclusively at the terminal double bond with (**79**) to give a vinylmethylenecyclopropane (equation 100).[55] The diphenyl system (**81**) also reacts with simple 1,3-dienes to produce only diphenylidenecyclopentanes in the presence of Ni^0 or Pd^0 catalysts (equation 101).[34]

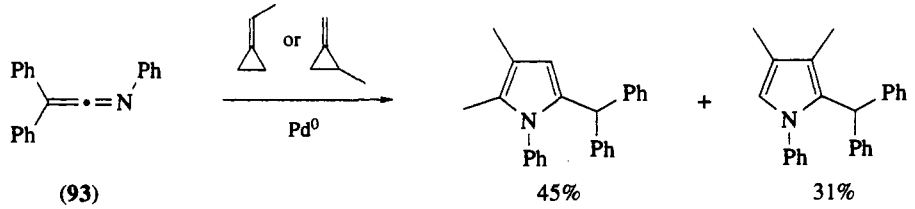


(100)

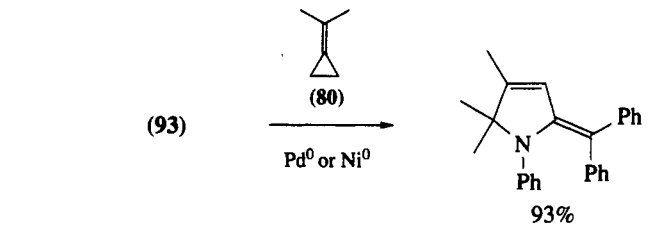


(101)

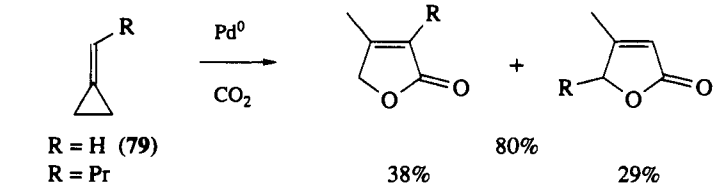
The ketenimine (**93**) reacts only at the C=N bond to give pyrroles and pyrrolines with methylene migration (equations 102, 103).[34,56] Carbon dioxide codimerizes smoothly with methylenecyclopropanes to yield lactones with alkene isomerization (equations 104, 105).[57,58] The Pd^0-catalyzed rearrangement of γ-butyrolactone (**94**) to butenolide (**95**) indicates that this CO_2 insertion reaction is reversible. This is further supported by the observation that lactone (**94**) can serve as a TMM precursor in the codimerization with aldehydes and electron-deficient alkenes (equations 106, 107).[59] No cycloaddition to ketenes or simple ketone carbonyls has ever been reported.



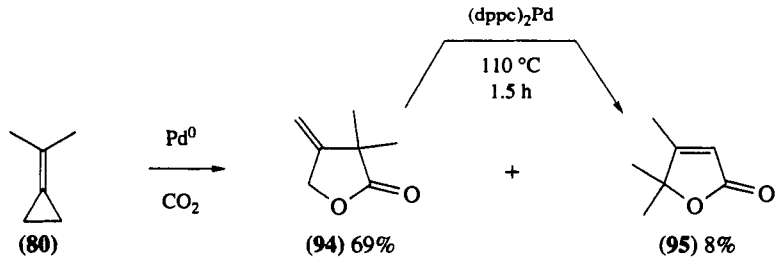
(102)



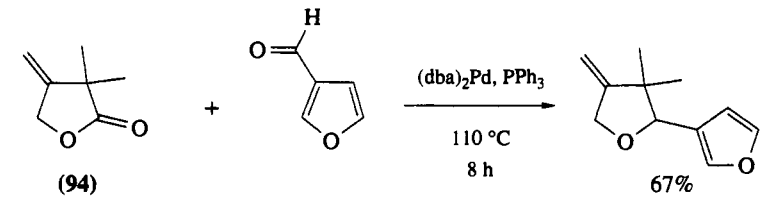
(103)



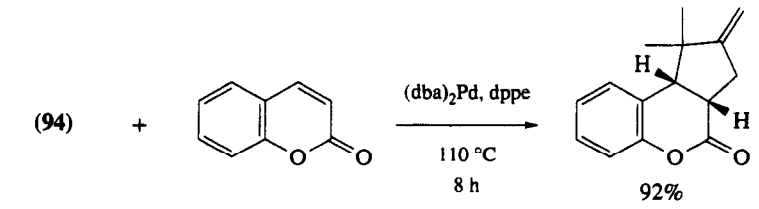
(104)



(105)



(106)



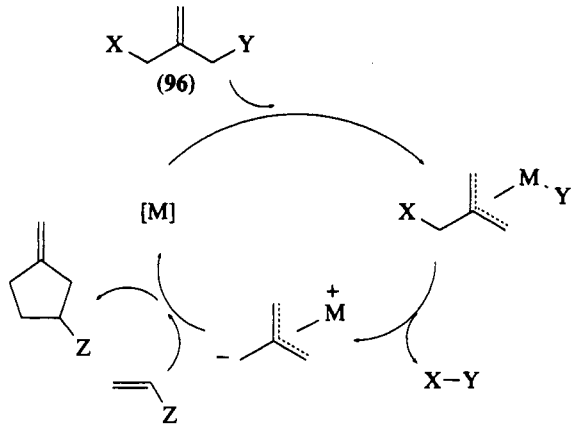
(107)

3.2.5.2 TMM from Bifunctional Conjunctive Reagents

Bifunctional conjunctive reagents (BCRs), such as a 1,3-substituted 2-methylenepropane (**96**), can serve as effective TMM synthons *via* transition metal catalysis. In this case, the transition metal complex can promote the elimination of the elements X—Y from (**96**) to form a coordinated TMM species. Cyclization of this intermediate with an alkene thus produces the methylenecyclopropane product and also regenerates the catalyst (Scheme 5). In the last decade a number of BCRs utilizing this concept, or some modifications thereof, has been developed for various TMM synthons.[35]

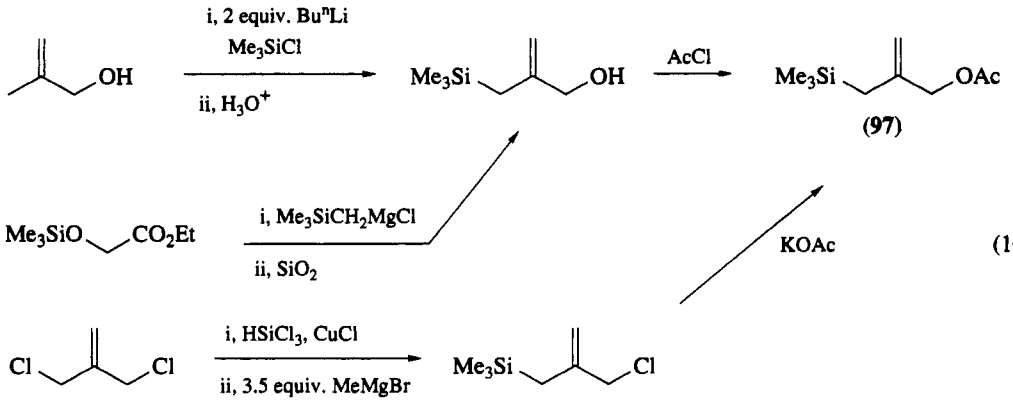
3.2.5.2.1 Cycloaddition with the parent system

The use of BCR methodology for the present TMM synthon was first demonstrated by Trost and Chan using a Pd^0 catalyst and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**97**) as the bifunctional prototype.[60–63] In this system the trimethylsilyl and the acetoxy moieties provide the carbanion and the carbocation equivalents, producing TMSOAc as the by-product. Silyl acetate (**97**) and some of its precursors,



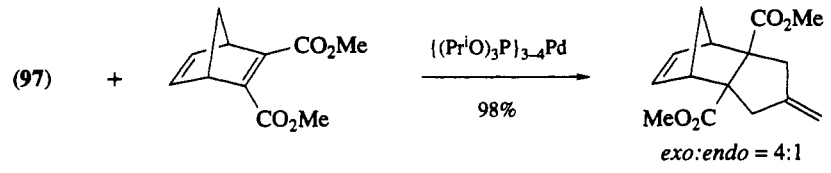
Scheme 5

2-[(trimethylsilyl)methyl]-2-propen-1-ol and 2-chloromethyl-3-trimethylsilyl-1-propene, are commercially available.[64] Alternatively, it can be readily prepared from methallyl alcohol in high yield.[65,66] Other synthetic routes to this bifunctional reagent, starting with 2-(chloromethyl)-3-chloropropene, or trimethylsilyl ethyl glycolate, have also been reported (equation 108).[67,68]



(108)

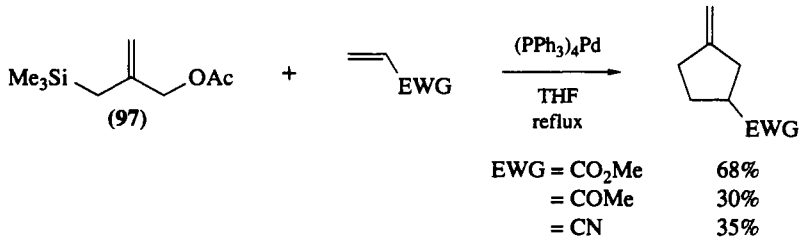
The Pd^0-catalyzed [3 + 2] cycloaddition reactions of (**97**) exhibit very different selectivities from those of the corresponding methylenecyclopropane codimerizations. One major distinction is the chemoselectivity: only electron-deficient alkenes will react to form methylenecyclopentane. The nucleophilic nature of this TMM synthon is indicated in the exclusive annulation of the electron-poor double bond of 2,3-dimethoxycarbonylnorbornadiene (equation 109).[35,62] No such differentiation of alkenes is evident in the methylenecyclopropane codimerization with the same diene (equation 65).



(109)

The cycloaddition is normally performed by heating a solution of the silyl acetate with the electron-deficient alkene in the presence of 0.1–9 mol % of a palladium catalyst in an aprotic solvent, such as THF, toluene, DME, DMF or acetonitrile.[69] The commercially available $(PPh_3)_4Pd$ is a good catalyst for this reaction. Other effective catalysts can also be generated *in situ* by the reduction of a Pd^{II} salt in the presence of at least two equivalents of a phosphorus-containing ligand. For example, a highly active catalyst is obtained by simply mixing $Pd(OAc)_2$ with 6–8 equivalents of triisopropyl phosphite.[70] In this case the phosphite ligand also serves as the reducing agent. The alkenic substrate for this BCR cycloaddition has properties parallel to that of a dienophile in Diels–Alder reactions. A wide range of alkenes possessing a ketone, ester, cyano, sulfoxide or sulfone function have been shown to react.[62] Thus, this

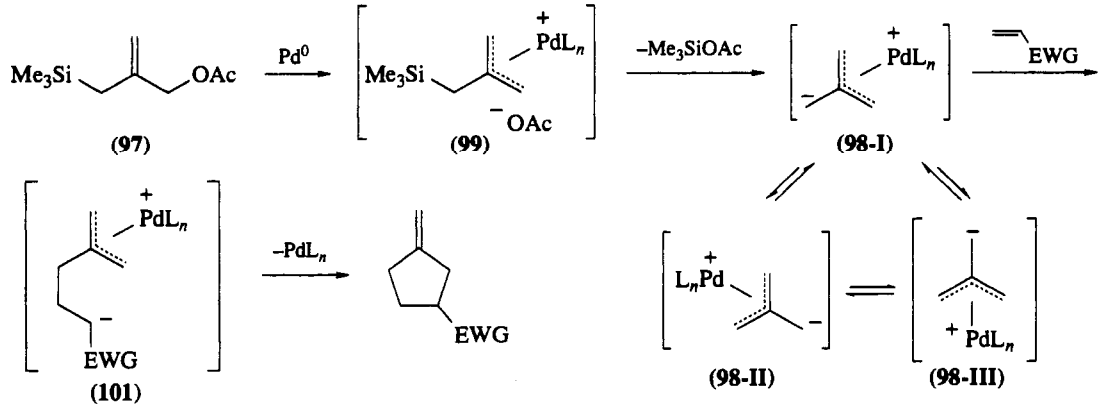
annulation procedure is compatible with many reactive functional groups, with even a broader scope of reactivity than the methylenecyclopropane codimerization. Some examples of methylenecyclopentane formation from (**97**) are depicted in equation (110).



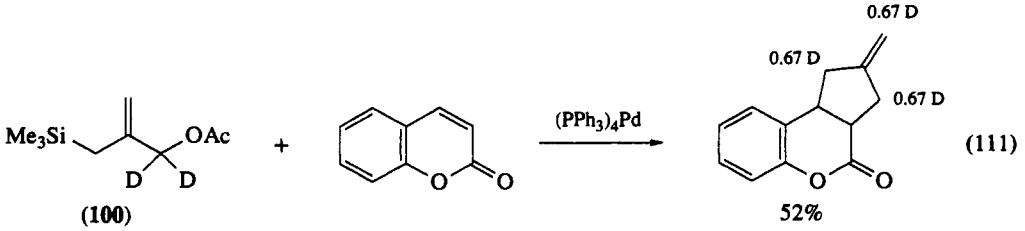
(110)

The cycloaddition of (**97**) appears to involve an (η^3-TMM)palladium intermediate (**98**), which is generated from the desilylation of the initially formed (η^3-allyl)Pd complex (**99**) (Scheme 6).[63] The nonsymmetrical nature and the nucleophilic/basic character of this TMM species are predicted by theorectical calculations,[63,71–73] and further deduced from reactions with nucleophiles containing a proton source.[63] Although the bonding nature of (**98**) implies a nonequivalence of the carbon termini on the TMM ligand, there is rapid equilibration among the three η^3 structures (**98-I, -II, -III**), which results in a functionally symmetrical synthon. This fast interconversion would account for complete scrambling of the deuterium label in the cycloaddition with the dideuterated derivative (**100**) (equation 111).[63] The isolation of stable TMM complexes of Ir, Ru, Os and Rh from analogs of (**97**) further supports the validity of this proposed mechanism.[74] The methylenecyclopentane adduct is presumed to form in a stepwise fashion *via* a Michael addition of the (TMM)Pd intermediate (**98**) to the alkene, which is then followed by ring closure of intermediate (**101**) (Scheme 6). This nonconcertedness of product formation is reflected in the moderate stereospecificity of the cycloaddition.[63,75] It is not surprising that dimethyl maleate gives a mixture of *cis* and *trans* adducts, whereas the corresponding fumarate yields virtually all *trans* material (equation 112).[62] As in the case with methylenecyclopropane codimerization, annulations with *cis* alkenic substrates are frequently complicated by their isomerization during the reaction.[69]

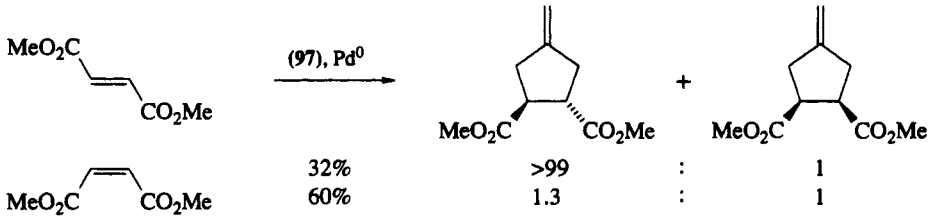
The Pd-catalyzed BCR cycloaddition is highly diastereoselective. For example, exclusive addition at the least-hindered face of the δ-oxaeneone (**102**) is observed (equation 113).[76] Similarly, the six-membered ring sulfone (**103**) also gives essentially a single adduct (**104**).[35] This compound can be readily transformed, *via* ozonolysis and sulfone elimination, to a bicyclic enone that is equivalent to a cyclopen-



Scheme 6

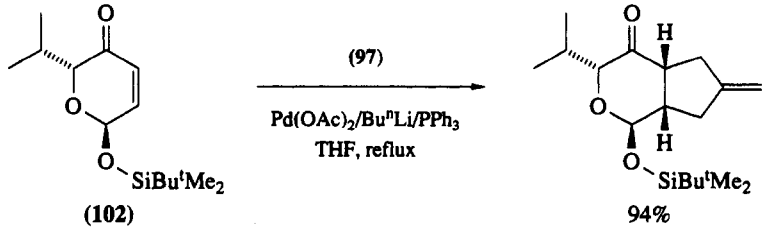


(111)

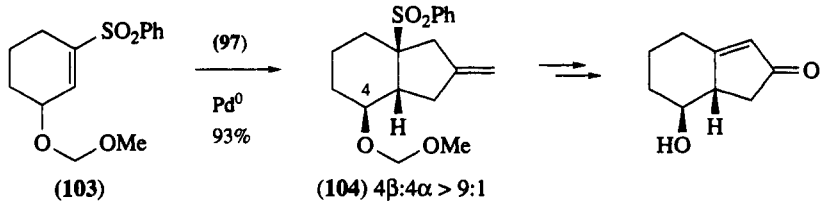


(112)

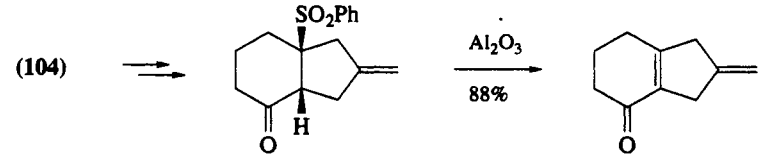
tenone annulation procedure (equation 114). Alternatively, it is easily converted into a product that would have derived from the theoretical 2-cyclohexynone (equation 115). Good asymmetric induction is noted in the cycloaddition of (**97**) with a chiral vinyl sulfoxide (equation 116).[77]



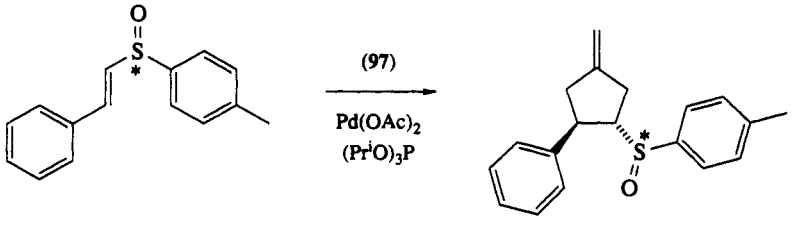
(113)



(114)



(115)



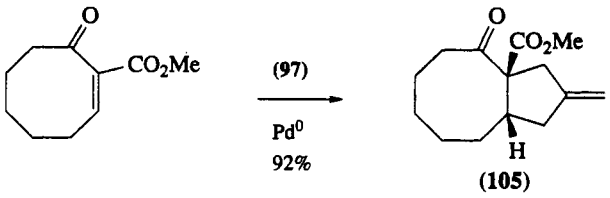
(116)

72% (+ 8% Z-isomer)
80% *de*

Although 2-cyclopentenone reacts smoothly with this BCR, cyclohexenone and 2-methylcyclohexenone produce low yields of the bicyclic adduct, and cycloheptenone does not react at all.[62,78] The introduction of an ester function at the α-position significantly improves the reactivity of these sluggish cyclic alkenones toward cycloaddition.[78] In an eight-membered ring case, the [5,8] cycloadduct (**105**) is obtained in excellent yield (equation 117). Considering the synthetic versatility of an ester function, this particular strategy to improve the reaction efficiency is very useful.

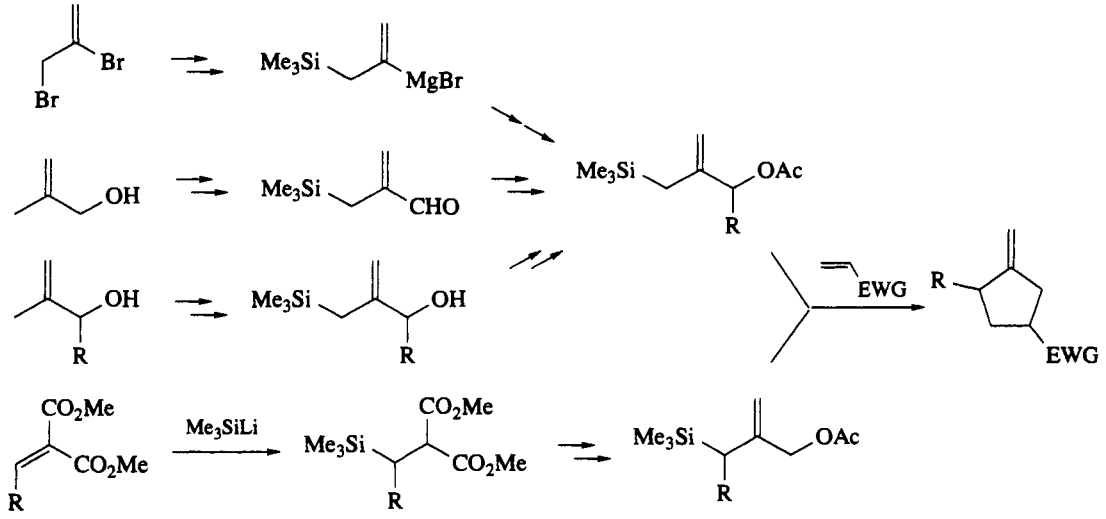
3.2.5.2.2 Cycloaddition with substituted systems

The Pd^0-catalyzed [3 + 2] reactions of substituted BCRs are highly regioselective. There is a particularly strong preference for formation of the cyclic adduct having a 1,3 relationship between the activating



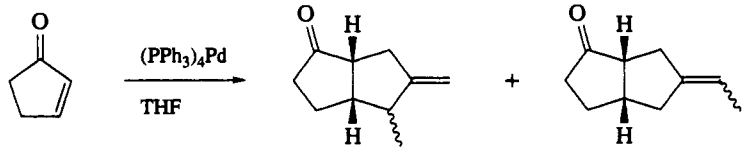
(117)

group of the alkene and the substituent of the precursor. Furthermore, this preference is independent of the substitution pattern in the precursors because of the facile equilibration of the initially formed TMM intermediate to the other isomeric forms. The substituted silyl acetate derivatives are readily prepared, as outlined in Scheme 7.[35]



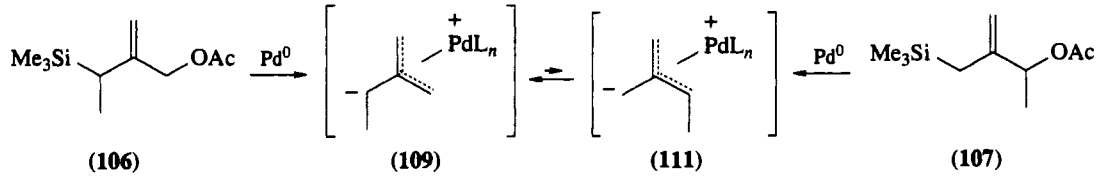
Scheme 7

Cycloaddition of either of the methyl-substituted precursors (**106**) or (**107**) to 2-cyclopentenone produces the same regioisomer (**108**) with very high selectivity (equation 118).[79] This cycloadduct apparently originates from the TMM intermediate (**109**) according to the proposed mechanism. Thus it appears that TMM intermediate (**111**), which is formed initially from the precursor (**106**), equilibrates to the more reactive isomer (**109**) faster than it undergoes cycloaddition. Theorectical calculations also suggest that (**109**) is the thermodynamically preferred isomer.[73] Regioselectivity can be influenced by the nature of the alkene receptor. For example, the reaction of (**106**) or (**107**) with dimethyl benzylidenemalonate produces more of the minor regioadduct (equation 119).

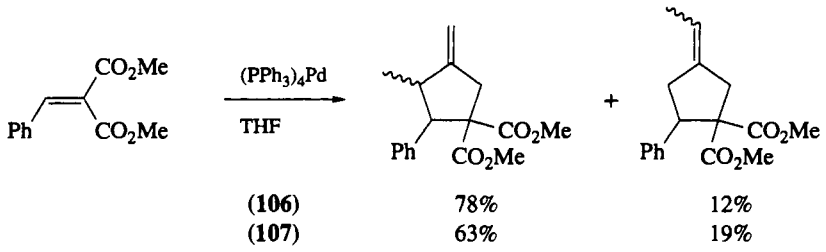


	(108)	
(106)	43%	2%
(107)	49%	3%

(118)



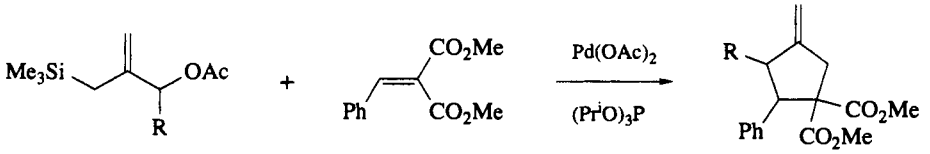
(106) (109) (111) (107)



(119)

(106)	78%	12%
(107)	63%	19%

The regioselectivity is even better with other BCR systems. Thus only one regioisomer is obtained with substituted silyl acetate (**112**) and the same benzylidenemalonate (equation 120).[80] The successful cycloaddition with these substituted bifunctional reagents indicates that this TMM synthon can again accommodate a number of reactive functional groups such as cyano, keto and alkoxycarbonyl. It is remarkable that the regioselectivity remains the same despite the tremendous electronic pertubation produced by these substituents, *i.e.* electron-withdrawing, electron-donating and π-conjugation. In addition, the mildness of the reaction conditions is responsible for product stability with respect to potential alkene isomerization (R = Ph), and possible further reaction with the catalyst (R = OAc).



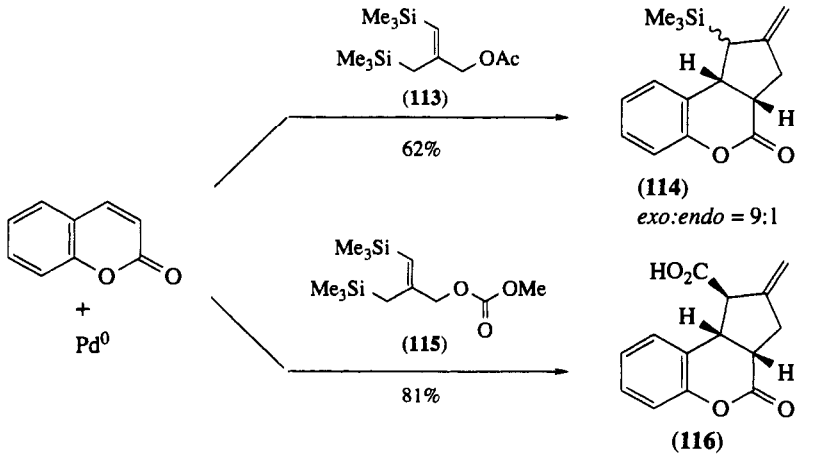
(120)

(112)

54–89%

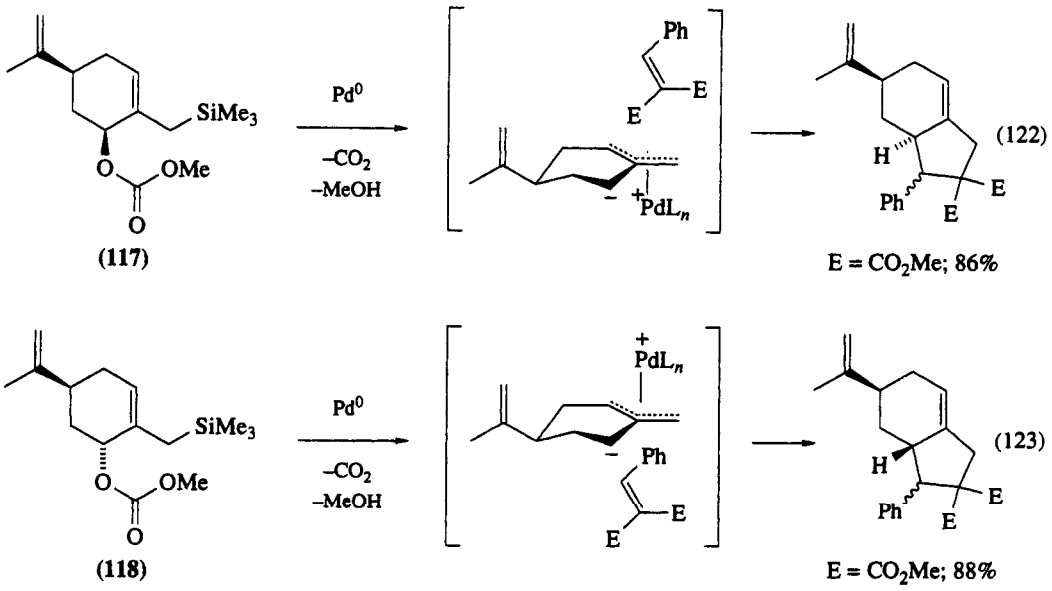
R = CN, CO_2Et, Ph, cyclopropyl, $CH{=}CH_2$, OAc

Carbonate analogs of the corresponding silyl acetates are also good TMM synthons. In this case the carbonate leaving group from initial π-complex formation undergoes decarboxylation to give an alkoxide, which then initiates the desilylation. The type of BCR is employed in the annulation can be critical in determining the reaction pathway. The bis(silyl) acetate (**113**) generates a trimethylsilyl-substituted adduct (**114**), whereas the corresponding carbonate (**115**) yields exclusively a carboxylic methylenecyclopentane (**116**) (equation 121).[66] The latter is presumably derived from trapping of the (TMM)Pd intermediate by the incipient CO_2, which is the by-product of carbonate decarboxylation.

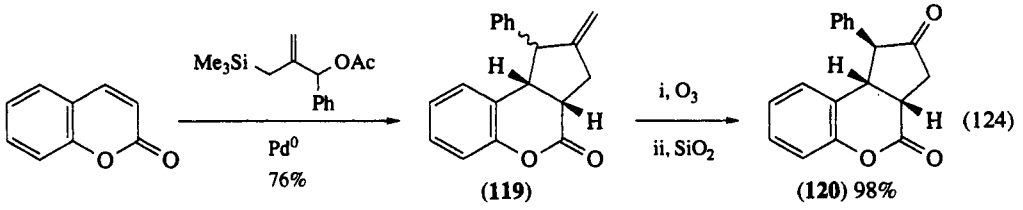


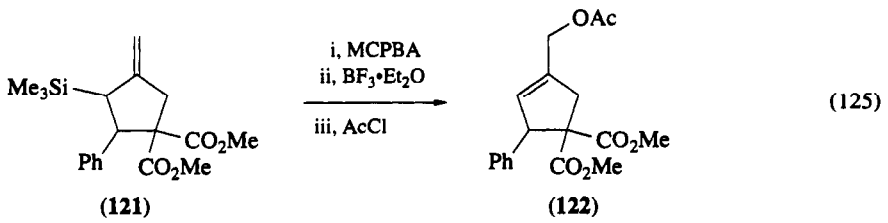
(121)

The BCR cycloaddition is diastereoselective with respect to the TMM unit, with the alkene approaching from the side opposite to the metal center. This accounts for an overall net retention of configuration of the starting material in the cycloadducts obtained from the silyl carbonates (**117**) and (**118**) (equations 122, 123).[81] Thus, no prior coordination of the electron-deficient alkene to the Pd center is necessary for reaction. This is quite different from the methylenecyclopropane mechanism as depicted in Scheme 5. It would also explain the need for a higher ligand-to-metal ratio of the catalyst.



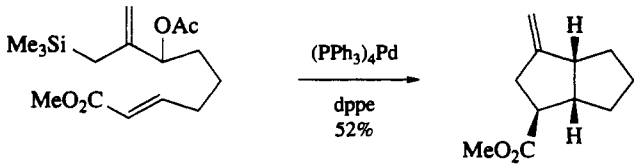
The regioselective cycloadditions can generate useful synthetic intermediates. Conversion of adduct (**119**) to (**120**) provides the equivalent of an α-phenylcyclopentanone annulation (equation 124).[80] The allylsilane moiety generated by the bis(silyl) acetate (**113**) is a useful entity. For example, the cycloadduct (**121**) can be easily transformed to (**122**), which is a regioisomer of the adduct resulting from reaction with (**112**; R = OAc) (equation 125).[66]



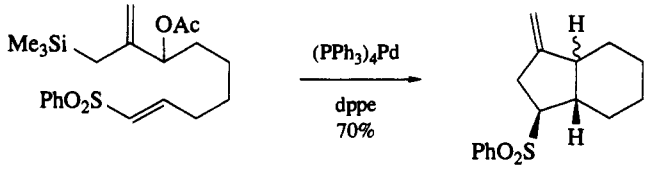


Extension of the TMM strategy to intramolecular reactions greatly expands the scope of this BCR methodology. The precursors are readily available, *e.g.* from the silyl Grignard reagent (**123**) and ω-oxo-α,β-unsaturated substrates (equation 126). Ester- and sulfonyl-substituted bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems are readily constructed in a single step from acyclic material (equations 127, 128).[82]

Silyl carbonates (**124**) possessing an anion-stabilizing function have been developed by Tsuji and coworkers as TMM synthons in [3 + 2] reactions.[83] In this case the *in situ* generated alkoxide serves as a



(127)

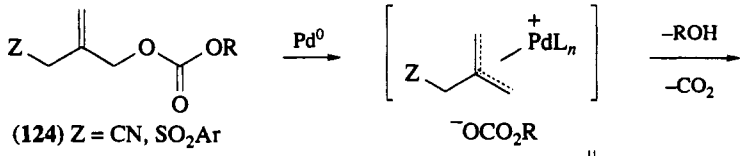


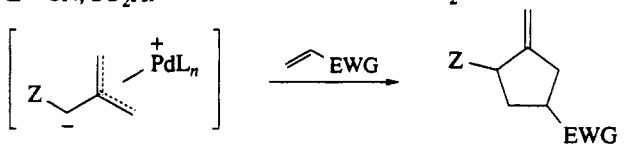
(128)

cis:trans = 2:1

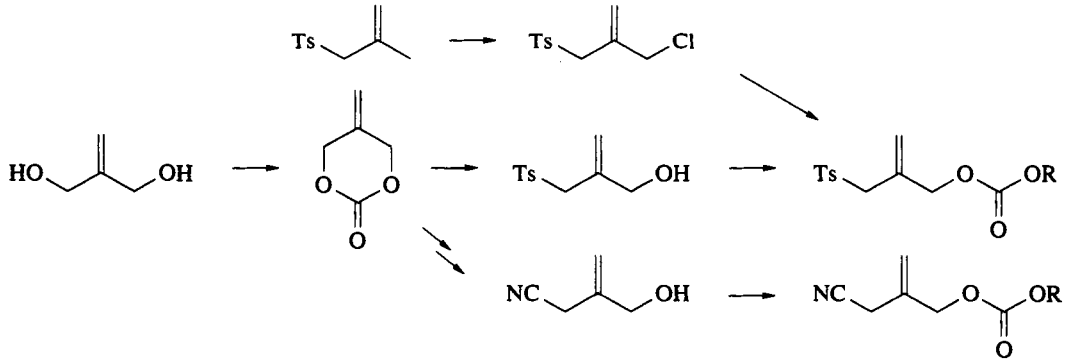
base to effect proton abstraction from the π-allyl intermediate (equation 129). These bifunctional reagents can be prepared from 2-methylene-1,3-propanediol, or methallyl phenyl sulfone in the case of the sulfonyl precursor (Scheme 8). The Pd-catalyzed cycloaddition with (**124**) is similar in scope and regioselectivity to the silyl acetate system. However, alkene migration does occur in the cyano system (equations 130, 131).[84] The sulfonyl(methylene)cyclopentanes resulting from this reagent are useful synthetic intermediates. Some further elaborations of an acrylate adduct are summarized in Scheme 9.[85] A sulfone-substituted BCR has also been successfully generated with aqueous hydroxide for cycloaddition under phase-transfer conditions (equation 132).[86]

The use of chiral ligands to facilitate asymmetric synthesis with these TMM synthons is difficult because the bond-formation process occurs away from the metal center. None the less, an enantioselective synthesis using a Tsuji TMM synthon has been achieved with a catalyst containing a chiral phosphine ligand (equation 133).[87] While the enantiomeric excess is not very high in this case, the fact that one can achieve asymmetric induction at all is quite remarkable.

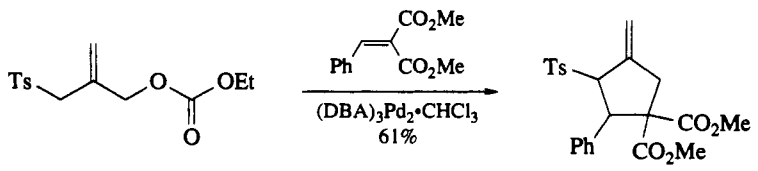




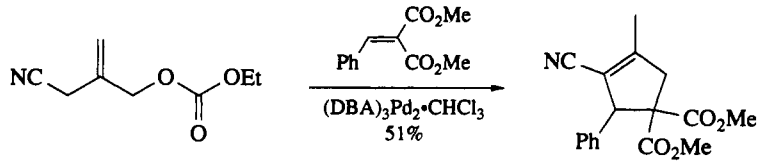
(129)



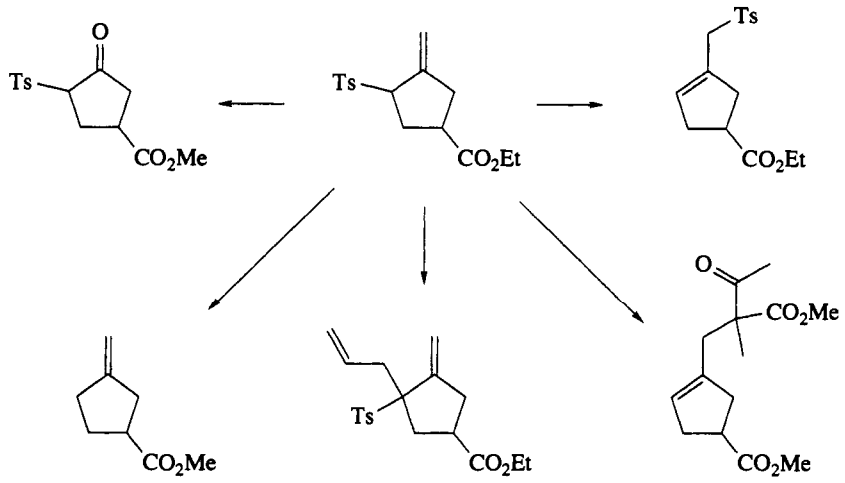
Scheme 8



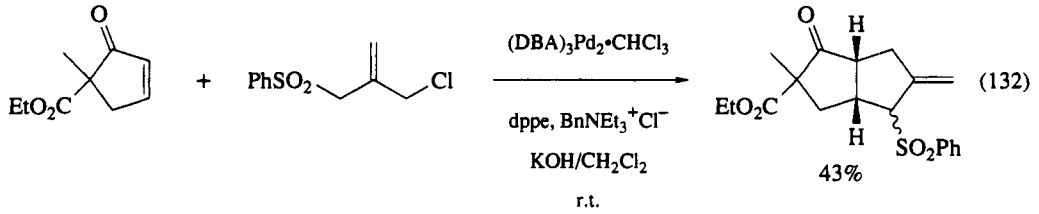
(130)



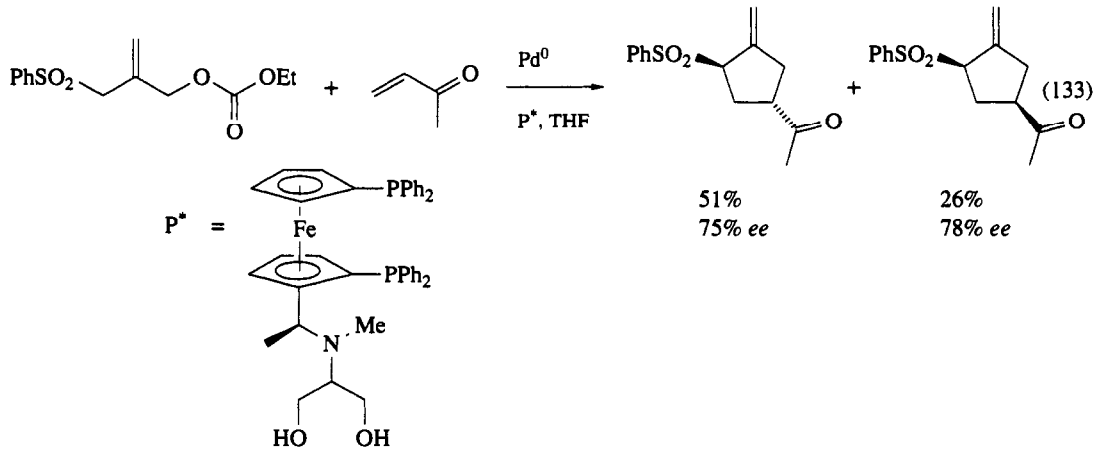
(131)



Scheme 9



(132)

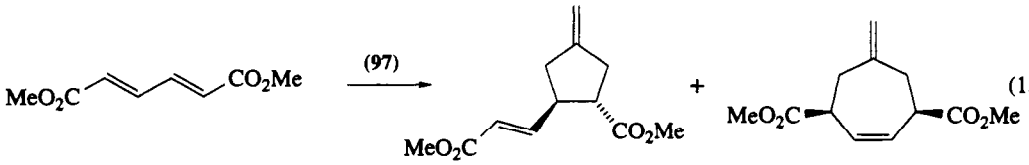


(133)

The highly regioselective cycloadditions of the substituted BCRs can be contrasted to the [3 + 2] reactions employing the corresponding methylenecyclopropanes. While the latter can provide a complementary regiochemistry, *i.e.* formation of alkylidenecyclopentanes, they often give lower selectivity and are very sensitive to the catalyst systems, as well as the substitution pattern of the three-membered ring precursors.

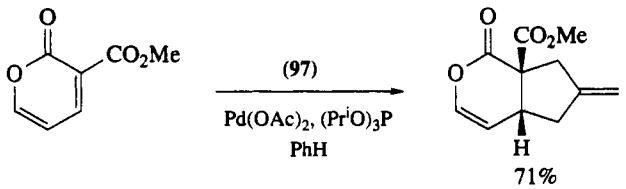
3.2.5.2.3 Diene, C=O and C=N cycloadditions

The relative amount of [3 + 2] and [4 + 3] product in the annulation of dimethyl (*E,E*)-muconate with the parent silyl acetate (**97**) depends critically on the reaction conditions (equation 134).[88] The most notable effect on the ratio of the seven- to five-membered rings is the temperature of the reaction, with a higher temperature favoring methylenecyclopentane formation. Steric factors are also important, as a phenyl-substituted BCR (**124**; R = Ph) generates only [3 + 2] cycloadducts with the same diene. It should be noted that the corresponding reaction using methylenecyclopropane as the TMM synthon produces only the seven-membered ring [4 + 3] adduct. Pyrones are also interesting conjugated dienyl substrates. While the parent and alkyl-substituted system yield only [4 + 3] adducts with (**97**), introduction of a methoxycarbonyl group on the 2-position promotes the exclusive formation of the [3 + 2] adduct (equation 135).[89] However, a 4-methoxycarbonyl function results in a mixture of products from both types of cycloaddition.



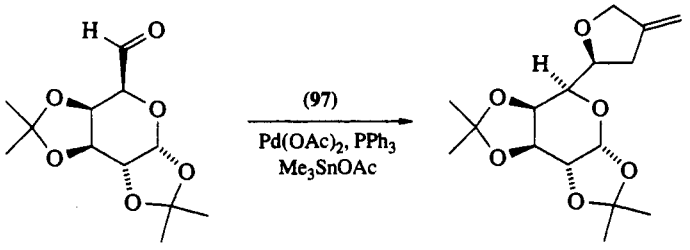
(134)

$(PPh_3)_4Pd$, dppe, dioxane	77%	21%
$(PPh_3)_4Pd$, dppe, THF	29%	18%
$Pd(OAc)_2$, $4(Pr^iO)_3P$, THF	47%	42%



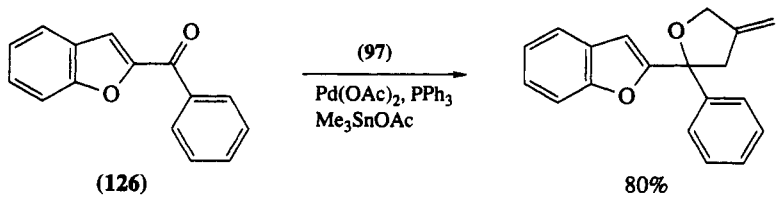
(135)

Annulation to carbonyl functions has also been achieved with Trost's bifunctional reagents.[35] Whereas the parent silyl acetate (**97**) yields only simple alkylation products with aldehydes under normal conditions, addition of only a few mole % of trimethyltin acetate to the reaction mixture results in facile formation of methylenetetrahydrofurans![90] Furthermore, excellent diastereoselectivity is observed in the cycloaddition to a galactose-derived aldehyde (**125**) (equation 136). The tin acetate co-catalyst also promotes addition to relatively unreactive ketone carbonyls, such as in the case of benzofuran (**126**) and the acetylenic ketone (**127**) (equations 137, 138). It is remarkable that even the sterically hindered enone (**128**) reacts preferentially at the ketone function (equation 139). A tributyltin analog (**129**) of (**97**) has been used in the stepwise formation of a methylenetetrahydrofuran from aldehydes.[91,92] Similarly, pyrrolidines can be prepared from the corresponding imines in two steps *via* a Lewis acid-catalyzed 1,2-addition of the tin reagent, which is then followed by a Pd-catalyzed cyclization (equation 140).[91] Direct formation of pyrrolidine from the imine is possible if one uses a mesylate analog of (**97**) and a nickel(0) catalyst (equation 141).[93]

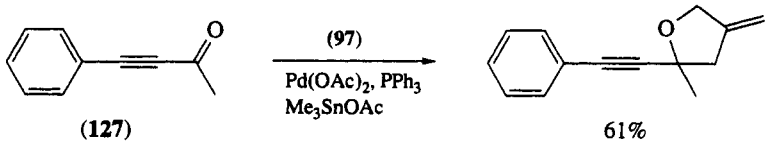


(125) 84%

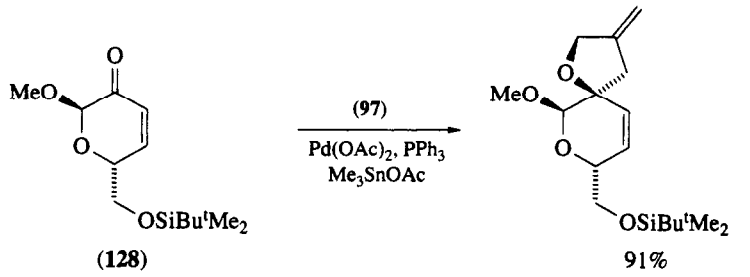
(136)



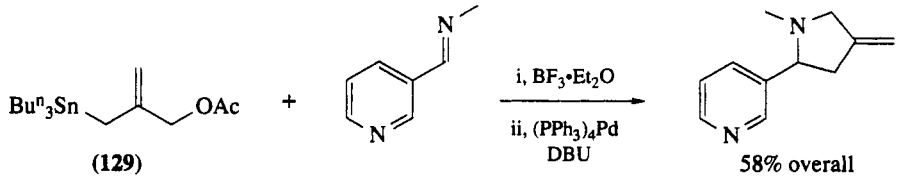
(137)



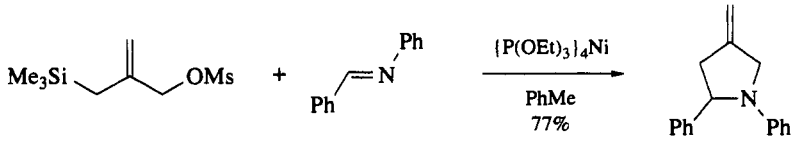
(138)



(139)



(140)

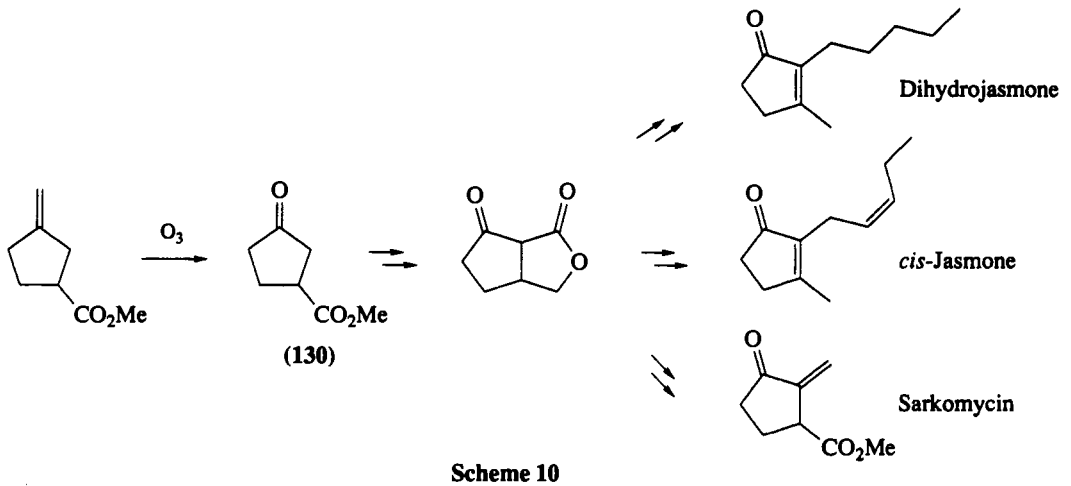


(141)

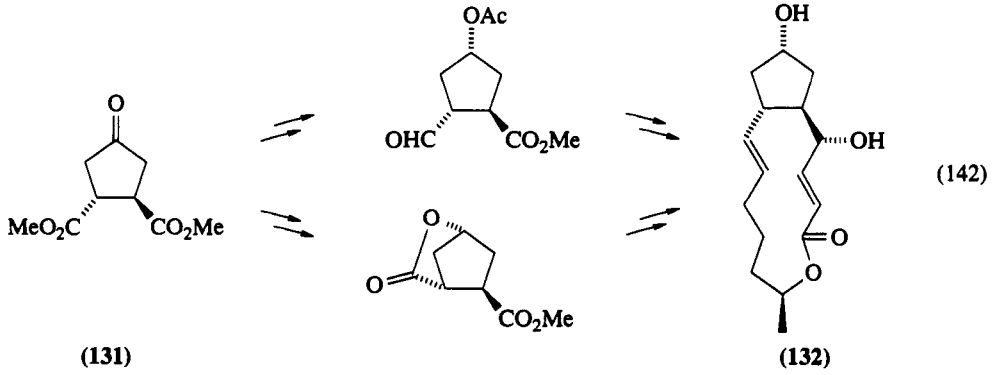
3.2.5.3 TMM Cycloaddition in Natural Product Synthesis

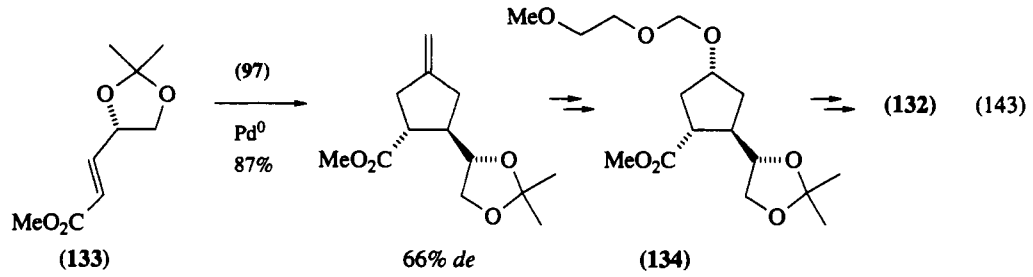
The TMM cycloaddition has been applied to a number of total syntheses and synthetic studies of various natural products.[34,35] The main advantage of this methodology is the stereoselective construction of a five-membered ring in one step from readily available starting materials. The exocyclic alkene of the cycloadduct is another crucial element of this strategy because of its synthetic versatility. The following examples illustrate some of the applications of this [3 + 2] strategy in the area of cyclopentanoid syntheses.

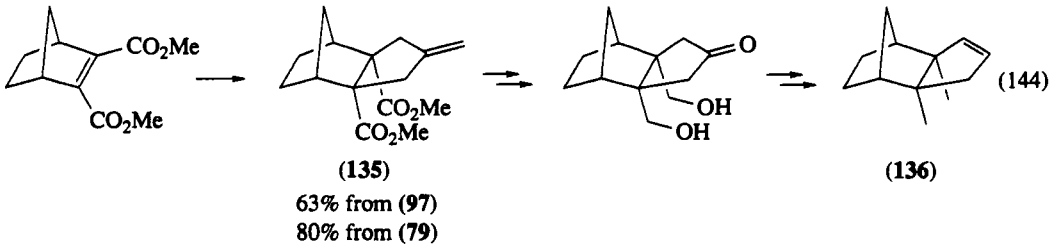
The cycloadduct of methyl acrylate undergoes smooth oxidative cleavage to the cyclopentanone (**130**), which is a useful starting material in the synthesis of dihydrojasmone, *cis*-jasmone and sarkomycin (Scheme 10).[34] *trans*-Diester (**131**),[94] likewise derived from a TMM adduct of dimethyl fumarate, provides a starting point for two total syntheses of (±)-brefeldin A (**132**) (equation 142).[95,96] The same diester has also been used in a prostaglandin synthesis. An enantioselective synthesis of (+)-brefeldin A has also been achieved *via* diastereoselective annulation of (**97**) to the chiral α,β-unsaturated ester (**133**). The product from this reaction is easily elaborated into the key intermediate (**134**), which possesses all but one chiral center of the target molecule (equation 143).[97] Cycloaddition of methylenecyclopropane (**79**) or BCR (**97**) occurs only at the *exo* face of 1,2-dimethoxycarbonylnorbornene to produce the adduct (**135**), a starting material for a short synthesis of (±)-albene (**136**) (equation 144).[70] In this case the methylene group provides a latent function for the requisite internal alkene of the natural product.



Scheme 10

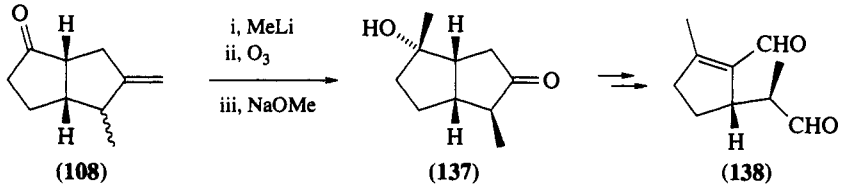




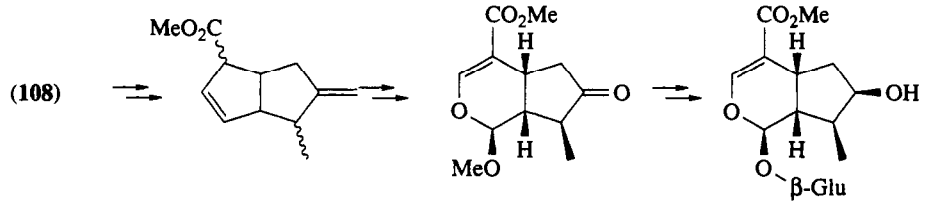


The methyl-substituted BCR is useful for the construction of some iridoid cyclopentanoids. Keto alcohol (**137**), a crucial intermediate for a synthesis of (±)-chrysomelidial (**138**), can be prepared from the cycloadduct (**108**) of cyclopentenone and the methyl-TMM synthon (equation 145).[79] This expedient approach to the keto alcohol, four steps and 83% overall yield from the bifunctional reagent (**107**), is a considerable improvement over a previous 14-step sequence using conventional methodologies. Although the initial bicyclic ketone (**108**) is a 1:1 epimeric mixture, base-catalyzed equilibration of the products from ozonolysis results in only one epimer, having the required stereochemistry. This

epimerization strategy is again employed in an efficient formal synthesis of (±)-loganin (**139**) (equation 146).[98] In this case the cyclopentanone ring of adduct (**108**) becomes a latent function for the 1,5-dialdehyde unit present in the loganin aglucon (**140**). The TMM approach to these two seco-iridoids, chrysomelidial and loganin, is made possible only through the unique regioselectivity of the BCR cycloaddition. It would be difficult to effect the same syntheses using the methylenecyclopropane strategy because of the very different regiochemistry.

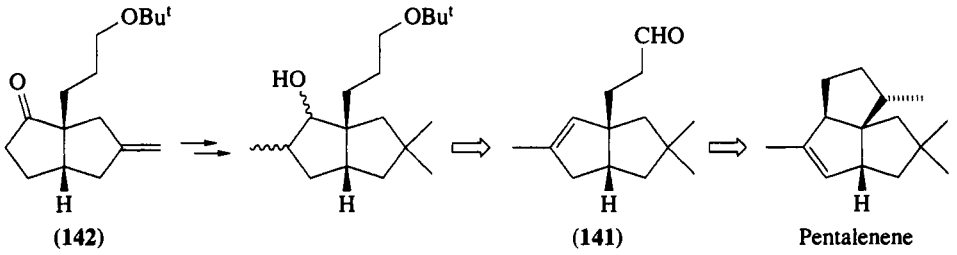


(108) (137) (138) (145)

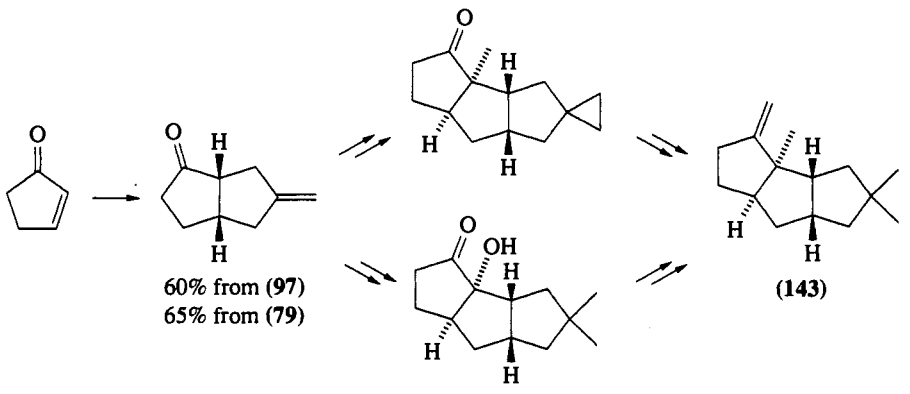


(108) (140) (139) (146)

The pentalenene precursor (**141**) can be derived from a TMM cycloadduct (**142**) (equation 147).[99] This synthetic approach is expedited by the facile conversion of the methylene unit of (**142**) to a *gem*-dimethyl function found in (**141**). This is normally accomplished by a simple cyclopropanation–hydrogenolysis sequence.[100] The two reported TMM-based syntheses of the linear triquinane (±)-hirsutene (**143**) also utilize this particular strategy for the *gem*-dimethyl formation (equation 148).[35,101]

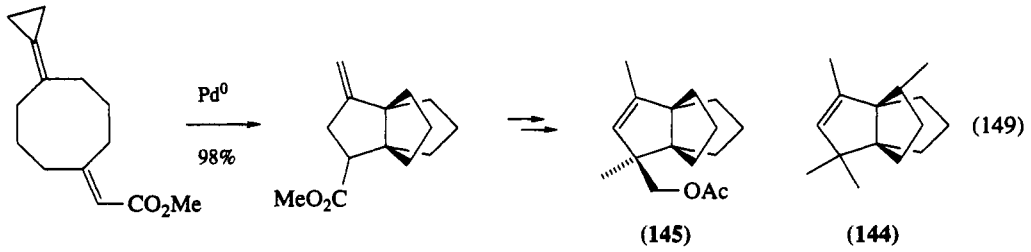


(142) (141) Pentalenene (147)

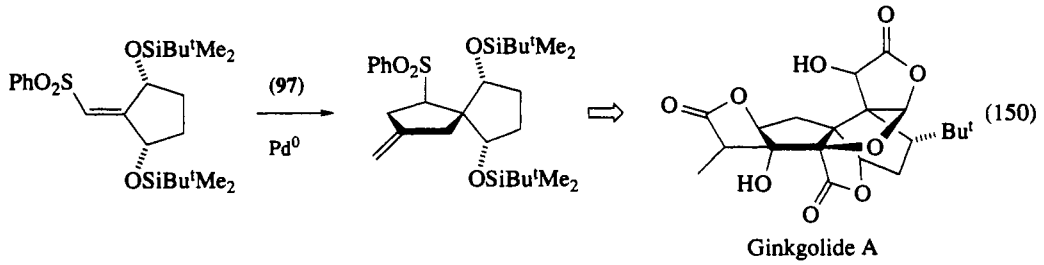


(143) (148)

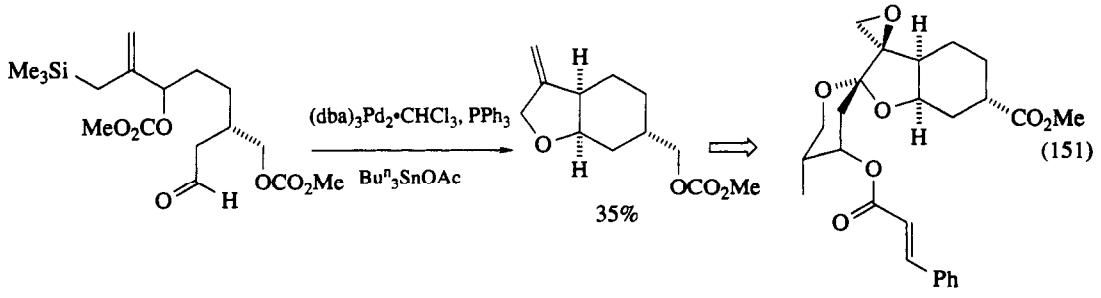
Intramolecular exocyclic transannular cycloaddition of TMM can provide a viable route to propellanes, such as the sesquiterpene modhephene (**144**). This methodology is demonstrated in an efficient synthesis of a [3.3.3]propellane (**145**) (equation 149).[101] The methylenecyclopropane approach is preferred in this case because it works well with dialkyl-substituted systems.



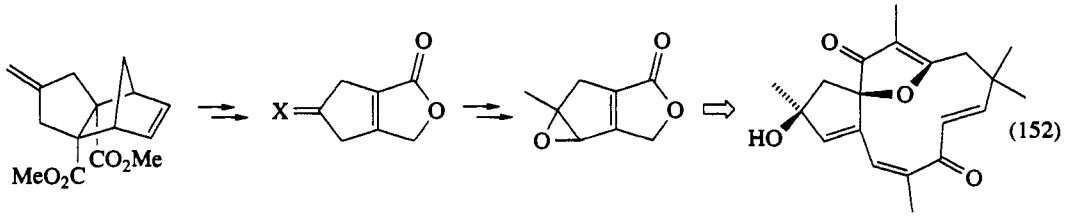
The TMM cycloaddition has also been applied successfully in the synthetic studies of various types of cyclopentanoid natural products, such as ginkolides,[102] phyllanthocin[103] and 2β-hydroxyjatrophone[35] (equations 150–152). The last case employs an equivalent of an alkyne cycloaddition using a retro Diels–Alder strategy.[104] This is a viable alternative for the formation of methylenecyclopentenes from BCRs because electron-deficient alkynes fail to cycloadd with the silyl acetate (**97**).[69] A highly diastereoselective annulation of the (*p*-anisyl)silyl acetate (**146**) to a benzylidenemalonate possessing a chiral auxiliary has been reported.[105] The resulting adduct can be converted to an enantiomerically pure ketone (**147**), which serves as a starting point for an asymmetric synthesis of the antileukemic (–)-rocaglamide (**148**) (equation 153).[106] The exomethylene unit of the BCR cycloadduct provides the crucial dienophile unit in an intramolecular Diels–Alder reaction (equation 154).[106] This novel approach to the phyllocladane ring system is an interesting example of complementarity between [4 + 2] and [3 + 2] cycloaddition strategies.



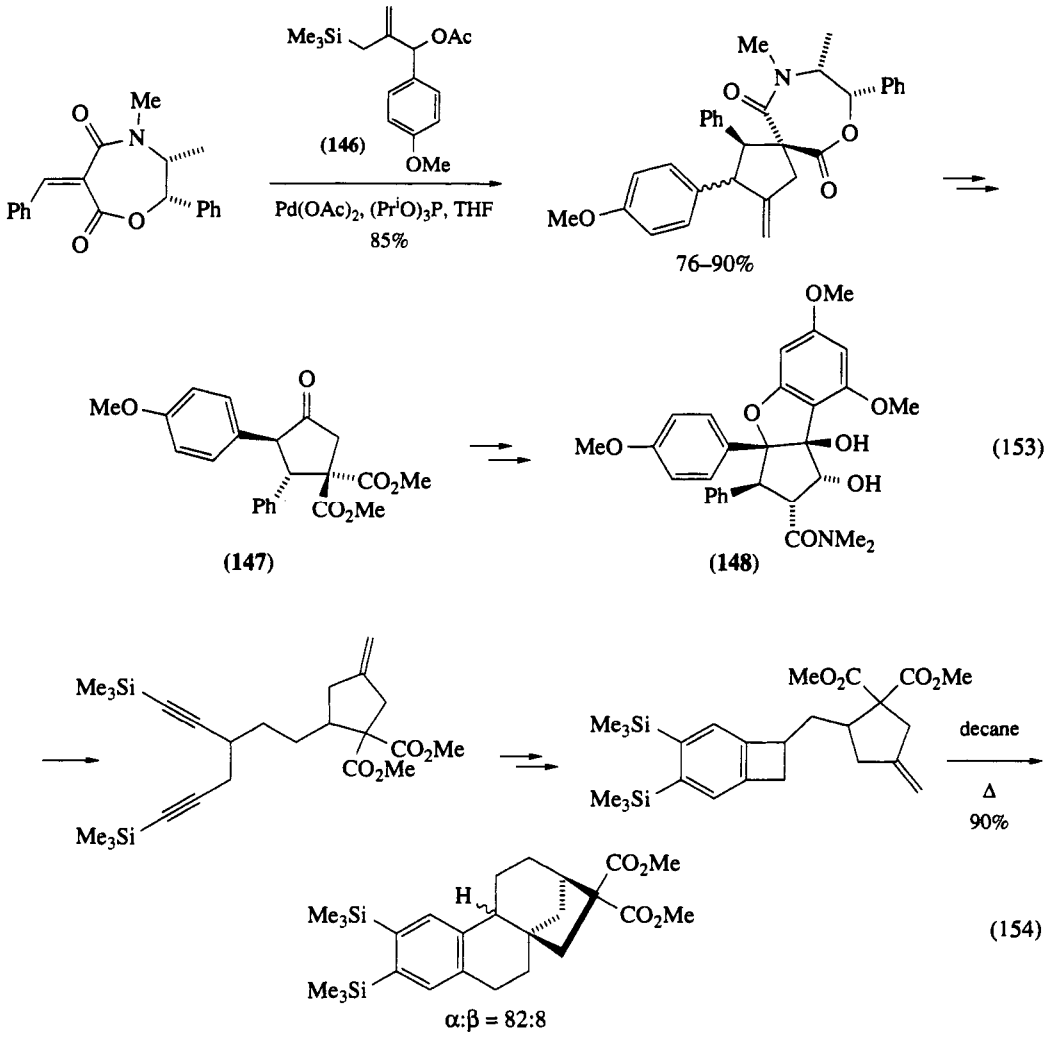
Ginkgolide A



Phyllanthocin



2β-Hydroxyjatrophone



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4.1
Intermolecular Diels–Alder Reactions

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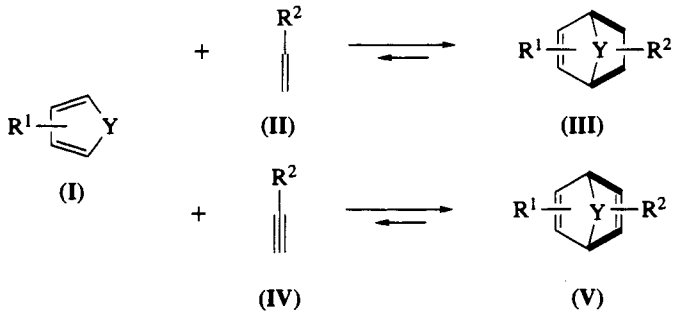
4.1.1 INTRODUCTION

4.1.1.1 Definition, Background and Thermodynamics

Discovered in 1928,[1] the Diels–Alder reaction, *i.e.* the [4 + 2] cycloaddition of a diene (**I**) and a dienophile (**II**) or (**IV**) (Scheme 1), has become, arguably, the most powerful carbon–carbon bond forming process. It is therefore surprising that the last comprehensive survey of the Diels–Alder reaction dates back to 1972.[2] Since then, substantial gains in insight and methodology have been accomplished hand-in-hand with a body of creative and conceptually new applications in organic synthesis. In view of the extensive literature, this chapter is limited to the formation of 'all-carbon' six-membered rings *via* bimolecular additions of 1,3-dienes to alkenes and alkynes.



Scheme 1

During this reaction (Scheme 1), two new carbon–carbon single bonds are formed at the expense of two double bonds or one triple bond, which usually provides a significant driving force ($\Delta G°$). Diels–Alder reactions involving benzynes as dienophiles (Section 4.1.7) or, alternatively, *o*-quinodimethanes as dienes (Section 4.1.8) are even more exothermic owing to a restoration of aromaticity. Only some aromatic dienes such as furans show unfavorable reaction equilibria which, nevertheless, can be shifted toward the cycloadducts by employing high pressure (Section 4.1.4.2) or by reaction with a high-energy dienophile (*e.g.* benzyne; Section 4.1.7).

Owing to their exergonic nature, Diels–Alder reactions are mostly run in an irreversible manner, resulting in kinetically determined regio- and stereo-chemistry. Therefore it is the successful control of its kinetics (featuring values of $\Delta H^{\ddagger} \approx 16$ to 18 kcal mol–1 and $\Delta S^{\ddagger} \approx -30$ to –40 kcal K–1 mol^{-1}) which is fundamental to the pivotal role of the Diels–Alder reaction in organic synthesis.

4.1.1.2 Reactivity

To react with the majority of dienes, the dienophilic double or triple bond needs to be strained (*e.g.* benzynes; Section 4.1.7) or electron deficient. Recently, transient allyl cations have been introduced as highly reactive, electron-poor dienophiles (Section 4.1.4.1). However, dienophile activation is most often achieved by substitution with at least one electron-withdrawing substituent (*e.g.* C=O, CO_2R, CN, NO_2 or SO_2Ar). Molecular orbital considerations[3] provide the following rationalization. In a 'normal' Diels–

Alder reaction of an electron-poor dienophile with an electron-rich diene, the main interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied orbital (LUMO) of the dienophile. Electron-attracting substituents lower the frontier orbital energies of the dienophile, thereby decreasing the dienophile-LUMO/diene-HOMO energy difference and, consequently, the activation enthalpy ($\Delta H^{\ddagger}$) of the reaction. The remarkable Lewis acid induced acceleration of Diels–Alder reactions (Section 4.1.4.1) is also in agreement with a lowering of the frontier orbital energies of the dienophile by coordination with the Lewis acid. Furthermore, consistent with this reasoning, the reaction rate of Diels–Alder reactions is often increased by electron-donating substituents in the diene (*e.g.* NR_2, OR, SR, Section 4.1.3).

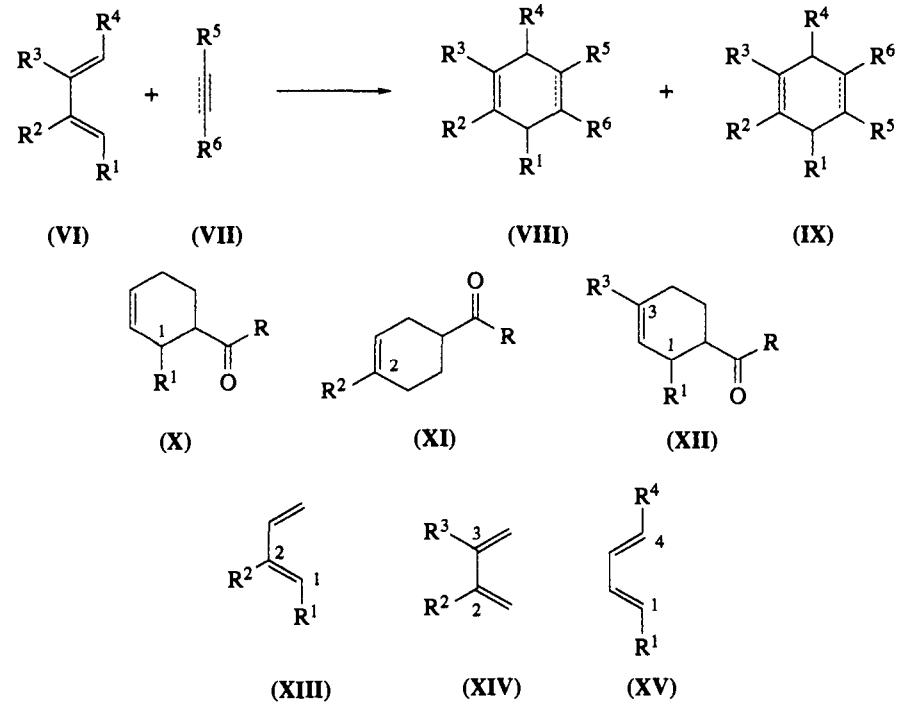
There is also a small number of [4 + 2] cycloadditions involving electron-rich dienophiles (*e.g.* enamines, vinyl ethers and vinyl sulfides) and electron-deficient dienes. These 'inverse-electron-demand' Diels–Alder reactions correspond to a predominant dienophile-HOMO/diene-LUMO overlap.

Isolated alkenes and alkynes, such as ethylene and acetylene, are notoriously poor dienophiles. This limitation has been largely overcome by the development of dienophiles containing an 'activating' moiety (*e.g.* NO_2, SO_2Ar) which is readily removed after cycloaddition, with or without introduction of further functionality. These reactive dienophiles can, accordingly, be regarded as synthetic equivalents of unreactive or inaccessible species (Section 4.1.2).

An entirely different type of rate enhancement relies on rendering the activation entropy ($\Delta S^{\ddagger}$) less negative. In this sense, advantage can be taken of using high pressure, ultrasound, aggregation effects in water, adsorption on dry SiO2, or clays and zeolites (Section 4.1.4.2).

4.1.1.3 Regiochemistry

A question of regioselectivity arises when both the diene (**VI**) and the dienophile (**VII**) are nonsymmetrically substituted as this can give a mixture of two regioisomers (**VIII**) + (**IX**). Their relative proportions depend on the individual nature of, and on the interplay between, substituent effects (Scheme 2).



Scheme 2

In frontier orbital terms, the regiochemistry is governed largely by the atomic orbital coefficients at the termini of the reaction partners, which are altered by the substituents.[3] Hence, in 'normal' Diels–Alder reactions a diene substituent at C-1 has the tendency to direct the addition of a carbonyl-conjugated alkene towards the '*ortho*' product (**X**), whereas a substituent at C-2 favors the '*para*' product (**XI**). The

individual directive effects of substituents are synergistic with 1,3-disubstituted dienes (*e.g.* favoring more strongly the formation of regioisomer **XII**), but antagonistic with 1,2- (**XIII**), 2,3- (**XIV**) and 1,4-disubstituted dienes (**XV**). The magnitude of the directing effect differs from one substituent to another (*e.g.* SAr > OR > SiR_3) and also with their position on the diene.

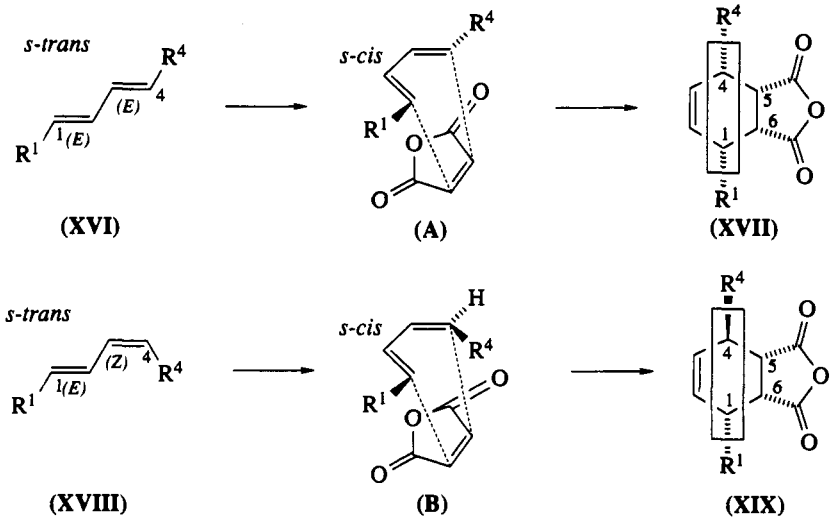
Similar arguments hold for the dienophile partner. Thus, the regiocontrolling effect of a substituent R^5 can outweigh that of R^6 in 1,2-disubstituted dienophiles (**VII**) (*e.g.* Me < SO_2Ar < NO_2 > C=O > Me).

This hierarchy of substituent effects can be exploited to obtain adducts with predictable and high regioselectivity through the use of dienes and dienophiles containing 'temporary' substituents which control the regiochemistry of the addition and are removed thereafter. Sulfide (diene) and nitro (dienophile) groups can serve in this manner as powerful regiocontrol elements (Sections 4.1.3.3 and 4.1.2.1).

Lewis acid coordination of carbonyl-conjugated dienophiles usually results in vastly improved regioselectivities on [4 + 2] cycloadditions to nonsymmetrical dienes (Section 4.1.4.1). Medium effects can also be usefully applied to achieve better regiochemical control (Section 4.1.4.2).

4.1.1.4 Stereochemistry

It is accepted that in the majority of Diels–Alder reactions the two new σ-bonds are formed in a concerted, although not necessarily synchronous, manner as depicted by transition state (**A**) (Scheme 3).



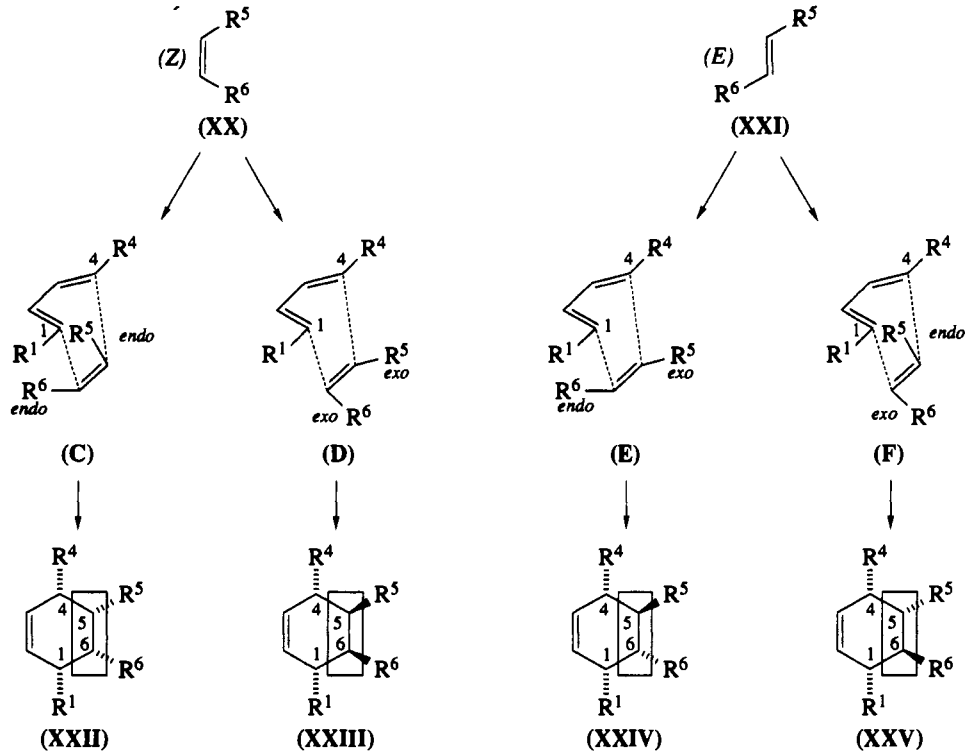
Scheme 3

This requires the diene to adopt the *s-cis* (cisoid) conformation. Consistent with this supra/supra/facial mode of addition,[4] Diels–Alder reactions are generally stereospecific, *i.e.* the configurations of both dienes and dienophiles are 'retained' in the adducts. Thus (*E,E*)-dienes (**XVI**) afford specifically adducts (**XVII**) with a R^1/R^4 *cis* relation, and (*E,Z*)-dienes (**XVIII**) give rise to a *trans* disposition of R^1 and R^4 in their adducts (**XIX**). Similarly, (*Z*)-dienophiles (**XX**) provide adducts (**XXII**) and (**XXIII**) showing a R^5/R^6 *cis* disposition, whereas (*E*)-dienophiles (**XXI**) yield adducts (**XXIV**) and (**XXV**) with *trans* related substituents R^5/R^6 (Scheme 4).

That each of the (*Z*)- or (*E*)-dienophiles yields a set of two diastereoisomers [(**XX**) → (**XXII**)/(**XXIII**) and (**XXI**) → (**XXIV**)/(**XXV**)] reflects the *endo* and *exo* orientations of the dienophile substituents in the transition states. Thus starting from a (*Z*)-dienophile (**XX**), both substituents R^5 and R^6 can be *endo* (**C**) or *exo* oriented (**D**) whereas an (*E*)-dienophile (**XXI**) entails transition states (**E**) and (**F**) featuring either an *endo* oriented R^6 or R^5, respectively.

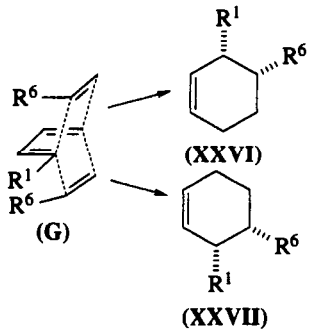
Alder's *endo* rule[2] specifies a preference for *endo* (**C**) over *exo* (**D**) addition. However, this rule appears to be strictly applicable only to the addition of cyclic dienophiles (*e.g.* maleic anhydride, *p*-quinones) to cyclic dienes (*e.g.* cyclopentadienes).

The '*endo* preference' of substituents varies, and can be selectively and dramatically increased by coordination with a Lewis acid (Section 4.1.4.1). Medium effects also help to improve the *endo/exo* product ratio (Section 4.1.4.2). This becomes an essential selectivity issue when the individual *endo* preferences of substituents are opposed, as in transition states (**E**) and (**F**).



Scheme 4

Finally, the most recently addressed stereochemical issue is that of π-facial control (Scheme 5). In the previous discussion, absolute configurations were depicted arbitrarily to describe relative configurations. Hence, in the absence of a π-facial control element, [4 + 2] cycloaddition of a dienophile occurs at the same rate to the top and bottom faces of a diene (*cf.* situation **G**) to give a 50:50 mixture of enantiomers (**XXVI**) and (**XXVII**).



Scheme 5

Recent years have witnessed remarkable progress in directing Diels–Alder additions with up to 99.5% selectivity to either face, thereby controlling the absolute configuration of the newly generated stereogenic centers. This chapter therefore culminates by dealing with this highly relevant topic in Sections 4.1.5 and 4.1.6.

No doubt the Diels–Alder reaction will lend itself to further extensions of scope and selectivity. Nevertheless, the current 'state of the art' and the pivotal applications of Diels–Alder adducts (**XXX**) for the efficient chemo-, regio- and stereo-selective syntheses of complex structures, *e.g. via* annulation processes (a, b) and/or cleavage reactions (c, d, e) speak for themselves (Scheme 6). An adequate treatise would vastly exceed the limits of this chapter.

(XXVIII) (XXIX) (XXX)

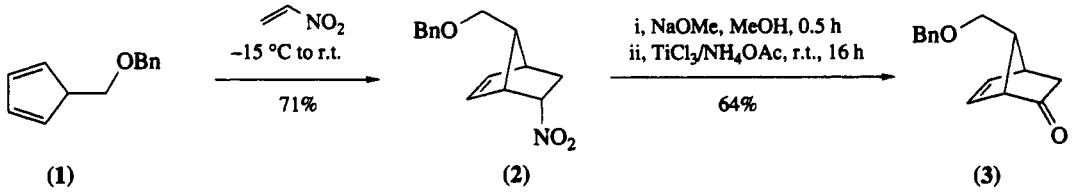
Scheme 6

4.1.2 HETEROATOM-SUBSTITUTED DIENOPHILES

Dienophiles substituted with appropriate heteroatoms may offer a number of advantages such as: (1) provide dienophilic equivalents of C=C and C≡C moieties which do not undergo [4 + 2] cycloadditions to 1,3-dienes because of low (*e.g.* isolated alkenes, alkynes, allenes) or different reactivities (*e.g.* ketenes); (2) enhance or invert the regiochemistry of the Diels–Alder process; (3) permit facile removal of the activating and/or regiocontrolling group after cycloaddition with or without introduction of further functionalities. The use of nitroalkenes as dienophiles demonstrates these issues most strikingly.

4.1.2.1 Nitroalkenes

Nitroethylene undergoes rapid cycloaddition to 1,3-dienes; subsequent conversion of the nitro to a carbonyl group, *e.g.* (**1**) → (**2**) → (**3**), exemplifies its application as a dienophilic ketene equivalent (Scheme 7).[5]



(1) (2) (3)

Scheme 7

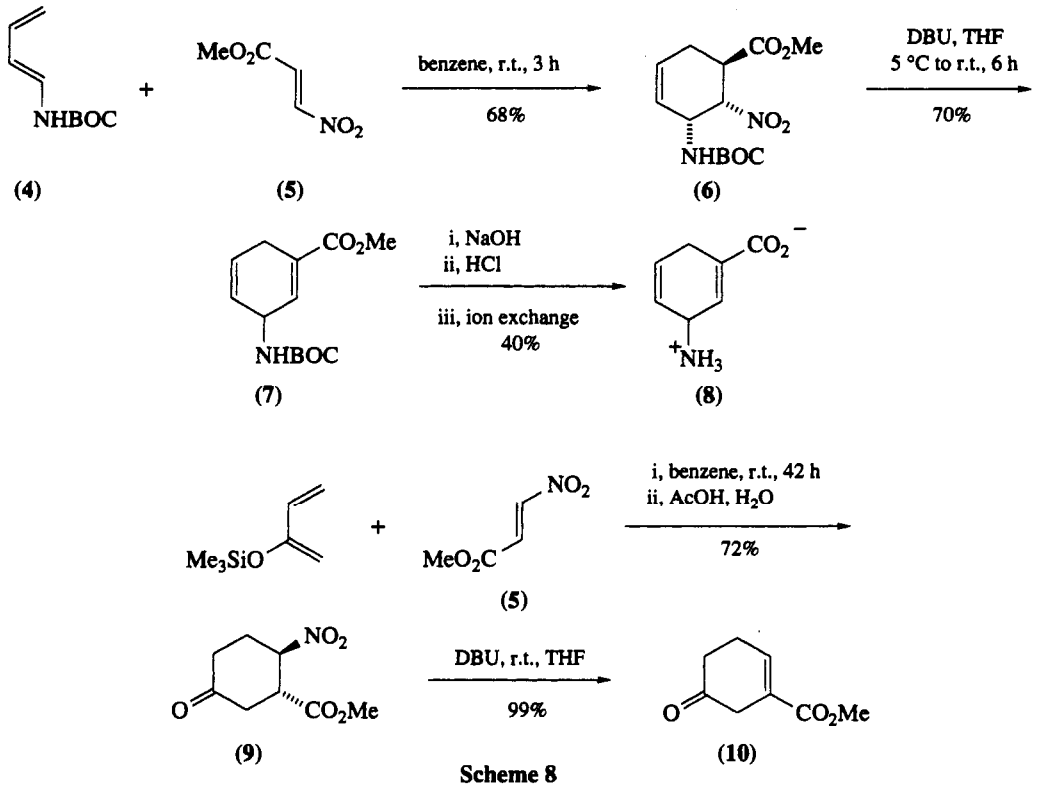
Furthermore, a pronounced regiochemical control has been recognized with nitroalkenes. For example, (*E*)-methyl β-nitroacrylate (**5**) is an outstanding dienophile. Its cycloadditions to 1,3-dienes display a high regioselectivity dominated by the nitro group, as illustrated by the synthesis of the cyclohexadiene-amino acid (**8**).[6] This involves Diels–Alder reaction with 1-(*N*-acylamino)-1,3-diene (**4**) followed by removal of the nitro group from cycloadduct (**6**) *via* DBU-induced elimination of nitrous acid, (**6**) → (**7**) (Scheme 8). A similar cycloaddition/desilylation/elimination sequence, starting from 2-(trimethylsilyloxy)1-1,3-butadiene, afforded the unusual cyclohexenone (**10**).[7]

The capacity of the nitro substituent to override the directing influence of the carbonyl group, providing 1,4-cyclohexadiene products with unconventional substitution patterns, is further demonstrated in Scheme 9. The [4 + 2] cycloaddition of diene (**11**) to ethyl propiolate (**11** → **12** + **13**) or, alternatively, to ethyl β-nitroacrylate (**11** → **15**) clearly reveals that these two dienophiles are regiochemical counterparts.[8]

Scheme 10 illustrates an analogous regioselective Diels–Alder reaction with 3-nitrocyclohexenone (**17**) serving as a 'cycloalkynone' dienophile equivalent.[9]

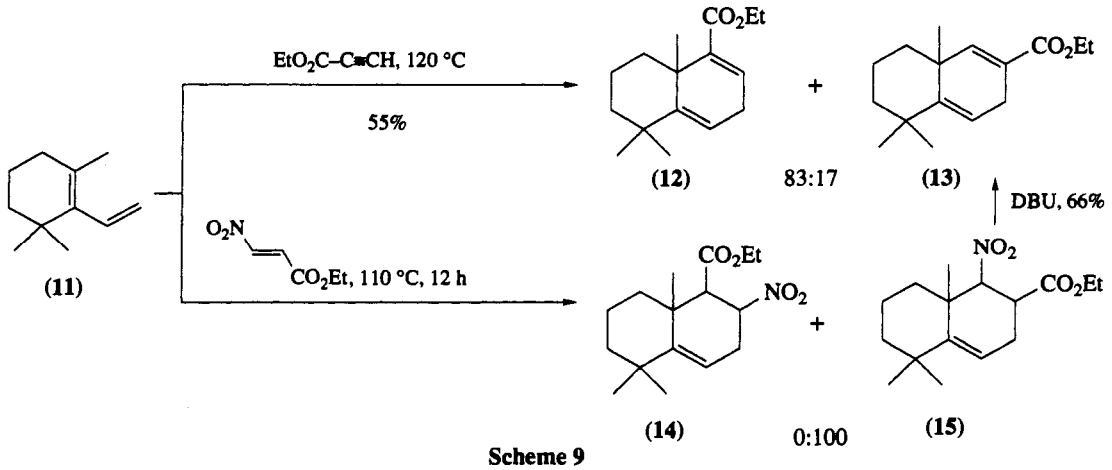
Nitroalkenes can also be regarded as dienophilic alkene equivalents owing to the recently reported substitution of the nitro group by a hydrogen atom. Thus treatment of the cycloadducts with Bu_3SnH in the presence of AIBN opens a new regioselective (but stereo-random) access to cyclohexenes (Scheme 11).[10]

β-Sulfonylnitroalkenes or β-sulfinylnitroethylene are excellent dienophiles and correspond to alkyne or nitroalkyne equivalents (Scheme 12).[11] Bisactivated dienophile (**26**) reacts with 1,3-dienes in a highly regioselective manner to give, on subsequent reductive elimination of the nitro and sulfonyl groups, cyclohexadienes, *e.g.* (**16**) + (**26**) → (**27**) → (**28**). β-Sulfinylnitroethylene (**30**) offers a regioselective

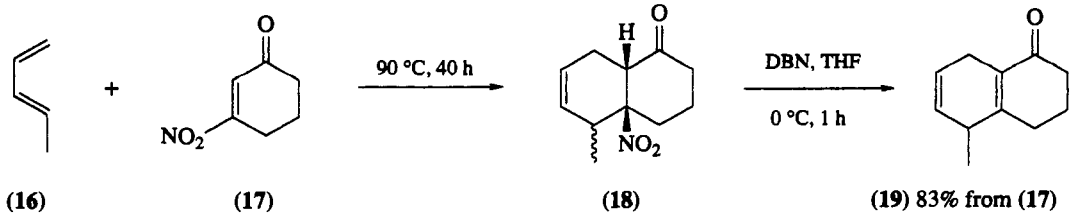


Scheme 8

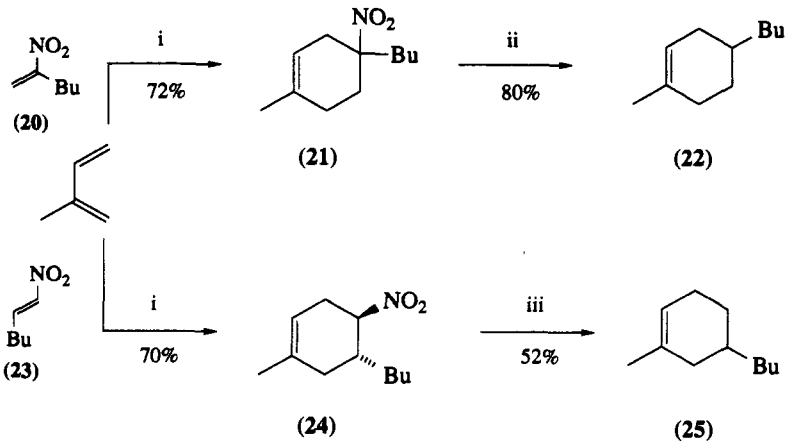
approach to nitrobenzenes, as illustrated by its addition to diene (**29**) followed by the SiO_2-promoted hydrolysis/sulfenic acid elimination yielding pure *p*-nitrophenol (**32**; 51%).



Scheme 9

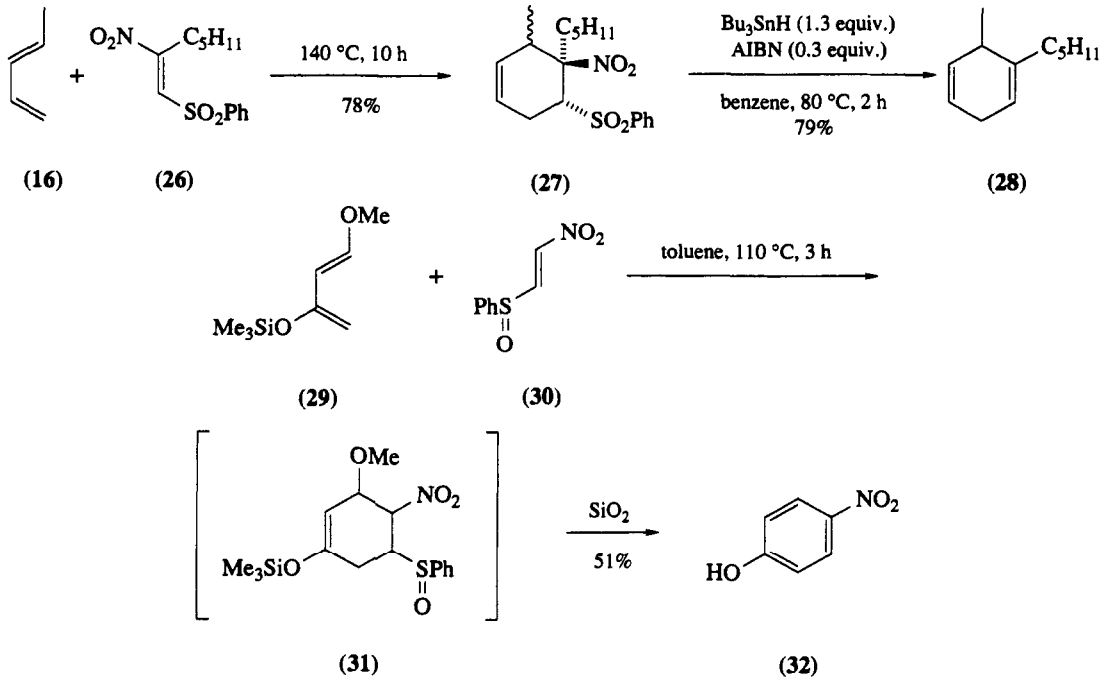


Scheme 10



i, $CHCl_3$, reflux, 72 h; ii, Bu_3SnH (1.2 equiv.), AIBN (0.2 equiv.), benzene, 80 °C, 2 h; iii, Bu_3SnH (5 equiv.), AIBN (0.5 equiv.), toluene, 110 °C, 0.5 h

Scheme 11

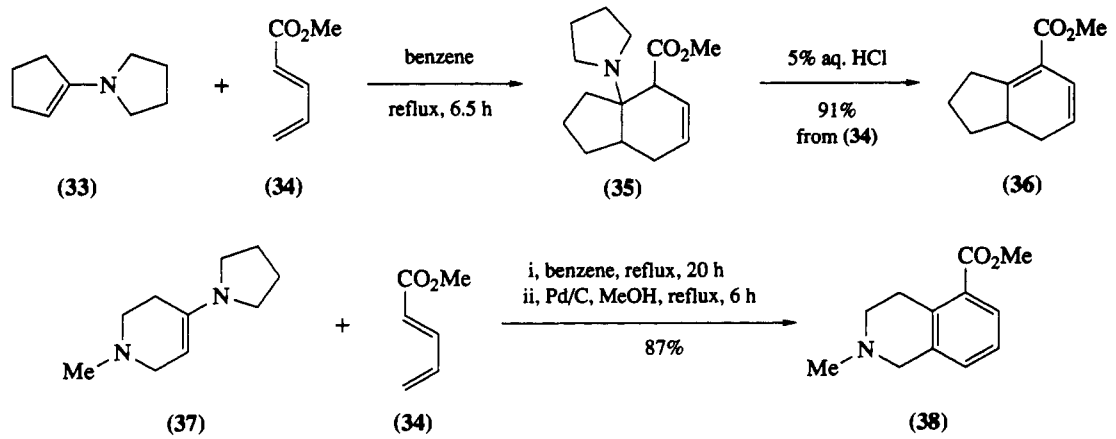


Scheme 12

4.1.2.2 Enamines and Enamides

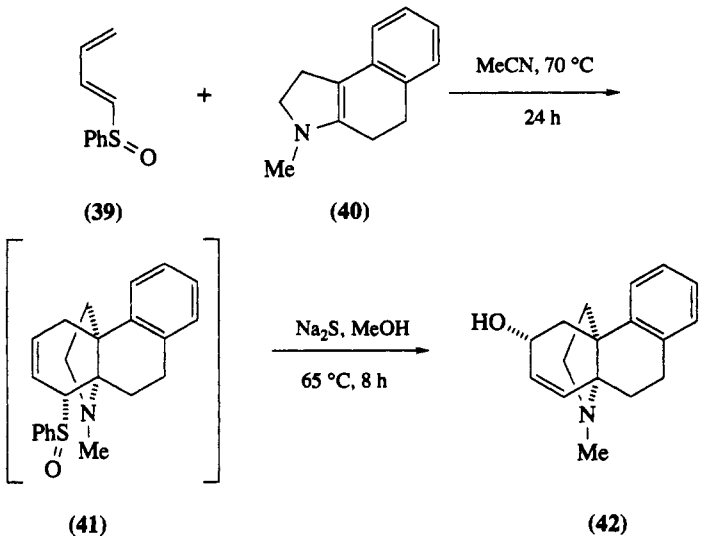
Lowering the oxidation state of the nitrogen substituent has a dramatic effect on its electronic properties. In marked contrast to nitroalkenes, enamines are electron-rich reagents and thus undergo 'inverse-electron-demand' Diels–Alder reactions with the electron-poor β-vinylacrylic esters. Acidic work-up gave 1,3-cyclohexadienecarboxylates as illustrated by the cycloaddition/elimination sequence (**33**) + (**34**) → (**35**) → (**36**) (Scheme 13).[12] Under analogous reaction conditions, including a Pd-catalyzed dehydrogenation step, the heterocyclic enamine (**37**) was transformed into (**38**; 87%), which represents an interesting route to tetrahydroisoquinolines.[13]

Diels–Alder addition of the endocyclic enamine (**40**) to the moderately electron-deficient (±)-1,3-dienyl sulfoxide (**39**) proceeded smoothly without loss of the nitrogen atom. Subsequent 2,3-sigmatropic



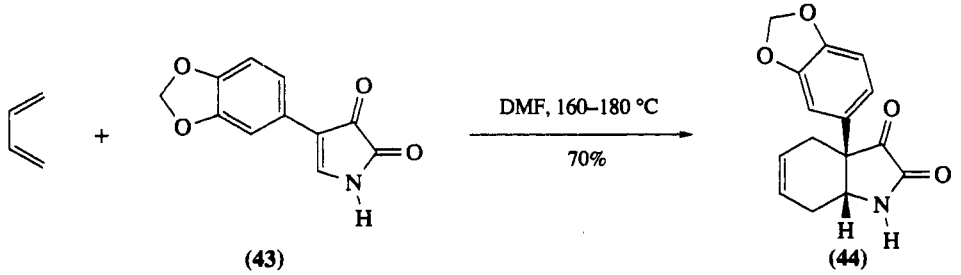
Scheme 13

rearrangement of the allyl sulfoxide (**41** → **42**) offered an elegant synthetic entry into derivatives of the hasubanan alkaloid family (Scheme 14).[14]

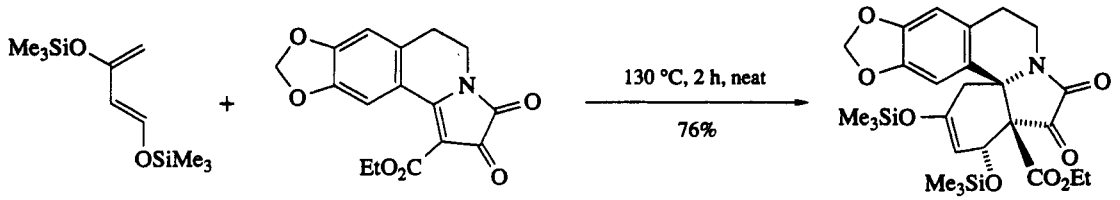


Scheme 14

More recently, dioxopyrrolines have been introduced as 'classical', electron-deficient dienophiles. For example, the addition of (*in situ* prepared) 3-aryldioxopyrroline (**43**) to butadiene afforded the hexahydroindole (**44**), a key precursor in a synthesis of Amaryllidaceae alkaloids (Scheme 15).[15] Similarly, highly regioselective [4 + 2] cycloaddition of isoquinolinodioxopyrroline (**46**) to 1,3-bis(trimethylsilyloxy)butadiene (**45**) afforded the tetracyclic adduct (**47**) with excellent control over the relative configuration of two quaternary and one tertiary stereogenic centers. Cycloadduct (**47**) served as a pivotal intermediate in erythrina alkaloid synthesis.[16]



Scheme 15



(45) (46) (47)

Scheme 15 *(continued)*

4.1.2.3 Alkenyl Sulfur Derivatives

The role of sulfur functionalities in activating alkenic and alkynic dienophiles, and directing their cycloadditions to 1,3-dienes, has been recently reviewed[17] and only some essential points are outlined here. Depending on the oxidation state of sulfur, its vinyl derivatives range from strongly or weakly electron-deficient (sulfones or sulfoxides) to electron-rich (sulfides) dienophiles.

Vinyl sulfones are the most versatile and widely used sulfur substituted dienophiles. They may serve as both activated ethylene and terminal alkene equivalents in highly regioselective Diels–Alder additions to 'classical', *i.e.* electron-rich, 1,3-dienes. The sulfonyl moiety facilitates the introduction of further functionality into the cycloadducts and can be easily removed by mild reduction (Scheme 16).[18a] These features have been exploited in a synthesis of the terpenoid zingiberenol (**56**) (Scheme 17).[18b]

The 'temporary' functionalization of cyclic or acyclic alkenes with a phenylsulfonyl group, followed by [4 + 2] cycloadditions of 1,3-bis-oxygenated dienes, opens a regiocontrolled route to annulated or 5-substituted cyclohexenones (Scheme 18).[18b,19]

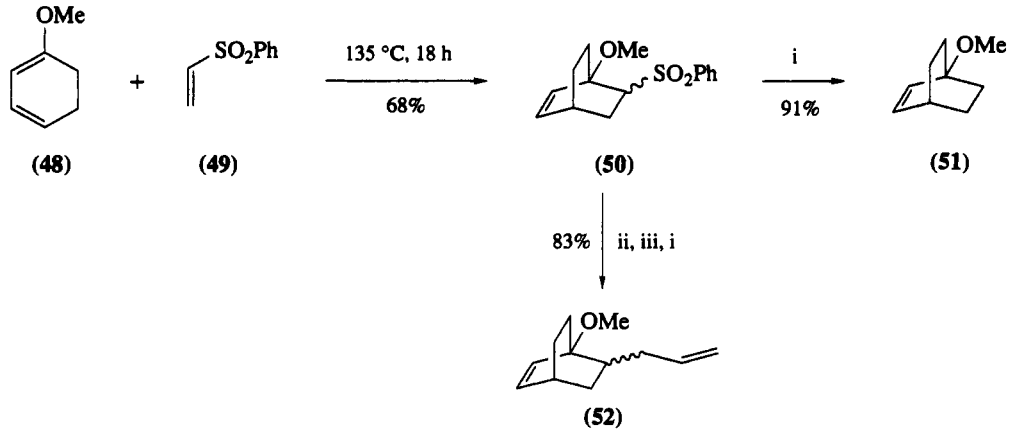
Methyl α-bromovinyl sulfone (**64**) corresponds to an activated allene equivalent when subjected to a Diels–Alder/Ramberg–Bäcklund reaction sequence providing, for example, *exo*-methylenenorbornene (**66**) (Scheme 19).[18b,20]

Tolylsulfonylacetylene (**68**) has found use as a dienophilic substitute for acetylene, as exemplified by the synthesis of the structurally unique hydrocarbon [4]-peristylane (**71**) (Scheme 20).[21]

Vinyl sulfoxides mostly require a second electron-withdrawing group to increase their dienophilic character. Thus vinyl sulfoxides bearing a carbonyl moiety at C_β undergo 'carbonyl-directed' diene addition followed by a spontaneous elimination of sulfenic acid, as applied to a synthesis of disodium prephenate (**74**) (Scheme 21).[22]

The chirality at sulfur also confers to (*Z*)-β-carbonylmenthoxy vinyl sulfoxides a useful topological bias which will be discussed in context with asymmetric Diels–Alder reactions (Section 4.1.6.2.1 (vi)).

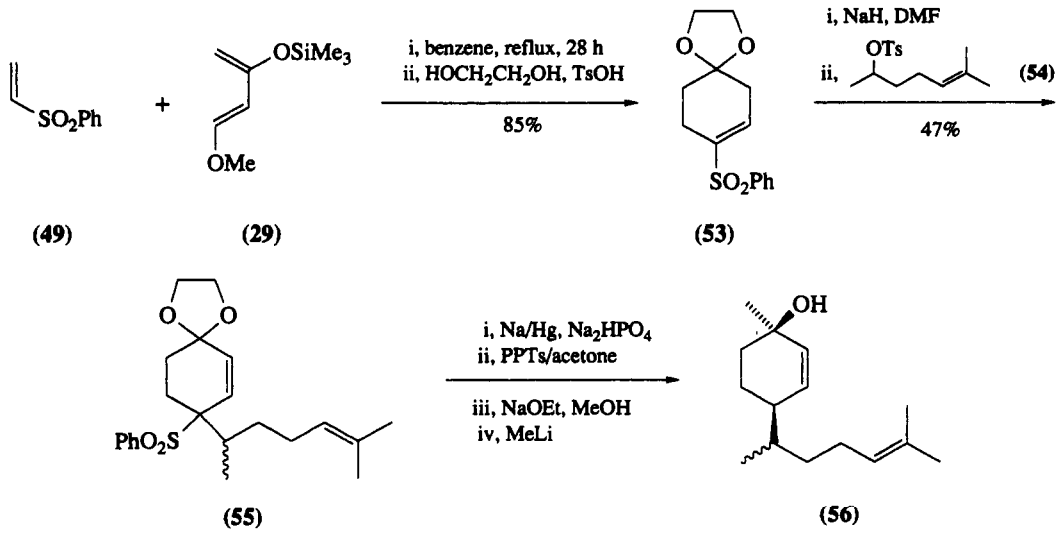
A C_α-positioned sulfoxide (as well as a sulfide) group enhances significantly the dienophilicity of α,β-unsaturated carbonyl compounds in Diels–Alder reactions with 'standard' dienes. Moreover, the synergistic influence of the two functional groups secures a high regiochemical control, *e.g.* (**75**) + (**76**) → (**77**) (Scheme 22).[23]



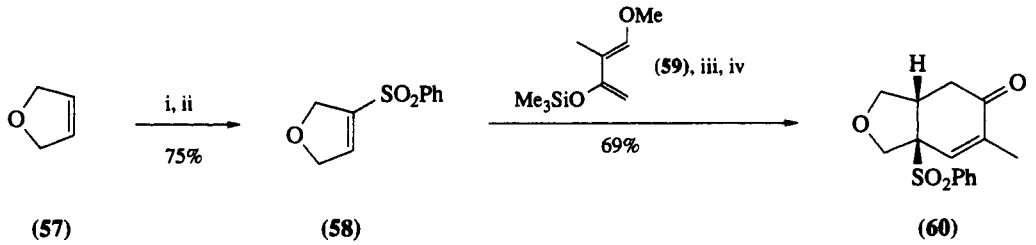
(48) (49) (50) (51) (52)

i, Na/Hg excess, Na_2HPO_4/MeOH, –20 °C; ii, BuLi, THF/HMPA (9:1); iii, $BrCH_2CH{=}CH_2$

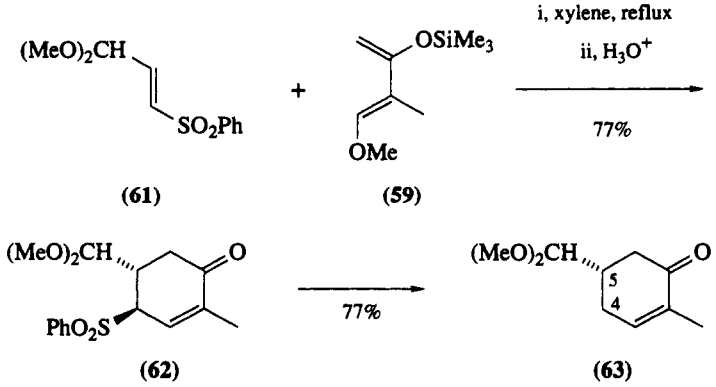
Scheme 16



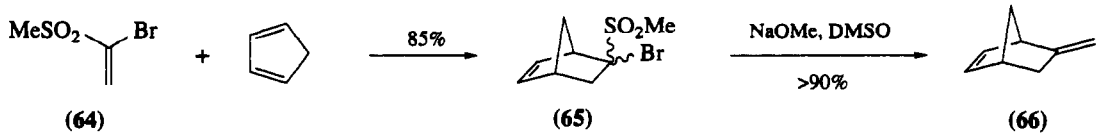
Scheme 17



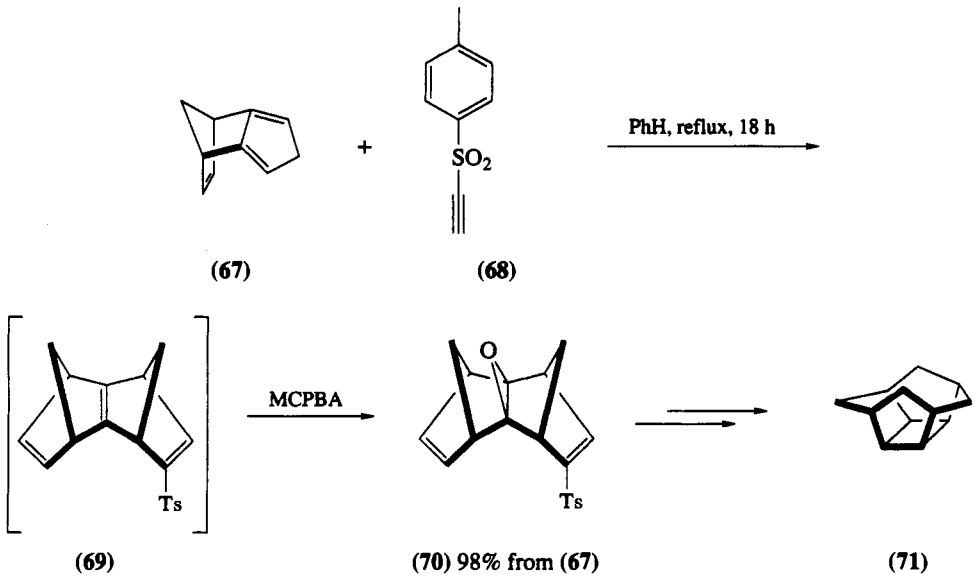
i, $PhSeSO_2Ph$, *h*v (254 nm), CCl_4, 1.5 h; ii, 15% aq. H_2O_2, CH_2Cl_2, 0 °C, 0.5 h then r.t, 0.5 h; iii, xylene, reflux, 48 h; iv, 1N aq. HCl, THF, 5 h



Scheme 18

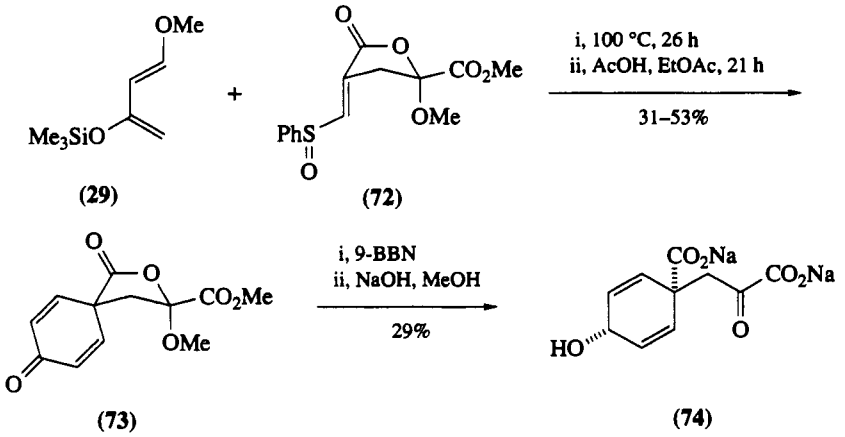


Scheme 19



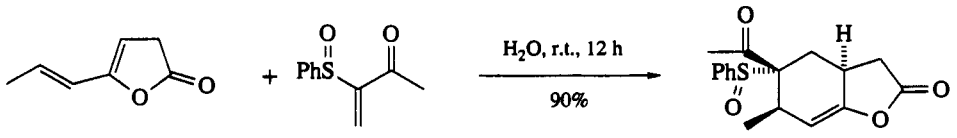
(67) (68) (69) (70) 98% from (67) (71)

Scheme 20



(29) (72) (73) (74)

Scheme 21

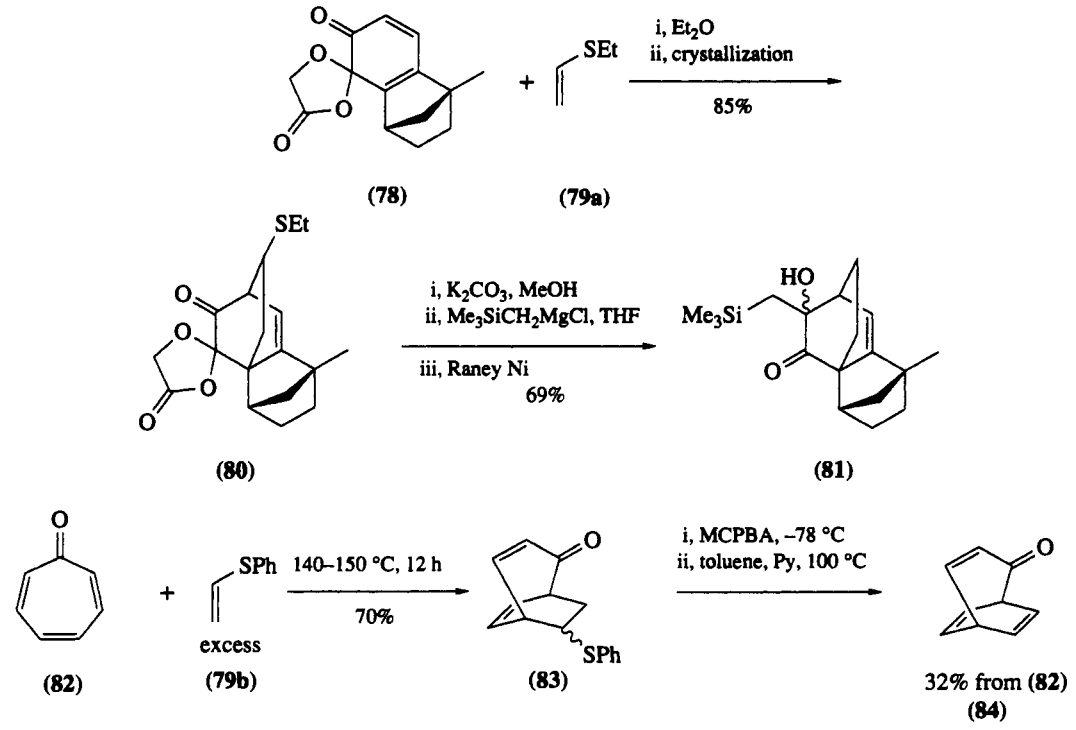


(75) (76) (77)

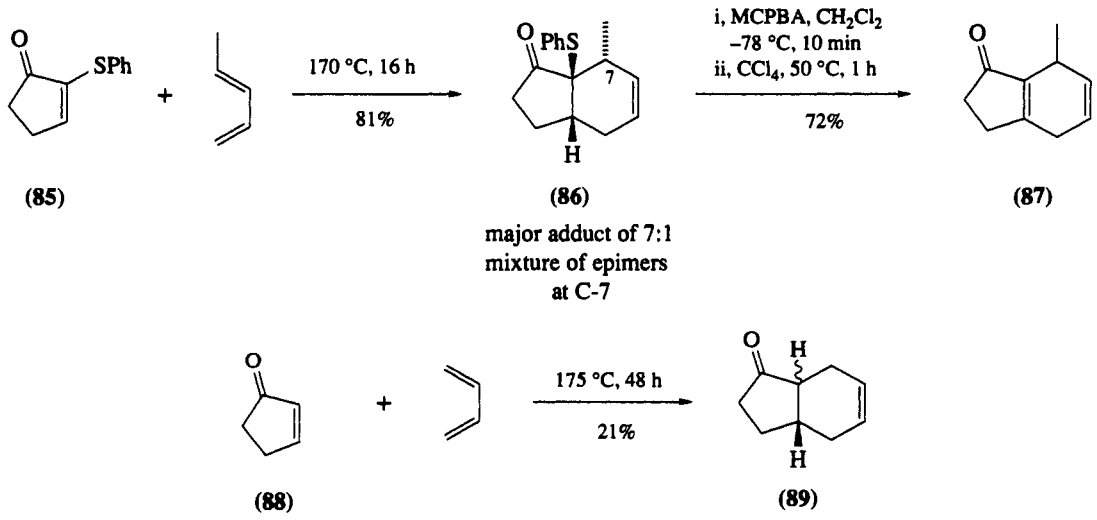
Scheme 22

As already mentioned, vinyl sulfides are electron-rich dienophiles and react, therefore, preferentially with electron-poor dienes, *i.e.* in 'inverse-electron-demand' processes such as those depicted in Scheme 23.[24,25] The auxiliary sulfur substituent may be removed at some stage after the cycloaddition, either by hydrogenolysis (*e.g.* → **81**)[24] or oxidation/sulfenic acid elimination (*e.g.* → **84**),[25] illustrating the potential of vinyl sulfides as ethylene or acetylene equivalents.

However, enones carrying a sulfide group at C_α react (similar to sulfoxide **76**) much more rapidly with 'classical' dienes than the corresponding C_α-unsubstituted enones (Scheme 24).[26]



Scheme 23

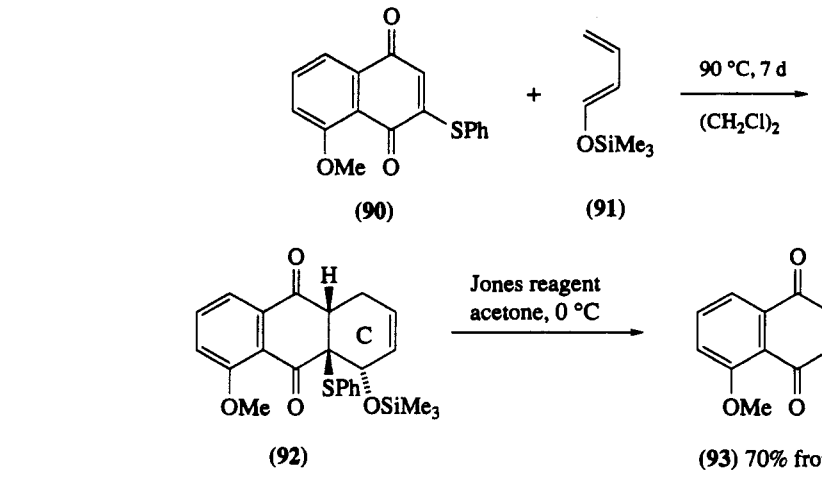


Scheme 24

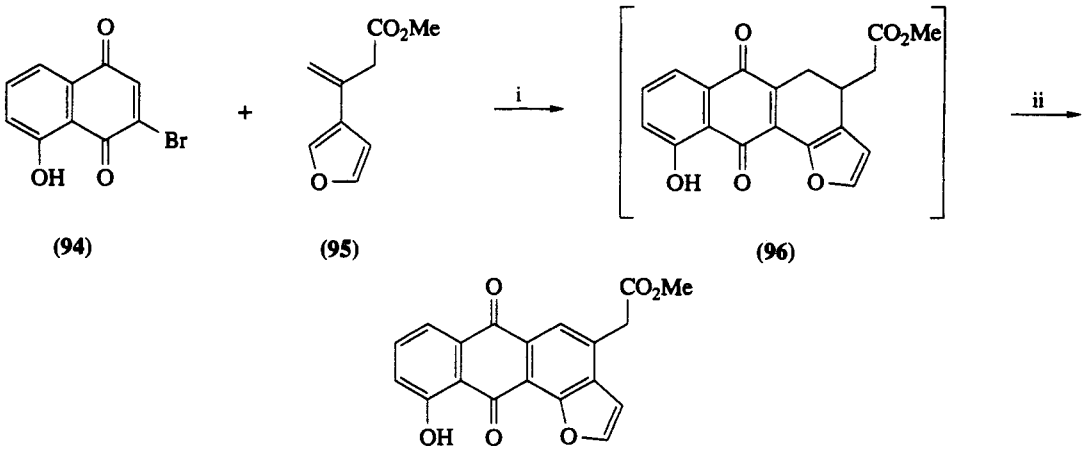
The regiochemical control provided by the sulfide moiety is a further asset, most strikingly exploited in the synthesis of anthracyclines (*cf.* Scheme 25).[27] The phenylthio group in cycloadduct (**92**) also prevents aromatization of the newly formed ring c, allowing its appropriate functionalization *via* enone (**93**).

4.1.2.4 Alkenyl Halogen Derivatives

Kishi's synthesis of aklavinone (**625**) (Section 4.1.8.4) exploits the regiodirecting bias of a bromide substituent in dienophile (**94**) (which parallels that of the phenylthio group in **90**) (Scheme 26).[28] The initially formed cycloadduct underwent spontaneous elimination of HBr (neutralized by $SrCO_3$) and oxidation (air, Pr^i_2NEt) to give the anthraquinone product (**97**) as the exclusive regioisomer.



Scheme 25

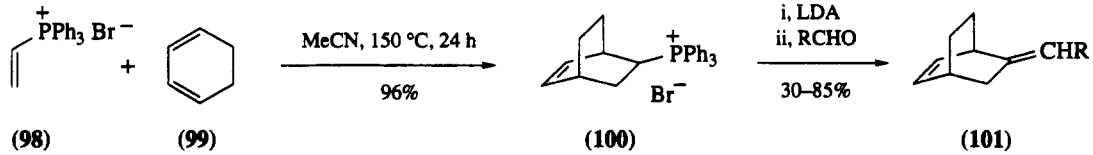


i, (**94**) + (**95**) (3 equiv.), C_6H_6, $SrCO_3$, 4,4'-thiobis(6-t-butyl-3-methylphenol), reflux;
ii, air, Pr^i_2NEt, $CHCl_3$, r.t.

Scheme 26

4.1.2.5 Vinylphosphonium Salts

Vinyltriphenylphosphonium bromide (**98**) reacted with a number of dienes to form cyclic phosphonium salts which afford *exo*-methylene compounds *via* a subsequent Wittig reaction (Scheme 27).[29]



Scheme 27

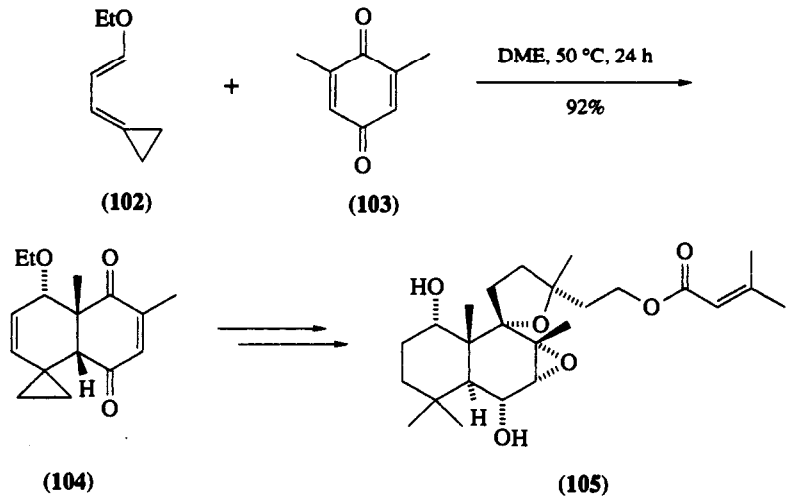
4.1.3 HETEROATOM-SUBSTITUTED DIENES

The efficiency and regioselectivity of intermolecular [4 + 2] cycloadditions can be improved by placing heteroatom substituents not only on the dienophile but also on the diene partner, as already illustrated

by several examples in the foregoing section. Heteroatom-substituted dienes and their use in the Diels–Alder reaction were reviewed extensively in 1981;[30] therefore discussion here will be limited to representative examples and some more recent developments.

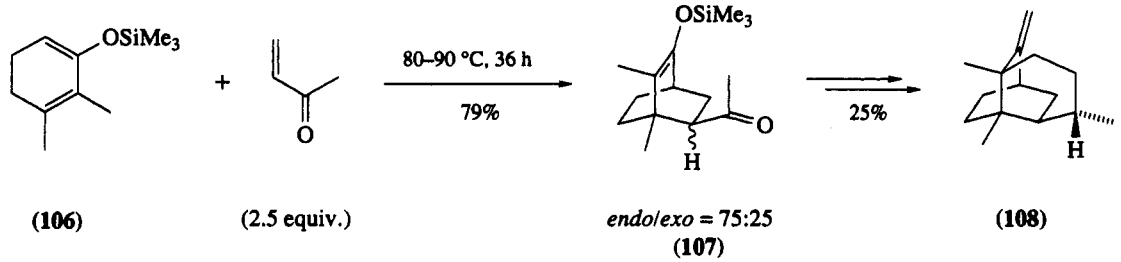
4.1.3.1 Oxygen-substituted Dienes

Monoalkoxy- and trimethylsilyloxy-1,3-butadienes are electron-rich dienes and have been extensively used in Diels–Alder reactions with electron-poor dienophiles, as already shown in Section 4.1.2 (Schemes 8 and 25). A very recent example is the synthesis of the labdane diterpenoid (±)-erigerol (**105**), which centers on the key step (**102**) + (**103**) → (**104**) (Scheme 28).[31] Diene (**102**) features, apart from the regiodirecting ethoxy group, a cyclopropylidene moiety and, thus, serves as an equivalent for the much less reactive 1-ethoxy-4-methyl-1,3-pentadiene. Indeed, the depicted Diels–Alder reaction proceeded efficiently under mild conditions in a highly regio- and 'C=O *endo*'-selective manner.



Scheme 28

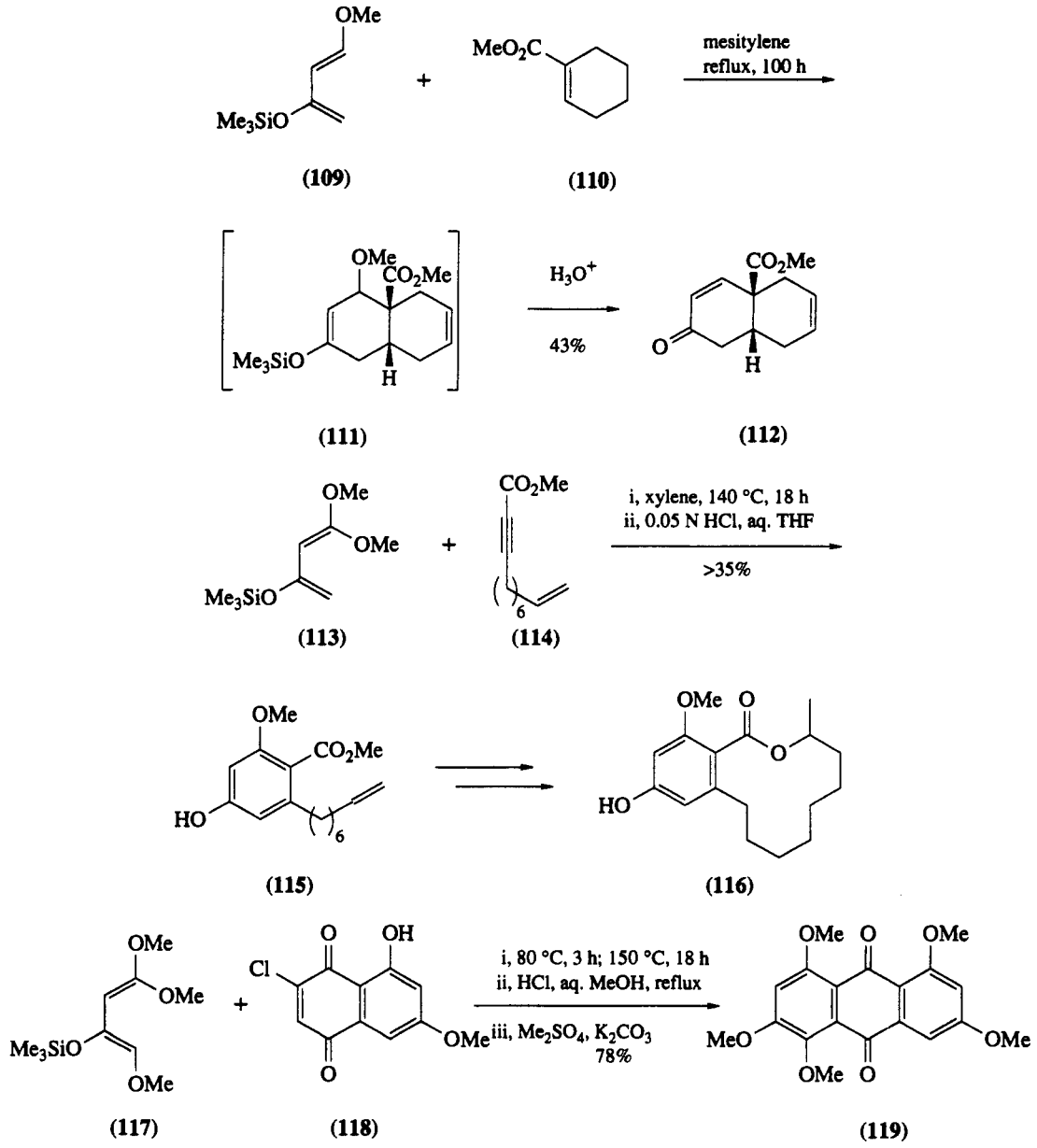
[4 + 2] Cycloaddition of the endocyclic 2-silyloxydiene (**106**) to methyl vinyl ketone gave the bicyclo[2.2.2]octenes (**107**) with a silyloxy-directed regiochemistry. The major *endo* product was then transformed into the tricyclic sesquiterpene (±)-seychellene (**108**) (Scheme 29).[32]



Scheme 29

One of the most popular dioxygenated dienes is 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**109**), the so-called 'Danishefsky diene' (Scheme 30). The elegant application of this and related polyoxygenated dienes in synthesis was reviewed in 1981.[30,33] [4 + 2] Cycloadditions of diene (**109**), with typical electron-poor dienophiles, display increased reactivity and regiochemical control owing to the synergism of the two oxygen atoms. Acidic hydrolysis of the initial cycloadducts readily affords cyclohexenones, phenols or cyclohexadienones (*cf.* Section 4.1.2, Schemes 12, 17, 18 and 21). A pertinent example is the

addition of (**109**) to the relatively unreactive dienophile (**110**) to yield the angularly substituted cyclohexenone (**112**), an intermediate for a synthesis of vernolepin.[34] The related 1,1-dimethoxy-3-trimethylsilyloxybutadiene (**113**) reacts readily with alkynic dienophiles to give, after treatment with aqueous acid, polysubstituted phenols. This highly regioselective type of transformation was applied to a synthesis of the macrolide lasiodiplodin (**116**).[35]

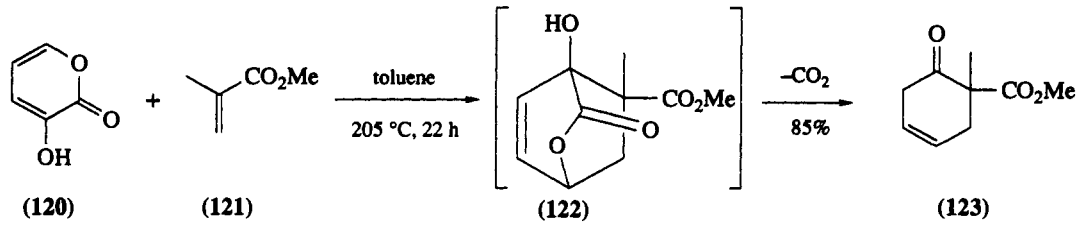


Scheme 30

Even the tetrasubstituted diene (**117**) underwent smooth cycloaddition to *p*-quinones, thereby opening a convenient route to polyoxygenated anthraquinone pigments, *e.g.* (**117**) + (**118**) → (**119**).[36]

Diels–Alder reactions of furans were the subject of a recent review (1986).[37] Their intermolecular versions profit notably from high-pressure conditions (Section 4.1.4.2.1) or the use of benzynes as dienophiles (Section 4.1.7).

Another type of oxacyclic diene are the pyrones, *e.g.* (**120**),[38] which react with typical dienophiles at temperatures ranging from 80 to 205 °C with spontaneous loss of carbon dioxide (Scheme 31).

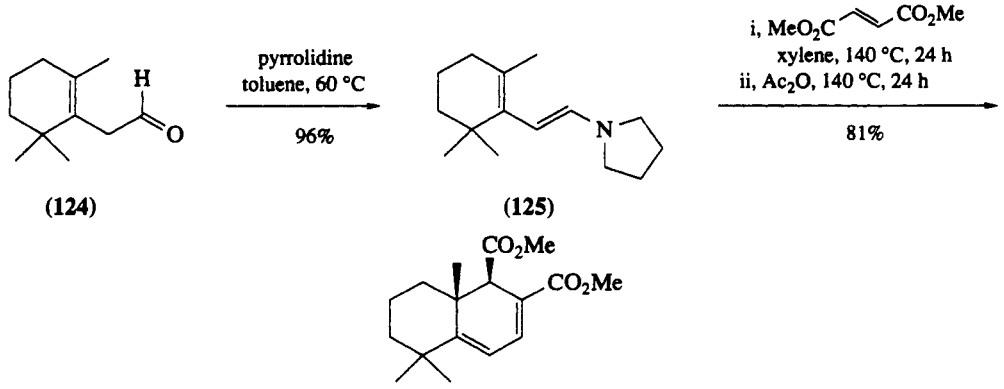


(120) (121) (122) (123)

Scheme 31

4.1.3.2 Nitrogen-substituted Dienes

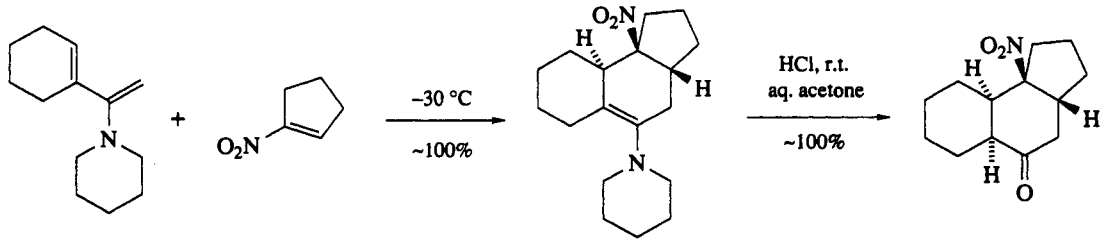
Acyclic dienamines are relatively unstable, but very reactive towards electron-poor dienophiles as described in a review article (1984).[39] A more recent example shows the preparation of sterically encumbered 1-amino-1,3-diene (**125**) and its, nevertheless, efficient and highly stereoselective [4 + 2] cycloaddition to dimethyl fumarate (Scheme 32).[40] Elimination of pyrrolidine, by heating the non-isolated cycloadduct with acetic anhydride, afforded hexahydronaphthalene (**126**), a key intermediate for a synthesis of drimane-type sesquiterpenes.



(124) (125) (126)

Scheme 32

2-Dialkylamino-1,3-dienes are even less stable, but may react at low temperature, *e.g.* with nitroalkenes. The exclusive formation of one regio- and stereo-isomer, (**127**) + (**128**) → (**129**), resulting from *endo* orientation of the nitro group, is exemplified in Scheme 33.[41]

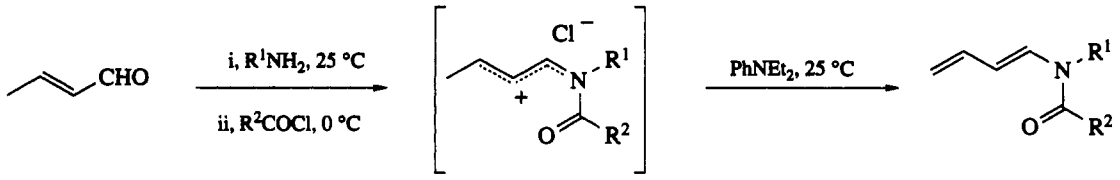


(127) (128) (129) (130)

Scheme 33

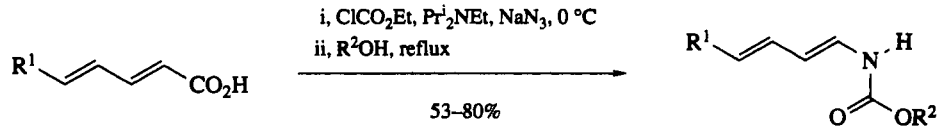
N-Acylaminodienes are more stable than the corresponding dienamines and are easily accessible in one synthetic operation from conjugated enals, (**131**) → (**132**) → (**133**),[42] or alternatively from dienoic acids, (**134**) → (**135**) (Scheme 34).[43]

Dienamides (**133**) readily undergo intermolecular [4 + 2] cycloadditions, as exemplified by the highly *endo*-selective reaction of (**136**) with maleic anhydride giving (**137**) (Scheme 35).[42b] However, the main advantage of the simple diene preparation (**131**) → (**133**) is the facile 'introduction' of an alkenic chain,



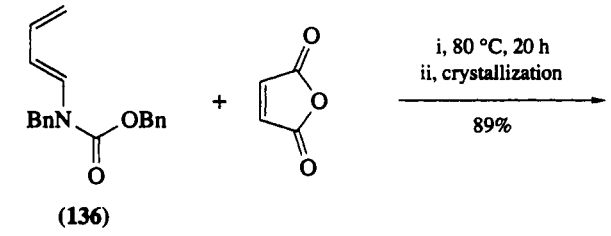
(131) (132) (133)

56–95% from (131)

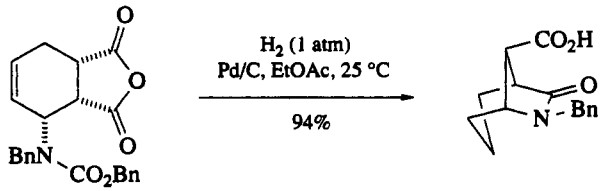


(134) (135)

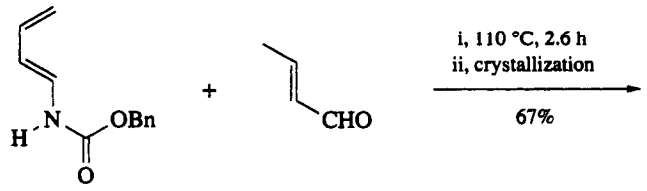
Scheme 34



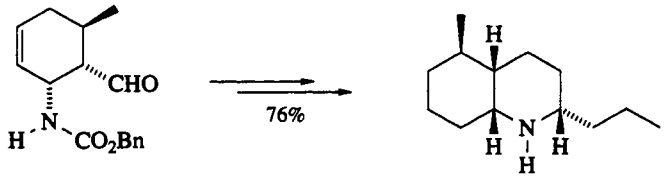
(136)



(137) (138)



(139) (140)



(141) (±)-(142)

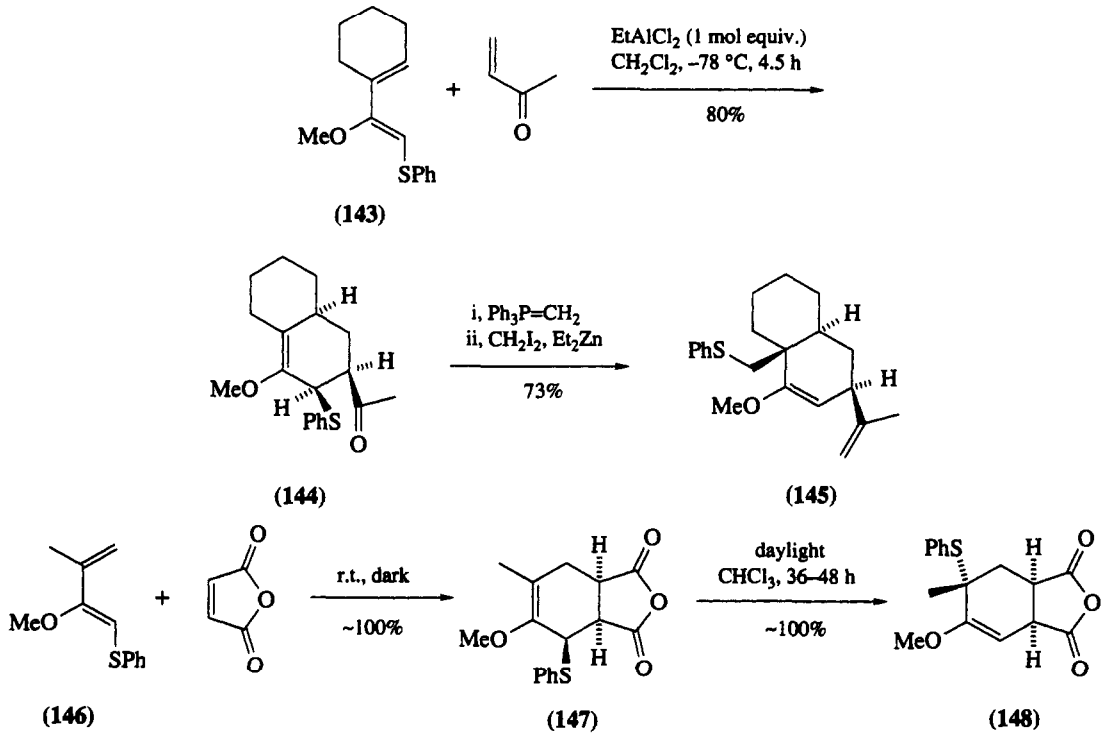
Scheme 35

either as substituent R^1 or R^2. Hence dienamides (**133**) are versatile precursors for intramolecular Diels–Alder reactions (Chapter 4.4), *e.g.* as applied to the stereoselective conversion of (*S*)-norvaline into enantiomerically pure (–)-pumiliotoxin C (**142**).[42c] A synthesis of the racemic alkaloid (**142**) features the regio- and 'CHO *endo*'-selective intermolecular Diels–Alder reaction (**139**) + (**140**) → (**141**).[43b] An enantioselective version of this approach is presented in Section 4.1.6.2.1(ii) (Scheme 84).

4.1.3.3 Sulfur-substituted Dienes

1-(Phenylthio)-1,3-butadienes undergo sulfur-directed Diels–Alder reactions to form adducts from which the sulfur moiety can be removed by reduction, or (after oxidation to the sulfoxide) by elimination or 2,3-sigmatropic rearrangement (*cf.* Section 4.1.2, Schemes 12, 14).[30]

(*Z*)-2-Methoxy-1-(phenylthio)-1,3-butadienes react with methyl vinyl ketone and with 2-cyclohexen-1-one under catalysis by magnesium bromide or ethylaluminum dichloride. This provides exclusively the 'C=O *endo*' adducts in which the regiochemistry is completely controlled by the sulfur substituent despite the juxtaposed influence of the OMe group, *e.g.* (**143**) → (**144**) (Scheme 36).[44a]

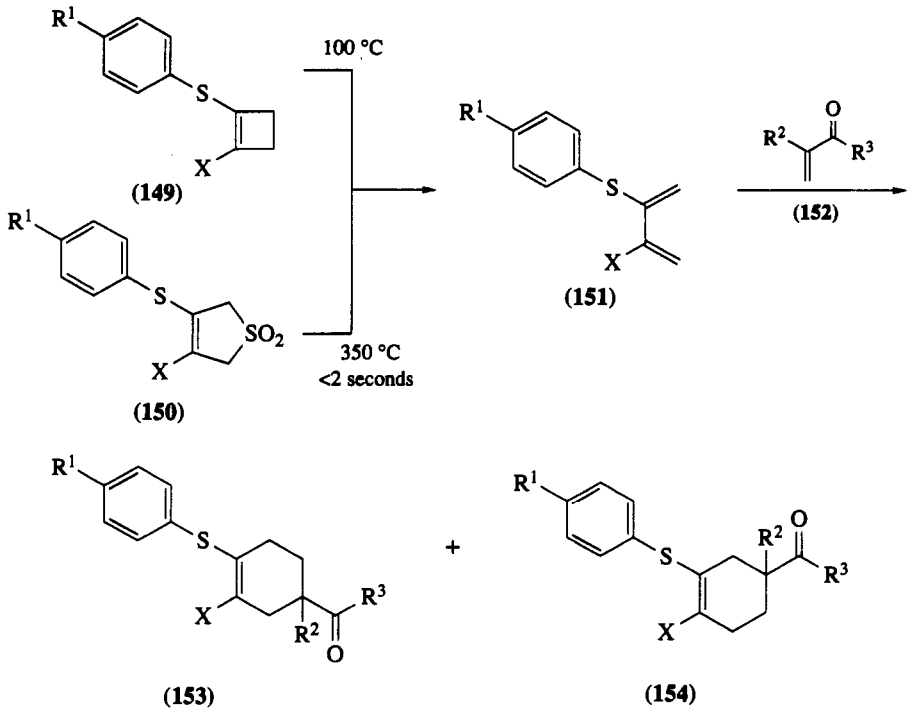


Scheme 36

The allylic position of the sulfide group in the cycloadducts may be employed for 2,3-sigmatropic reactions, as demonstrated by the alkenation/sulfur ylide rearrangement sequence (**144**) → (**145**).[44a] A noteworthy allyl rearrangement (**147**) → (**148**) was observed on exposing the related Diels–Alder adduct (**147**) to daylight; the thiophenyl group underwent a formal 'antarafacial migration' consistent with a free-radical chain mechanism.[44b]

1,3-Butadienes carrying an aryl sulfide substituent at C-2 also display a sulfur-dominated regiochemistry which overrides the influence of a C-3 positioned OMe, OAc or SO_2Ph group (Scheme 37, Table 1).[45] Dienes (**151**), prepared by electrocyclic ring opening or chelotropic SO_2 extrusion, reacted with methyl vinyl ketone, methacrolein or methyl acrylate to give, preferentially, regioisomers (**153**). Table 1 highlights the Lewis acid reinforced regioselectivity, provided that the competing substituent (X) is a relatively weak Lewis base (*cf.* entries 4/5, 6/7).

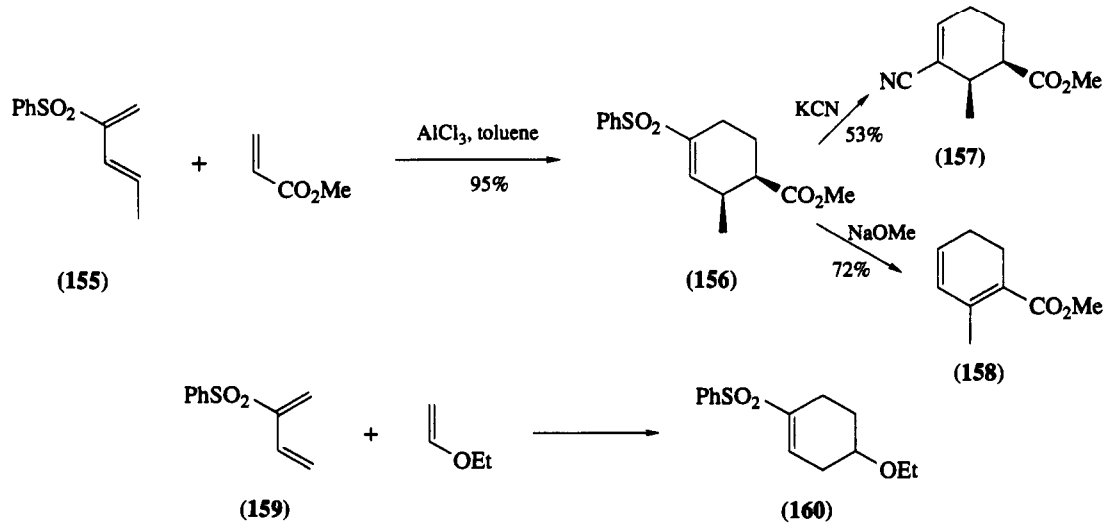
2-(Phenylsulfonyl)-1,3-dienes, *e.g.* (**155**) and (**159**), show an interesting 'dual-electron-demand' reactivity, *i.e.* they react with both electron-deficient and electron-rich alkenes (Scheme 38).[46] Adduct (**156**) can be transformed to its elimination product (**158**) or, more interestingly, to nitrile (**157**) *via* simple treatment with KCN.



Scheme 37

Table 1 Diels–Alder Reactions of 2-Substituted 3-Arylthiobuta-1,3-dienes (Scheme 37)

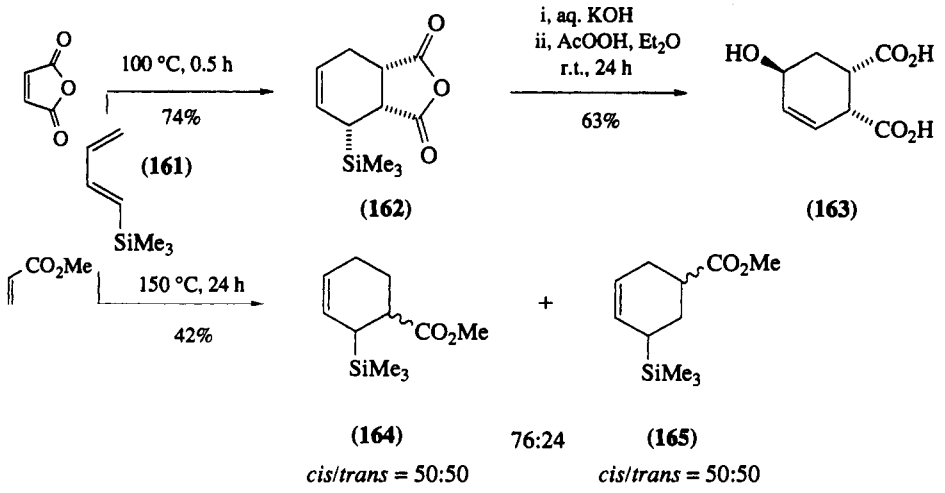
Entry	*Diene* R^1	*Diene* X	*Dienophile* R^2	*Dienophile* R^3	*Solvent*	*Lewis acid*	*Temp.* (°C) (*time*, h)	*Yield* (%) (153) + (154)	*Ratio* (153)/(154)
1 **a**	H	H	H	Me	Toluene	None	110	97	91:9
2 **b**	H	OMe	Me	H	Methacrolein	None	Reflux	72	89:11
3 **c**	H	OAc	Me	H	Methacrolein	None	Reflux (18)	84	90:10
4 **d**	OMe	OAc	Me	H	Methacrolein	None	Reflux (17)	82	93:7
5 **d**	OMe	OAc	Me	H	Methacrolein	$BF_3{\cdot}OEt_2$	r.t. (1.6)	94	>98:<2
6 **e**	H	SO_2Ph	H	OMe	*p*-Xylene	None	200 (8)	98	75:25
7 **e**	H	SO_2Ph	H	OMe	*p*-Xylene	$ZnCl_2$	r.t. (72)	85	~100:0



Scheme 38

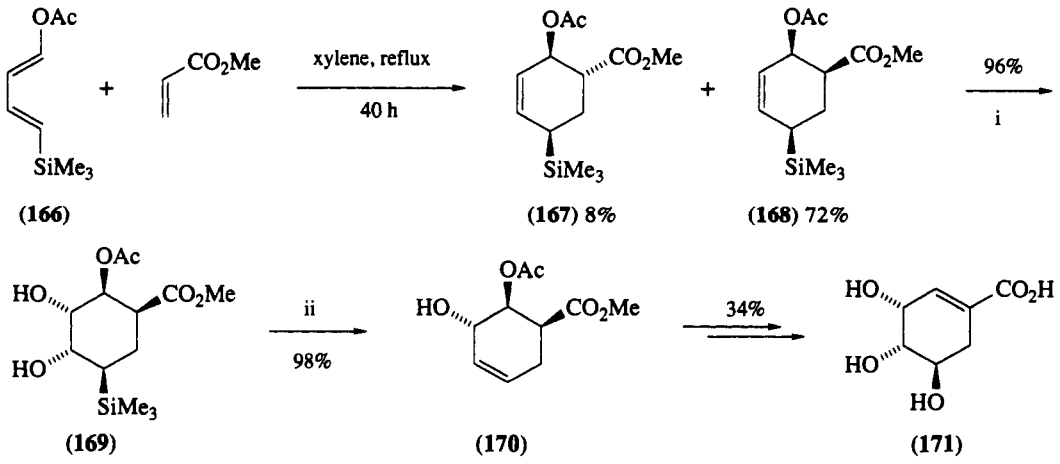
4.1.3.4 Silicon-, Tin- and Boron-substituted Dienes

1-Silylated 1,3-butadienes, *e.g.* (**161**), are potentially attractive reaction partners in [4 + 2] cycloadditions since the adducts are prone to various functionalizations of the allylsilane. For example, addition product (**162**) gave allylic alcohol (**163**) on hydrolysis/oxidation (Scheme 39).[47] However, addition of diene (**161**) to methyl acrylate is inefficient and largely devoid of regio- and stereo-chemical control.



Scheme 39

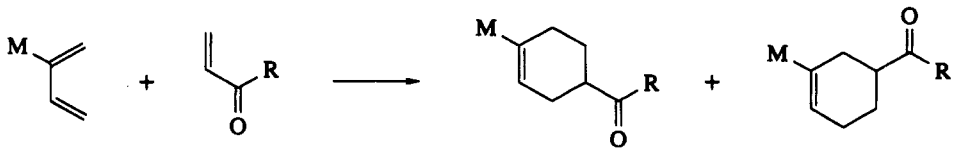
Nevertheless, because of its weak influence, the silyl substituent hardly interferes with more potent regiochemical control elements, as demonstrated by the acetoxy-directed Diels–Alder reaction of diene (**166**) with methyl acrylate (Scheme 40).[48] The major *endo* product (**168**) was then converted to (±)-shikimic acid (**171**).



i, OsO_4 (cat.)/*N*-methylmorpholine *N*-oxide, Bu^{t}OH, Me_2CO, H_2O;
ii, *p*-TsOH (benzene), reflux, 20 min

Scheme 40

[4 + 2] Cycloadditions of 2-triethylsilyl- and 2-tributylstannyl-1,3-butadienes (**172**) to ethyl acrylate and methyl vinyl ketone also proceeded with moderate regioselectivities which could be significantly enhanced by Lewis acid catalysis in favor of products (**174**) (Scheme 41, Table 2).[49] The resulting cyclohexenylstannanes (**174**; M = $SnBu_3$) show potential for C—C coupling reactions.



(172) (173) (174) (175)

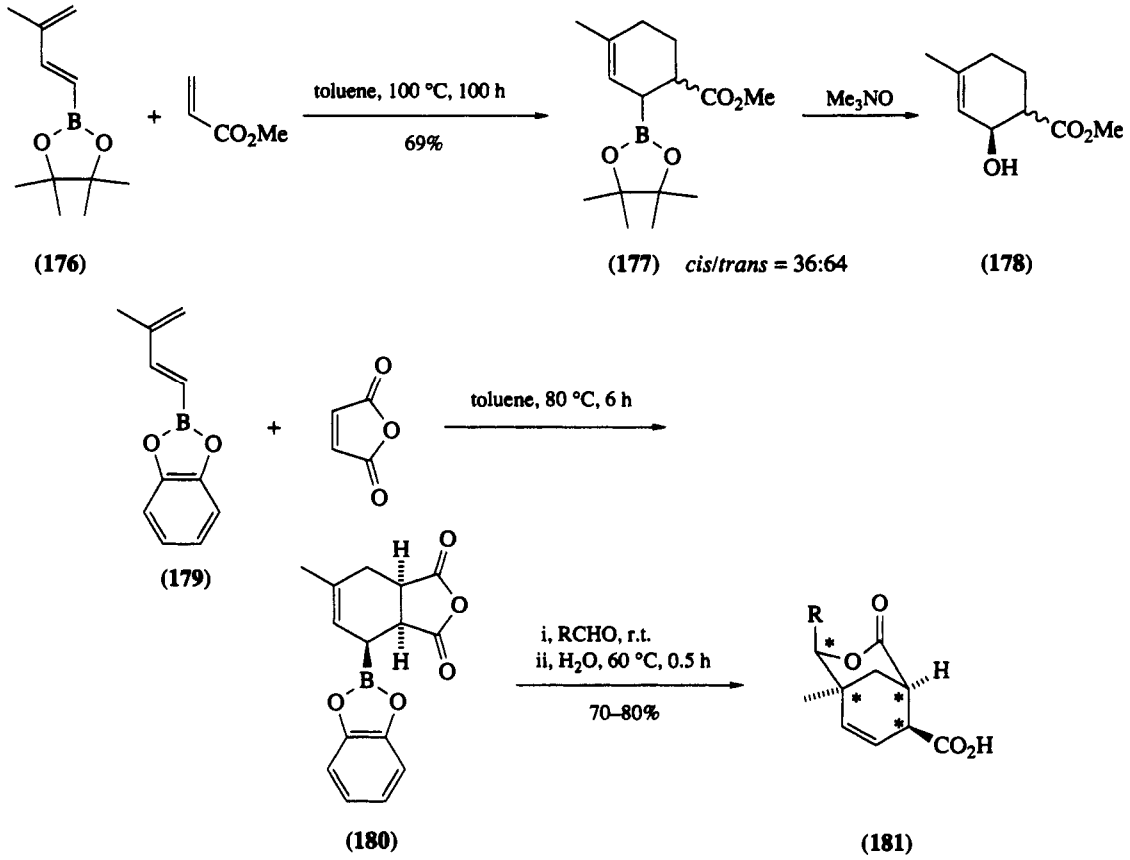
Scheme 41

Table 2 Diels–Alder Reactions of 2-Triethylsilyl- and 2-Tributylstannyl-1,3-butadienes with Conjugated Enoyl Compounds (Scheme 41)

Entry	*Diene M*	*Dienophile R*	*Solvent*	*Lewis acid*[a]	*Temp.* (°C) *(time,* h)	*Yield (%) (174) + (175)*	*Ratio (174)/(175)*
1 **a**	$SiEt_3$	OEt	Benzene	None	Reflux (6)	77	77:23
2 **a**	$SiEt_3$	OEt	Benzene	$BF_3{\cdot}Et_2O$	b	90	88:12
3 **b**	$SnBu_3$	Me	Benzene	None	Reflux (12)	50	75:25
4 **b**	$SnBu_3$	Me	CH_2Cl_2/hexane	Et_2AlCl	r.t.	75	94:6
5 **b**	$SnBu_3$	Me	$C_2H_4Cl_2$	Et_2BCl	r.t. (12)	69	95:5
6 **b**	$SnBu_3$	Me	CH_2Cl_2	$TiCl_4$	–78 to 0	31	98:2

[a] 0.1–0.3 mol equiv. of Lewis acid used. [b] Not reported.

1,3-Dienylboronate (**176**), easily available by hydroboration of 2-methylbut-1-en-3-yne, underwent a highly regiocontrolled, but only moderately *exo*-selective, Diels–Alder addition to methyl acrylate, yielding a mixture of *cis/trans* isomers (**177**) (Scheme 42).[50] The corresponding [4 + 2] cycloaddition of diene (**179**) to maleic anhydride gave only the *endo* product (**180**). Adducts (**177**) were oxidized to afford



(176) (177) *cis/trans* = 36:64 (178)

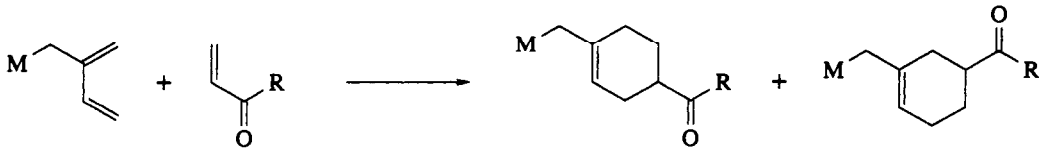
(179) (180) (181)

Scheme 42

allylic alcohols (**178**). More spectacular is the stereoselective addition of aldehydes to the allylboronate unit of adduct (**180**) followed by a lactonization. The resulting lactones (**181**) contain four stereogenic centers with perfectly controlled relative configuration.

4.1.3.5 2-[(Silyl-, Stannyl- and Thio-)methyl]-1,3-dienes

2-Trimethylsilylmethyl-1,3-butadiene (**182**; M = $SiMe_3$) is an excellent diene for highly regio- and stereo-selective Diels–Alder reactions with nonsymmetrical dienophiles (Scheme 43, Table 3).[51] Although the silicon atom is not directly attached to the diene system, the '*para*' selectivity of Diels–Alder reactions with methyl acrylate is more pronounced with (**182**; M = $SiMe_3$) than with isoprene (**182**; M = H) (*cf.* entries 1/3, 2/4). Stannylisoprene (**182**; M = $SnMe_3$) shows an even higher regiodirecting influence on thermal [4 + 2] cycloadditions to methyl vinyl ketone (*cf.* entries 5, 7). However, under catalysis by $AlCl_3$, virtually 100% regiochemical control was observed on Diels–Alder reactions of (**182**; M = $SiMe_3$) (entries 4, 6).



(**182**) (**173**) (**183**) (**184**)

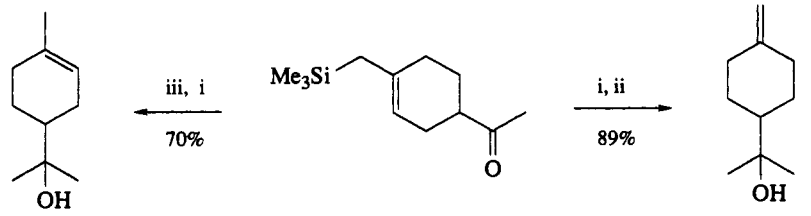
Scheme 43

Table 3 Diels–Alder Reactions of Isoprene, 2-Trimethylsilylmethyl- and 2-Trimethylstannylmethyl-1,3-butadienes with Conjugated Enoyl Compounds (Scheme 43)

Entry	*Diene M*	*Dienophile R*	*Lewis acid*[a]	*Temp.* (°C) *(time,* h)	*Yield (%) (183) + (184)*	*Ratio (183)/(184)*
1[b] **a**	H	OMe	None	120 (6)	83	70:30
2[b] **a**	H	OMe	$AlCl_3$	10–20 (3)	50	95:5
3 **b**	$SiMe_3$	OMe	None	80 (46)	58	84:16
4 **b**	$SiMe_3$	OMe	$AlCl_3$	50–60 (2)	75	99.5:0.5
5 **c**	$SiMe_3$	Me	None	80 (36)	83	83:17
6 **c**	$SiMe_3$	Me	$AlCl_3$	15–20 (3.5)	64	100:0
7 **d**	$SnMe_3$	Me	None	80 (69)	94	92:8

[a]0.1 equiv. of $AlCl_3$ in benzene. [b]Ref. 57b.

The exclusively obtained adduct (**183c**) has been converted to monoterpenes by simple reaction sequences involving protodesilylation of the allylsilane unit either by HCl/MeOH (→ **185**) or by fluoride/DMSO (→ **186**) (Scheme 44).

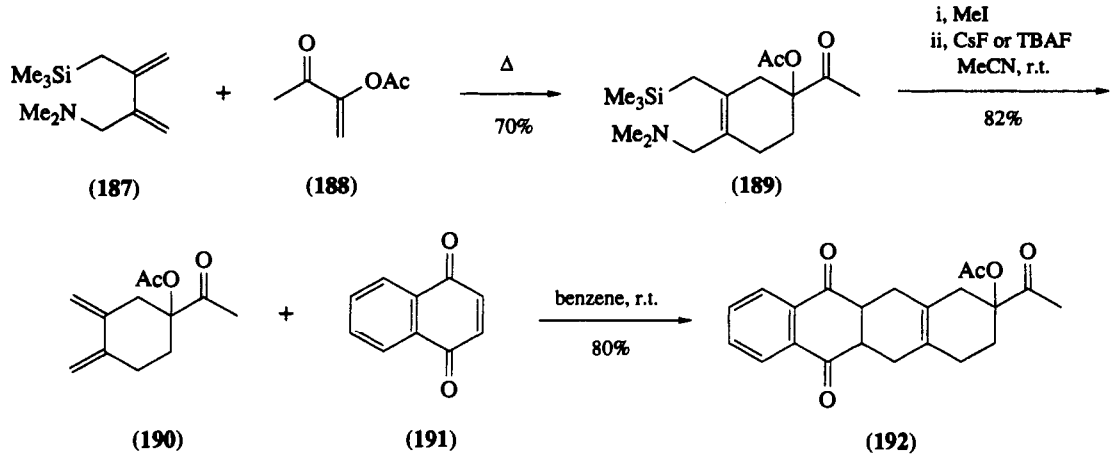


(**186**) (**183c**) (**185**)

i, MeMgBr, Et_2O; ii, HCl, MeOH; iii, KF, DMSO, 120 °C, 12 h

Scheme 44

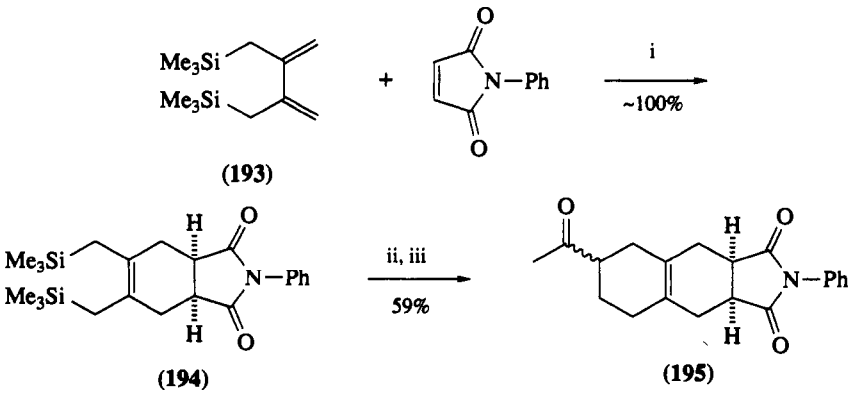
As an extension of this work, the use of 2-(*N*-dimethylaminomethyl)-3-(trimethylsilylmethyl)-1,3-butadiene (**187**) as a '2,2'-biallyl radical' equivalent has been demonstrated (Scheme 45).[52] For example, the initial cycloadduct (**189**), obtained from 3-acetoxy-3-buten-2-one, afforded on 1,4-elimination (*cf.* Scheme 127) 1,2-dimethylenecyclohexane (**190**) which reacted with a second dienophile to give the demethoxyanthracycline precursor (**192**) (*cf.* Scheme 140).



(**187**) (**188**) (**189**) (**190**) (**191**) (**192**)

Scheme 45

Independently, 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene (**193**) was shown to be a similar 'conjunctive' reagent for tandem Diels–Alder reactions (Scheme 46).[53] In this case the initial cycloadducts were subjected to an oxidative bis-desilylation with NBS and the resulting 1,2-dimethylenecyclohexanes were directly submitted to the second Diels–Alder step, as demonstrated by the reaction sequence (**193**) → (**194**) → (**195**).



(**193**) (**194**) (**195**)

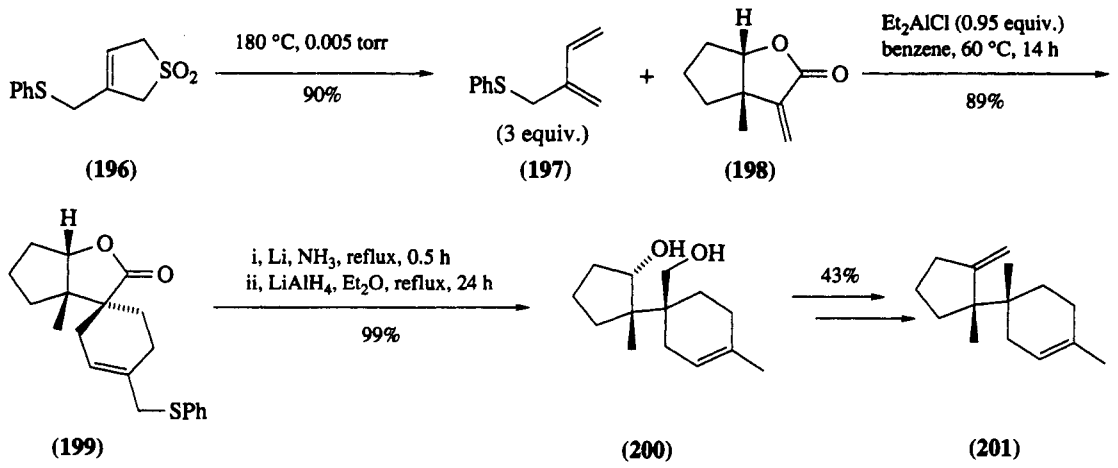
5:1 stereoisomer mixture

i, toluene, reflux; ii, NBS, THF, propylene oxide, –100 to –78 °C, 1 h; iii, MVK, –78 °C to r.t., 16 h

Scheme 46

An elegant diastereocontrolled synthesis of the sesquiterpene trichodiene (**201**) relies on a smooth regio- and stereo-selective Diels–Alder reaction of 2-[(phenylthio)methyl]-1,3-butadiene (**197**) with the α-methylenelactone (**198**), giving the '*para*' adduct (**199**) in 89% yield (Scheme 47).[54]

Analogous additions of isoprene or 2-[(trimethylsilyl)methyl]-1,3-butadiene (**182**; M = $SiMe_3$) to dienophile (**198**) resulted in 75:25 or 95:5 mixtures of '*para*' and '*meta*' adducts, respectively. Although obtained with good selectivity, the major silyl-substituted adduct furnished, on protodesilylation, an inseparable mixture of endo- and exo-cyclic alkenes. In favorable contrast, the exclusively formed adduct (**199**) allowed a quantitative reductive removal of the sulfur auxiliary without migration of the alkenic bond.



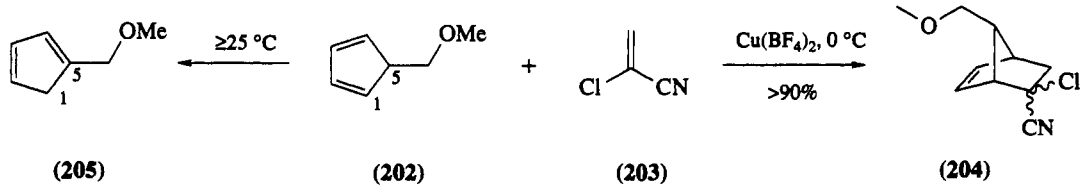
Scheme 47

4.1.4 LEWIS ACID AND MEDIUM PROMOTED DIELS–ALDER REACTIONS

4.1.4.1 Lewis Acids

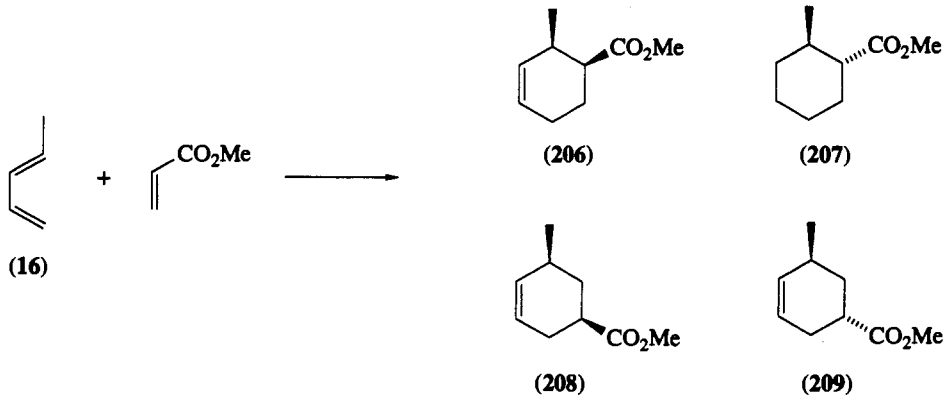
The discovery by Yates and Eaton (1960) that $AlCl_3$ dramatically accelerates [4 + 2] cycloadditions of maleic anhydride, dimethyl fumarate and *p*-benzoquinone to anthracene[55] had a remarkable impact on the scope and selectivity of the Diels–Alder reaction. Since then, it has been found that a plethora of Lewis acids, such as $EtAlCl_2$, Et_2AlCl, $BF_3{\cdot}OEt_2$, $TiCl_4$, $TiCl_2(OR)_2$, $SnCl_4$, $ZnCl_2$, $MgBr_2$, *etc.*, increase not only the rate but, moreover, the regio, *endo* and π-face selectivities of this process *via* coordination with the dienophile partner (*e.g.* to a conjugated C=O or C=N moiety). The latter issue, namely the outstanding role of Lewis acids in π-facially controlled Diels–Alder reactions, will be discussed in Sections 4.1.5 and 4.1.6. The effects of Lewis acids on the rate and regiochemistry of the Diels–Alder reaction are ascribed to a lowering of the frontier orbital energies and an alteration of the atomic orbital coefficients in the dienophile.[3]

A well-known example which underlines the vital advantage of this rate acceleration is the $Cu(BF_4)_2$catalyzed [4 + 2] cycloaddition of α-chloroacrylonitrile (**203**) to the 5-substituted cyclopentadiene (**202**).[56] Owing to the selective coordination of the copper(I) ion with the nitrile group of (**203**), the desired adduct (**204**) was formed readily at 0 °C, thus avoiding the otherwise dominating 1,5-rearrangement (**202**) → (**205**) (Scheme 48).



Scheme 48

The general Lewis acid induced enhancement of rates, regio- and *endo*-selectivities is clearly demonstrated by the [4 + 2] cycloaddition of (*E*)-2,4-pentadiene (**16**) to methyl acrylate (Scheme 49, Table 4).[57a] The uncatalyzed reaction at 120 °C shows an 84:16 regiochemical preference in favor of the '*ortho*' products (**206**) and (**207**), but almost no *endo* selectivity. These values improve only marginally at a reaction temperature of 25 °C (requiring 70 days) but rise sharply to ratios of 98:2 ('*ortho*/*meta*') and 95:5 (*endo*/*exo*) in the presence of $AlCl_3$ (0.15 mol equiv.) at 10–20 °C (3 h). Similar regiochemical improvements were observed on the corresponding additions of isoprene and its derivatives to methyl acrylate, methyl vinyl ketone and acrolein (Scheme 43, Table 3; Scheme 61, Table 10).[57b]

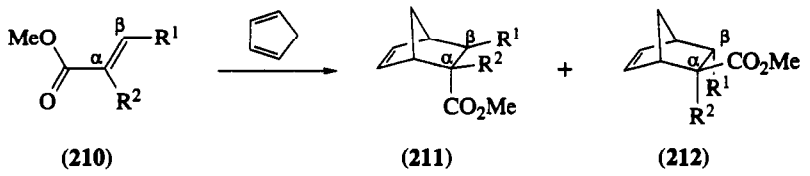


Scheme 49

Table 4 Influence of $AlCl_3$ on the Regio and *Endo* Selectivity of the Diels–Alder Reaction between (*E*)-2,4-Pentadiene and Methyl Acrylate in Benzene (Scheme 49)

Entry	*Temp.* (°C) *(time,* h)	*$AlCl_3$* (mol equiv.)	*Yield (%)* *(206) + (207) + (208) + (209)*	*Ratio* *(206)/(207)/(208)/(209)*
1	120 (6)	0	53	45.4:38.6:10.6:5.4
2	25 (1680)	0	39	51.3:38.7:7.3:2.7
3	10–20 (3)	0.15	50	93.1:4.9:1.9:0.1

Alkene dienophiles bearing two different substituents at C-1 or, *trans* related, at C-1 and C-2 often react with low *endo/exo* selectivities (*cf.* Scheme 50, Table 5). For example, the thermal Diels–Alder reactions of cyclopentadiene with methyl (*E*)-crotonate (**210b**) (entry 4) and methyl methacrylate (**210c**) (entry 6) show approximately equal proportions of products with an *endo*-oriented methoxycarbonyl or methyl group.[57c] Coordination of the CO_2Me unit clearly favors its *endo* orientation in the reaction of acrylate (**210a**) (entry 3) and crotonate (**210b**) (entry 5). However, the *endo*-directing influence of the C_α-methyl group was only poorly counteracted in the $AlCl_3$-promoted addition of methyl methacrylate (**210c**) (entry 7). Nevertheless, even dienophiles with 'competing' geminal substituents can react in a highly *endo/exo* selective manner depending on the substituents and the type of Lewis acid (*cf.* Scheme 111, Table 32). This reference to Section 4.1.6.3.3 may underline the vital importance of an almost complete *endo/exo* selectivity as a prerequisite for achieving useful asymmetric Diels–Alder reactions.



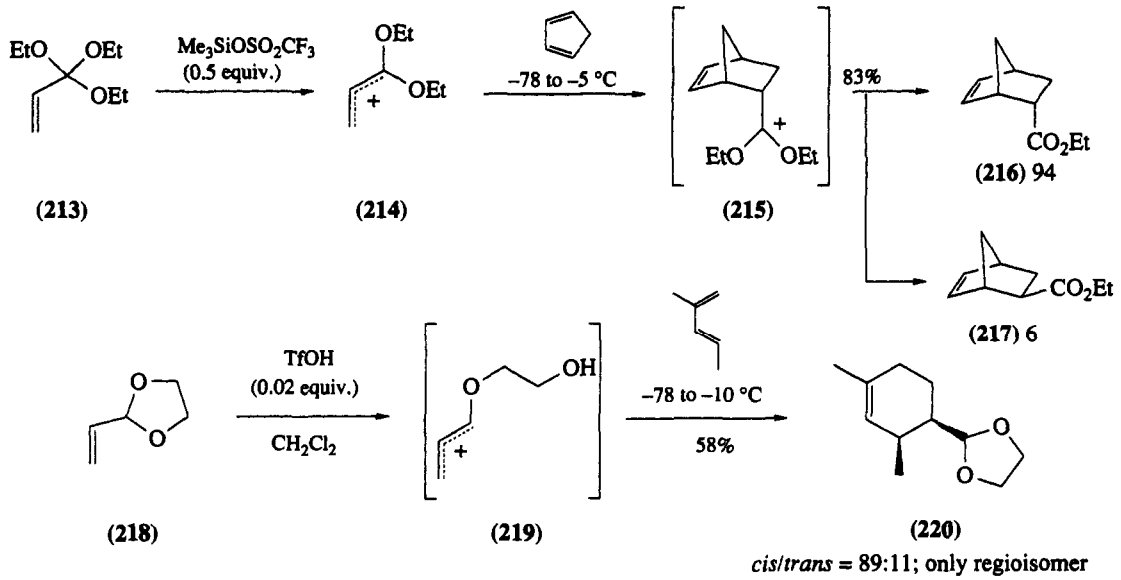
(210) (211) (212)

Scheme 50

Table 5 Influence of $AlCl_3$ on the *Endo/Exo* Selectivity of Diels–Alder Reactions between Cyclopentadiene and Methyl Enoates (Scheme 50)

Entry	*R^1*	*R^2*	*Lewis acid* (mol equiv.)	*Solvent*	*Temp.* (°C)	*Yield (%)* *(211) + (212)*	*Ratio (211)/(212)*	*Ref.*
1 **a**	H	H	—	CH_2Cl_2	0	22–51	82:18	57d
2 **a**	H	H	$AlCl_3{\cdot}OEt_2$ (0.1)	CH_2Cl_2	0	79–91	96:4	57d
3 **a**	H	H	$AlCl_3{\cdot}OEt_2$ (0.1)	CH_2Cl_2	–70	67–72	99:1	57d
4 **b**	Me	H	—	C_6H_6	30	—	54:46	57c
5 **b**	Me	H	$AlCl_3$ (0.9)	C_6H_6	30	—	94:6	57c
6 **c**	H	Me	—	C_6H_6	30	—	31:69	57c
7 **c**	H	Me	$AlCl_3$ (0.9)	C_6H_6	30	—	60:40	57c

Scheme 51 presents an entirely different mode of catalyzed [4 + 2] cycloadditions. Thus trimethylsilyl triflate or triflic acid apparently transform vinyl orthoesters and acrolein acetals to powerful transient allyl cation dienophiles (**214**) and (**219**), respectively. The 'ionic' Diels–Alder reactions (**213**) → (**216**) and (**218**) → (**220**) proceed at low reaction temperatures in a remarkably regio- and *endo*-selective manner.[58]



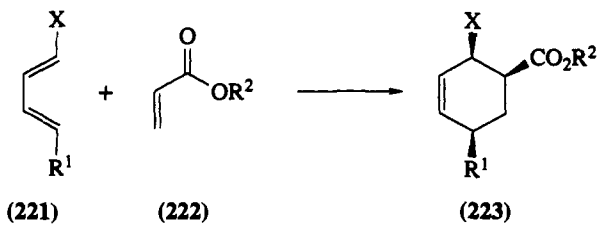
Scheme 51

4.1.4.2 Medium Effects

4.1.4.2.1 High pressure and ultrasound

Intermolecular [4 + 2] cycloadditions exhibit strongly negative activation volumes and reaction volumes. High pressure, therefore, can be applied to accelerate Diels–Alder reactions and to shift the reaction equilibrium towards the cycloadducts. These effects are of particular advantage to: (1) promote otherwise slow [4 + 2] cycloadditions involving heat or Lewis acid sensitive educts or products; (2) suppress cycloreversion processes which are either thermodynamically favored or would interfere with a kinetically controlled stereochemistry. In view of a recent review (1985)[59] only a few examples are presented here.

Scheme 52 and Table 6 emphasize the beneficial influence of high pressure on the Diels–Alder reactions of (Lewis acid sensitive) nitrogen- or oxygen-substituted dienes (**221**) to acrylates (**222**) (*cf.* entries 1/2 and 3/4).[60]

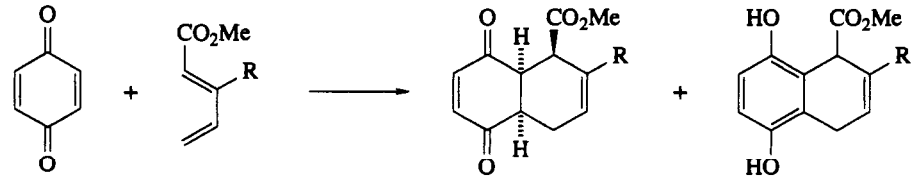


Scheme 52

A serious drawback of [4 + 2] cycloadditions to *p*-quinones is the aromatization of the cycloadducts, affording hydroquinones. Hence, the first step, (**224**) + (**225**; R = H) → (**226**; R = H), of Woodward's landmark synthesis of reserpine, carried out in benzene under reflux (10 h), gave the desired adduct (**226**; R = H) in only 18% yield because of its facile tautomerization to (**227**; R = H) (Scheme 53).[61a]

Table 6 Influence of High Pressure on the Diels–Alder Addition of Heteroatom-substituted Dienes to Acrylates (Scheme 52)

Entry	*Diene*		*Dienophile*	*Solvent*	*Temp.* (°C) *(time,* h)	*Pressure* (kbar)	*Yield (%) of* (**223**)	*Ref.*
	X	R^1	R^2					
1 **a**	NEt_2	H	Et	Benzene	20 (144)	0.001	94	60a
2 **a**	NEt_2	H	Et	Et_2O	r.t. (0.5)	13.6	95	60a
3 **b**	OMOM	CO_2Me	Me	Toluene	110 (72)	0.001	0	60b
4 **b**	OMOM	CO_2Me	Me	CH_2Cl_2	r.t. (24)	15	70	60b

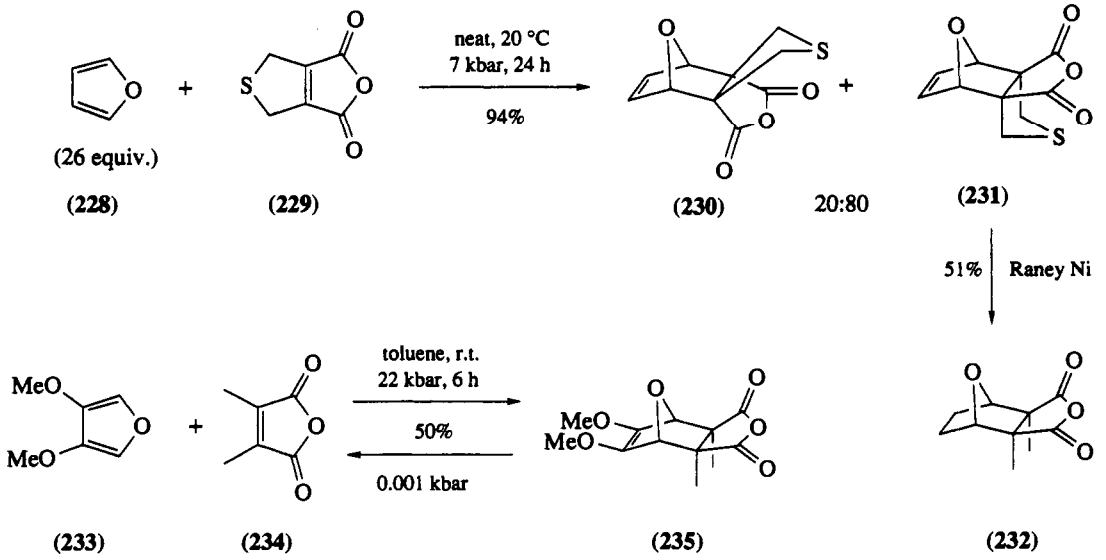


(**224**) (**225**) (**226**) (**227**)

Scheme 53

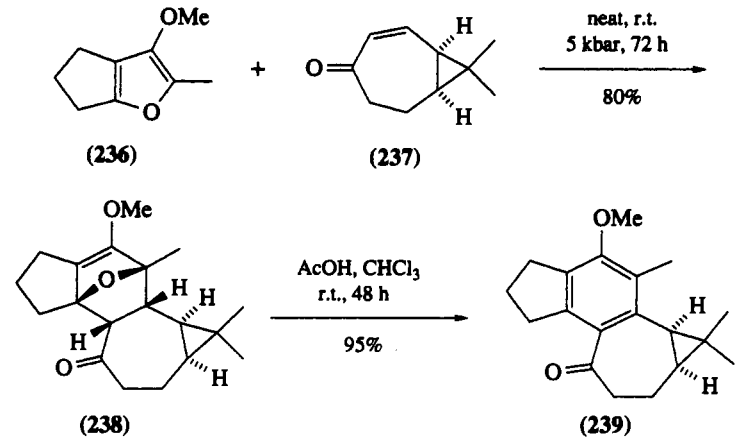
In contrast, this reaction, when run at room temperature under a pressure of 15 kbar (18 h), afforded bicyclic dienedione (**226**; R = H) in 64% yield.[61b] Similarly, the Diels–Alder reaction of *p*-benzoquinone (**224**) with dienyl ester (**225**; R = Et) was significantly improved by high pressure (15 kbar, r.t., 3 h), providing product (**226**; R = Et) in 60% yield; dione (**226**; R = Et) served as a key intermediate for a synthesis of (±)-aklavinone (**625**).[61c]

High pressure has been applied successfully to Diels–Alder reactions of furans, which are notoriously troublesome due to low activation barriers and low or even negative ΔG° values. For example, attempts to synthesize the potent vesicant cantharidin (**232**) *via* reaction of furan (**228**) with dimethylmaleic anhydride (**234**) date back to 1928. The failure of this approach has been attributed to a thermodynamic preference for cycloreversion over cycloaddition.[62a] More than 50 years later the problem was solved by employing high pressures and either a modified dienophile (**229**)[62b] or diene partner (**233**).[62c] Interestingly, product (**235**) reverts to 'reactants' (**233**) and (**234**) in solution at atmospheric pressure and room temperature (Scheme 54).



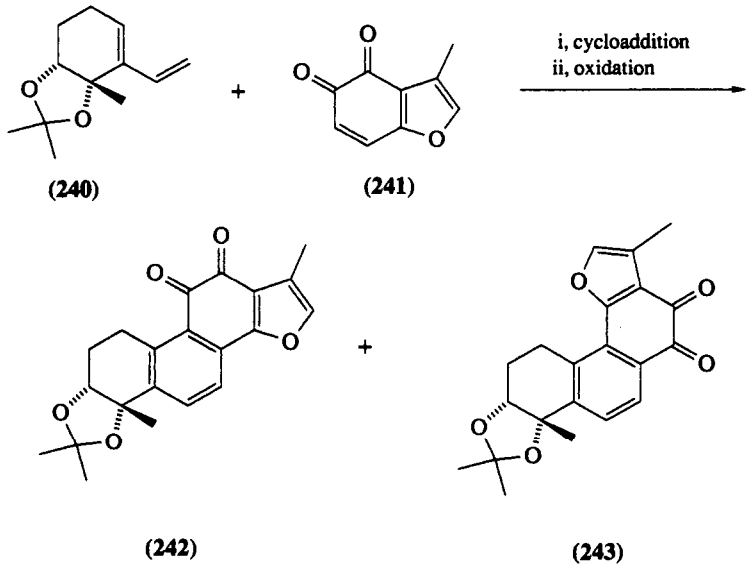
Scheme 54

A pressure of 5 kbar was also essential to accomplish the [4 + 2] cycloaddition of furan (**236**) to enone (**237**), the key step in a synthesis of the diterpenes jatropholones A and B (Scheme 55).[63]



Scheme 55

Ultrasound was reported to promote Diels–Alder reactions as well as improve their regioselectivity similarly to high pressure, but much more conveniently (Scheme 56, Table 7).[64] Comparison of entries 2/3 indicates the similarity of the yields and product ratios (**242**)/(**243**), obtained at 10 kbar (entry 2) and on sonication (entry 3). The latter were attributed to the implosion of the ultrasound-induced cavities which locally generate high pressures and temperatures (up to 1 kbar and 5000 K). Deacetalization of the major aromatized regioisomer (**242**) gave the natural product tanshindiol B.



Scheme 56

Table 7 Ultrasound Promoted Diels–Alder Reactions: Influence on Yield and Regiochemistry[a] (Scheme 56)

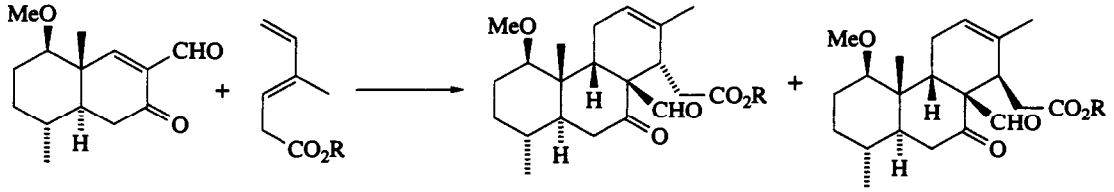
Entry	*Reaction conditions*	*Yield (%) (242) + (243)*	*Ratio (242)/(243)*
1	Benzene, reflux, 8 h	15	50:50
2	Toluene, 10 kbar, r.t., 1 h	73	87:13
3	Neat, ultrasound, 45 °C, 2 h	76	83:17

[a]Aromatization of the initial Diels–Alder products occurred under oxygen with SiO_2 or on heating with DDQ in benzene.

4.1.4.2.2 Water

The beneficial effect of water as a reaction medium for Diels–Alder reactions was first described in 1939,[65] but was not generally recognized for more than 40 years. In the early 1980s, Breslow and coworkers reported that the [4 + 2] cycloaddition of cyclopentadiene to methyl vinyl ketone is accelerated by a factor of 700 when carried out in water compared with isooctane.[66] This rate enhancement, paralleled by an increase of the *endo*/*exo* selectivity from 80:20 to 96:4, was ascribed to a hydrophobic association of the diene with the dienophile in water.

In context with synthetic work on quassinoids, Grieco and coworkers found an even more striking rate enhancement of aqueous Diels–Alder reactions when the diene partner contains a suitably placed ionic substituent (Scheme 57, Table 8).[67a] The concentration-dependent increase of rate, yield and *endo* selectivity observed, particularly, with the sodium salt of dienoic acid (**245b**) in water (entry 3) was assigned to an entropically favorable interaction of the reactants within an aggregate.



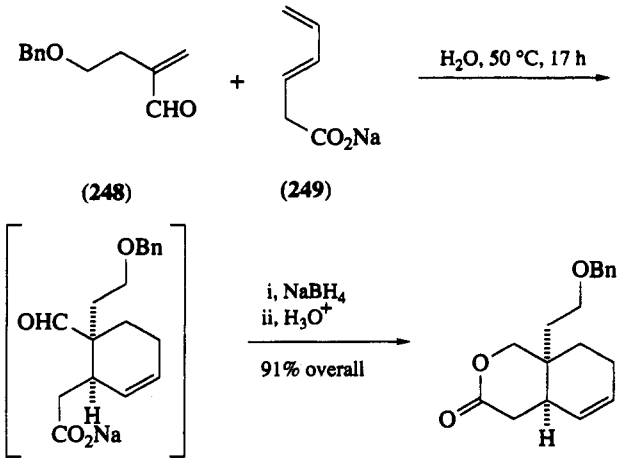
(244) (245) (246) (247)

Scheme 57

Table 8 Aqueous, Aggregation-promoted Diels–Alder Reactions of Quassinoid Intermediates at Room Temperature (Scheme 57)

Entry	*R*	*Solvent*	*Concentration of diene*	*Time* (h)	*Yield* (%) (**246**) + (**247**)	*Ratio* (**246**)/(**247**)
1 **a**	Et	C_6H_6	1.0 M	288	52	46:54
2 **a**	Et	H_2O	1.0 M	168	82	57:43
3 **b**	Na	H_2O	2.0 M	5	~100	75:25
4 **b**	Na	H_2O	0.1 M	120	46	47:53

Under analogous aqueous reaction conditions, the sodium salts of (*E*)-3,5-hexadienoic, (*E*,*E*)-6-methoxy-3,5-hexadienoic and (*E*)-4,6-heptadienoic acid underwent high-yielding [4 + 2] cycloadditions to a variety of dienophiles,[67b] *e.g.* to the C_α-substituted enal (**248**) (Scheme 58).[67c] The crude Diels–Alder



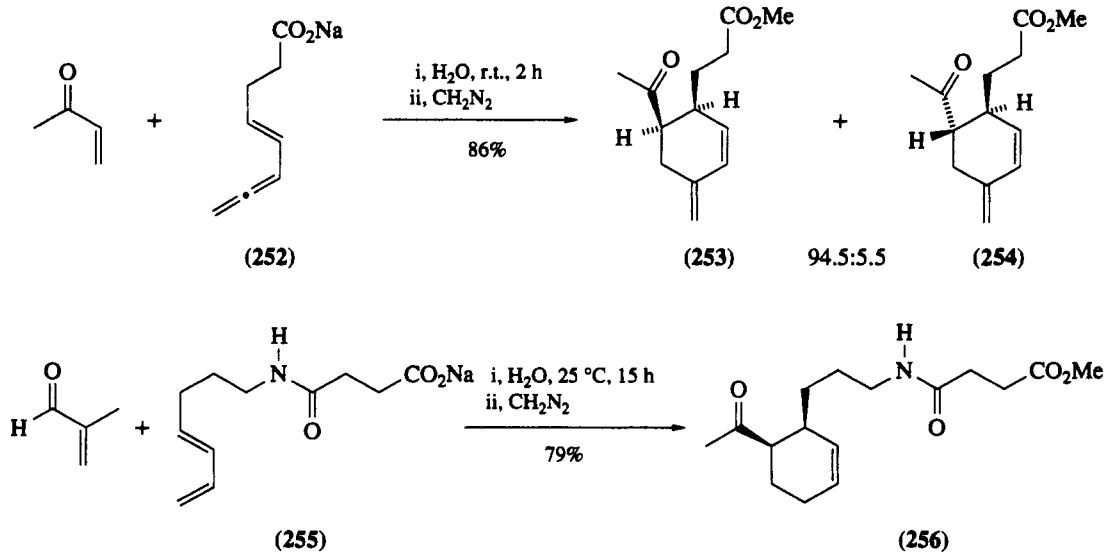
(248) (249) (250) (251)

Scheme 58

adduct (**250**), formed from (**248**) and (**249**) with a 91:9 *endo/exo* selectivity, was directly reduced with $NaBH_4$ and lactonized. This afforded, in 91% overall yield, bicyclic lactone (**251**), a precursor in a synthesis of vernolepin.

The aqueous addition of conjugated allene carboxylate (**252**) to typical dienophiles proceeded smoothly between 20 and 50 °C to yield predominantly, if not exclusively, 'C=O *endo*' adducts containing a conjugated *exo*-methylene group, *e.g.* the methyl vinyl ketone adduct (**253**) (Scheme 59).[67e] Also diene (**255**), featuring a sodium carboxylate unit attached *via* a nitrogen atom, reacted efficiently at 25 °C with various, even acid-sensitive, dienophiles as exemplified by the [4 + 2] cycloaddition of (**255**) to methacrolein (→ **256**).[67d]

Applications of the water-promoted aggregation effects in diastereoface controlled or 'iminium' Diels–Alder reactions will be discussed in Section 4.1.5.2 (Scheme 66) and in Chapter 4.2, respectively.



Scheme 59

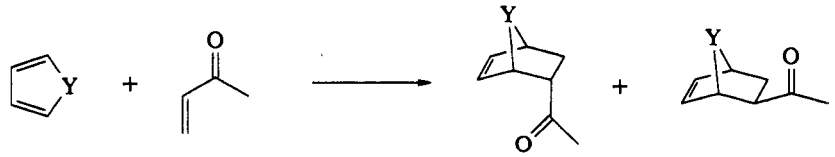
4.1.4.2.3 Clays, zeolites and silica gel

Diels–Alder reactions showed a pronounced increase of rate, *endo*- and regio-selectivity when carried out in organic solvents in the presence of modified clays[68] or zeolites.[69] Similar improvements could be accomplished by co-adsorption of the reactants on dry SiO_2 in the absence of organic solvents.[70] These trends are summarized below and compared with the results obtained by employing the 'classical-thermal',[71a] Lewis acid catalyzed,[57,68a,71b] 'high pressure'[71c] or 'aqueous'[66] reaction conditions.

For this comparison the [4 + 2] cycloadditions of methyl vinyl ketone to cyclopentadiene and to furan are chosen as reference reactions (Scheme 60, Table 9). Smectile clays, with the interlayer cations exchanged by Cr^{III} or Fe^{III} ions, catalyzed the addition of cyclopentadiene in providing the *endo* product (**258**; Y = CH_2) at a drastically reduced reaction temperature in high yield together with ≤10% of the *exo* product (**259**; Y = CH_2) (entries 3, 4). These results are comparable with those obtained under 'aqueous' reaction conditions (entry 2), which supports the idea that the presence of water pockets in clays could account for their catalytic activity. The Lewis acidity as well as one-electron-transfer processes, involving the internal Fe^{III} or Cr^{III} cations, have also been invoked as possible explanations.

On the other hand, the enhancements of rate and *endo* selection caused by adsorption of the reactants on dry silica gel (entry 5) seem to arise from an association of the nonsolvated reacting partners at the SiO_2 surface, which acts as a matrix.

Entries 6–10 deal with the Diels–Alder reactions of methyl vinyl ketone with furan and also include the use of $AlCl_3$ (entry 6), high pressure (entry 7) and Cu^{I} ion-exchanged Y-zeolite (entry 9). This series, however, displayed only modest *exo* selectivities. The highest product ratio (**258**; Y = O)/(**259**; Y = O) = 20:80 was found on adsorption of the educts on dry SiO_2·MgO (entry 10).



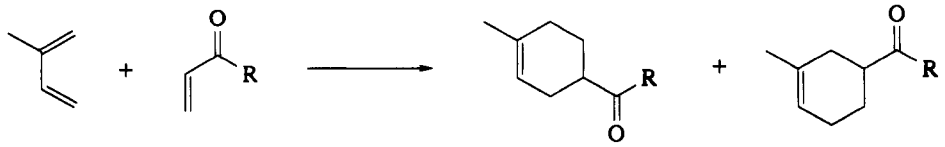
(257) (258) (259)

Scheme 60

Table 9 Diels–Alder Reactions of MVK with Cyclopentadiene and Furan: Influence of Reactions Conditions (Scheme 60)

Entry	*Y*	*Solvent*	*Catalyst or support*	*Temp.* (°C) *(time,* h)	*Yield* (%) *(258)* + *(259)*	*Ratio (258)/(259)*	*Ref.*
1	CH_2	Benzene	None	80	80	83:17	71a
2	CH_2	H_2O	None	25 (3)	80	95.5:4.5	66
3	CH_2	CH_2Cl_2	K10-Fe^{III}	–24 (4)	96	95.5:4.5	68a
4	CH_2	$CH2Cl_2$	Cr^{III} montmorillonite	22 (0.3)	91	90:10	68b
5	CH_2	None	SiO_2	–20 (1)	90	96:4	70
6	O	CH_2Cl_2	$AlCl_3$ (0.15)	–43 (0.25)	81	44:56	68a
7	O	CH_2Cl_2	15 kbar	r.t. (4)	48	50:50	71c
8	O	CH_2Cl_2	K10-Fe^{III}	–43 (6)	60	31:69	68a
9	O	CH_2Cl_2	Cu^{I} zeolite	0 (48)	73	29:71	69
10	O	none	SiO_2·MgO	20 (70)	48	20:80	70

Scheme 61 and Table 10 illustrate the influence of $SnCl_4$ or solid supports on the Diels–Alder reactions of methyl vinyl ketone or acrolein with isoprene. Apart from the reaction rate, the regiochemical control was substantially increased, *e.g.* from 59:41 to 99.5:0.5 (entries 5/7) in favor of the '*para*' products (**260**).



(173) (260) (261)

Scheme 61

Table 10 Influence of Lewis Acid and Solid Support on the Diels–Alder Reactions of MVK and Acrolein with Isoprene (Scheme 61)

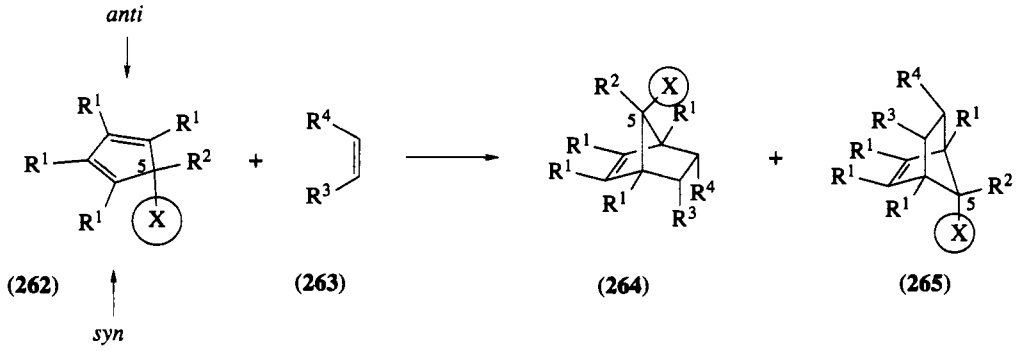
Entry	*Dienophile*	*Solvent*	*Catalyst or support*	*Temp.* (°C) *(time,* h)	*Yield* (%) *(260)* + *(261)*	*Ratio (260)/(261)*	*Ref.*
1	MVK	Toluene	None	120 (15)	—	71:29	71b
2	MVK	Benzene	$SnCl_4$·$5H_2O$ (0.18)	<25 (1)	—	93:7	71b
3	MVK	CH_2Cl_2	Cu^{I} zeolite	0 (3)	83	96:4	69
4	MVK	None	SiO_2	20 (0.5)	70	≥95:≤5	70
5	Acrolein	None	None	150	—	59:41	71b
6	Acrolein	Benzene	$SnCl_4$·$5H_2O$ (0.18)	<25 (1)	54	96:4	71b
7	Acrolein	CH_2Cl_2	Cu^{I} zeolite	0 (12)	65	99.5:0.5	69
8	Acrolein	None	SiO_2	20 (0.5)	56	≥95:≤5	70

4.1.5 DIASTEREOFACE-SELECTIVE DIELS–ALDER REACTIONS WITHOUT REMOVAL OF THE INDUCING MOIETY

As discussed previously, the Diels–Alder reactions of alkenic dienes and dienophiles involve the simultaneous formation of two carbon–carbon bonds and up to four contiguous stereogenic centers. Their relative topicity derives from the (*E,Z*) geometry of the diene and dienophile units coupled with the *endo/exo* mode of addition. A further stereochemical issue arises in directing the addition process to only one (diastereo- or enantio-topic) π-face of either reaction partner. This π-facial differentiation governs the relation between pre-existent and newly developing centers of chirality and/or the absolute configuration of the latter ones. These two aspects of facial differentiation will be emphasized separately in the following subsections.

4.1.5.1 Induction by a Prochiral Center: 5-Substituted Cyclopentadienes

[4 + 2] Cycloadditions to C-5 substituted 1,3-cyclopentadienes (**262**) represent a particular type of face discrimination owing to the potential of a prochiral center (C-5) to alter the reactivity of the two diene faces (Scheme 62, Table 11). Hence some attention has been devoted to whether a dienophile (**263**) would preferably add *syn* or *anti* relative to a substituent X.[72] Entries 1–3 show a predominant addition of $Cu(BF_4)_2$-coordinated 2-chloroacrylonitrile (or of acrylic acid and nitroethylene) *anti* to the CH_2OMe group, *i.e. syn* to $R^2 = H$. A similar *anti*-directing influence was shown (in decreasing order) for C-5 substituents X = CH_2OH > Me (entries 4, 5). Also, the methylthio and methylsulfonyl groups direct maleic anhydride to the *anti* face of cyclopentadienes (entries 8, 9). In contrast, C-5 substituents X = Cl,OH, OMe and NHAc exert a *syn*-directing bias on (**262**) (entries 6, 7, 10–12), the origin of which is subject to debate.



Scheme 62

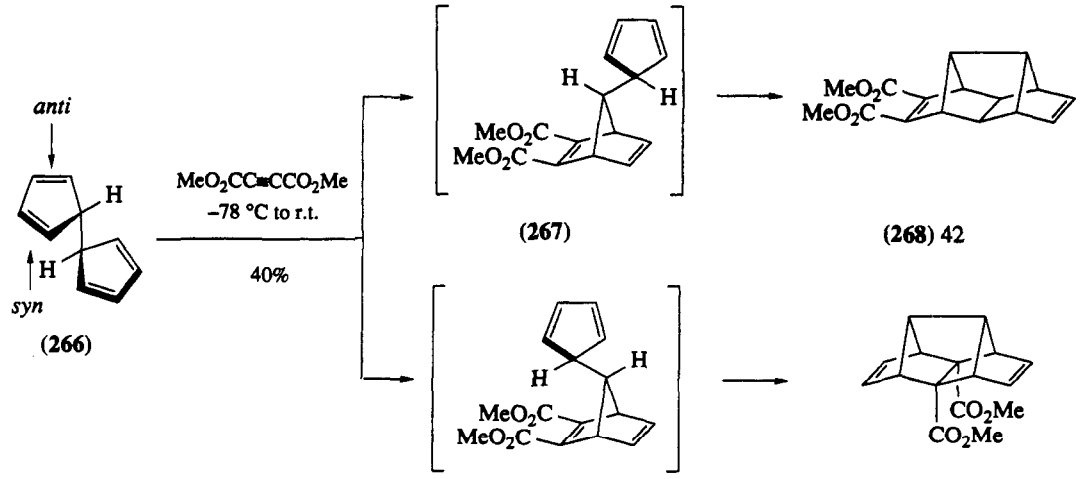
Table 11 Diels–Alder Reactions of C-5 Substituted 1,3-Cyclopentadienes (Scheme 62)

Entry	R^1	R^2	*X*	*Dienophile*	*Lewis acid* (mol equiv.)	*Temp.* (°C) *(time,* h*)*	*Yield (%) (264) + (265)*	*Ratio (264)/(265)*	*Ref.*
1 **a**	H	H	CH_2OMe	2-Chloroacrylonitrile	$Cu(BF_4)_2$	0	>90	<10:>90	56
2 **b**	H	H	CH_2OMe	Acrylic acid	None	−7	a	<3:>97	72a
3 **c**	H	H	CH_2OMe	Nitroethylene	None	−15 to r.t.	68	<5:>95	5
4 **d**	H	Me	CH_2OH	*N*-Phenylmaleimide	None	r.t. (120)	87	13:87	72b
5 **e**	Me	H	Me	Maleic anhydride	None	r.t.	a	21:79	72c
6 **f**	Cl	H	Cl	Maleic anhydride	None	105 (3)	73	91:9	72d
7 **f**	Cl	H	Cl	Maleic anhydride	$AlCl_3$ (1)	100 (2.5)	80	99:1	72e
8 **g**	Me	Me	SMe	Maleic anhydride	None	22 (27.5)	>90	10:90	72f
9 **h**	Me	Me	SO_2Me	Maleic anhydride	None	22 (216)	>90	<5:>95	72f
10 **i**	Me	Me	OH	Maleic anhydride	None	22 (<0.01)	>90	>95:<5	72f
11 **j**	Me	Me	OMe	Maleic anhydride	None	22 (<0.2)	>90	>95:<5	72f
12 **k**	Me	Me	NHAc	Maleic anhydride	None	22 (3.5)	>90	>95:<5	72f

[a]Yield not reported.

On the other hand, a C-5 cyclopentadiene moiety induced almost no face discrimination on addition of dimethyl acetylenedicarboxylate to 9,10-dihydrofulvalene (**266**) (Scheme 63).[73a] Products (**268**) and (**270**) result from a tandem inter-/intra-molecular Diels–Alder reaction (domino Diels–Alder reactions).

This seminal concept for the construction of polycyclic systems, developed by Paquette and coworkers, is highlighted by the conversion of product (**270**) into dodecahedrane.[73b]

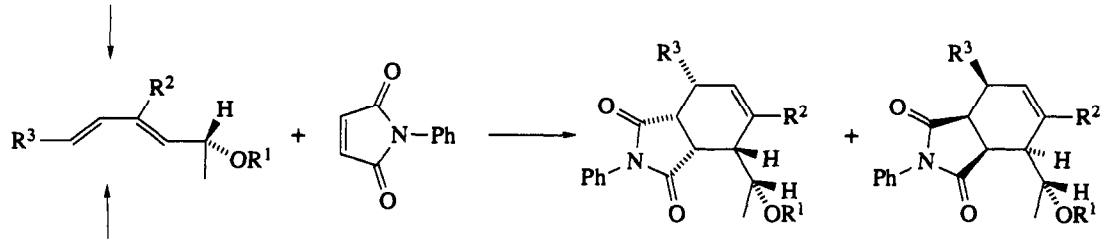


Scheme 63

4.1.5.2 Induction by Resident Stereocenter(s)

4.1.5.2.1 Chiral dienes

Acyclic 1,3-dienes containing an allylic stereogenic center may display a useful π-facial differentiation on addition of dienophiles. For example, 1,3-dienes (**271**) bearing an allylic oxygenated center of chirality at C-1 gave, on addition of *N*-phenylmaleimide, mixtures of diastereoisomers (**272**) and (**273**) in ratios from 63:37 (R^1 = H) up to 88:12 (R^1 = TMS) (Scheme 64, Table 12).[74a] This trend significantly increased with 2-alkoxydiene (**271d**), giving exclusively adduct (**272d**) (entry 4).[74b] The improved selectivity observed with (**271d**) was attributed to the 2-alkoxy substituent R^2 which restricts the rotational freedom of the bond between C-1 and the stereogenic center.



(271) (272) (273)

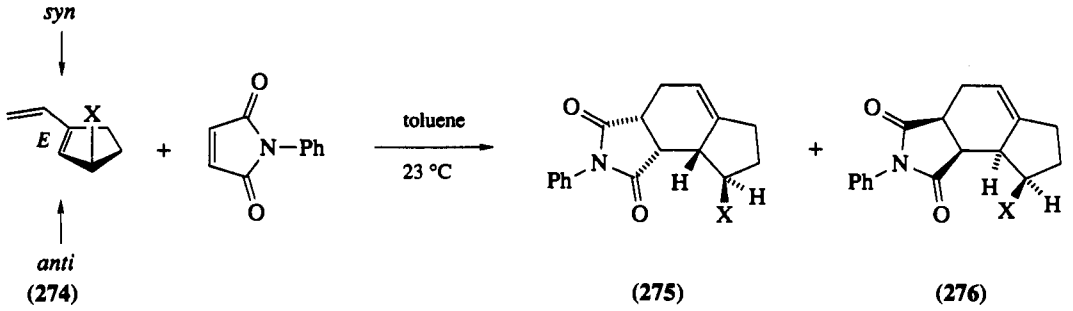
Scheme 64

Table 12 [4 + 2] Cycloadditions of *N*-Phenylmaleimide to Acyclic 1,3-Dienes Bearing an Oxygenated Allylic Center of Chirality (Scheme 64)

Entry	R^1	R^2	R^3	*Solvent*	*Temp.* (°C) *(time,* h)	*Yield* (%) *(272)* + *(273)*	*Ratio (272)/(273)*
1 **a**	H	H	Me	Benzene	r.t. (120)	78	63:37
2 **b**	Me	H	Me	Benzene	55 (72)	a	83:17
3 **c**	TMS	H	Me	Benzene	r.t. (240)	74.5	88:12
4 **d**	TMS	OMOM	Pr^i	Benzene	r.t. (12)	a	~100:0

[a]Yield not reported.

To remove the conformational ambiguity which obscures interpretations of these results, additions of various dienophiles to 3-substituted 1-vinylcyclopentenes (**274**) were studied.[75] Preferential cycloaddition from the diene face *anti* to the Me, OMe and, particularly, the OTBDMS group was observed (Scheme 65, Table 13). Cycloaddition of the hydroxy-substituted diene (**274b**) occurred with a weak *syn* preference in toluene (entry 2), but with an *anti* preference in more polar solvents.

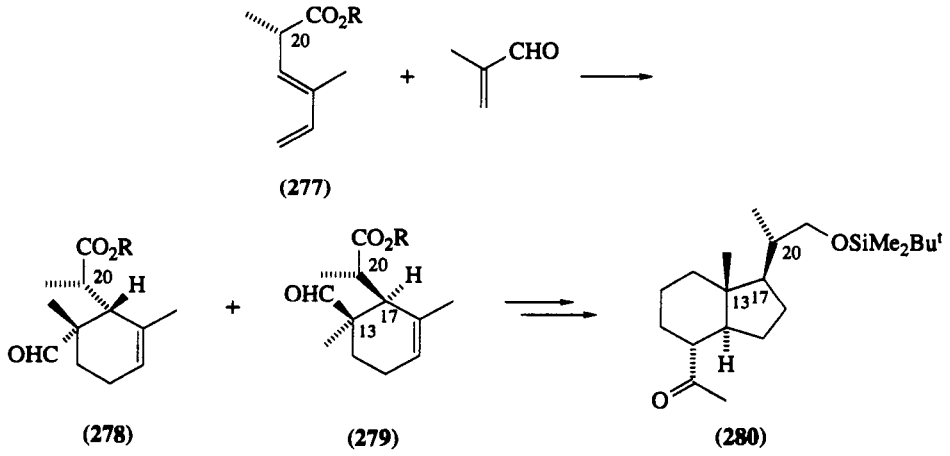


Scheme 65

Table 13 [4 + 2] Cycloadditions of *N*-Phenylmaleimide to C-3 Substituted 1-Vinylcyclopentenes in Toluene at Room Temperature (Scheme 65)

Entry	*X*	*Ratio (275)/(276)*
1 **a**	Me	83:17
2 **b**	OH	36:64
3 **d**	OMe	≥97:≤3
4 **d**	OTBDMS	100:0

A pertinent example of π-face differentiation by means of the 'aqueous Diels–Alder methodology' is the addition of dienyl sodium carboxylate (**277**; R = Na) to methacrolein in water, yielding adducts (**278**; R = Na) and (**279**; R = Na) in a ratio of 18:82 (85%) (Scheme 66, Table 14, entry 1).[76] This useful induction of centers C-13 and C-17 by the pre-existing center C-20 is essential for a synthesis of the vitamin D_3 precursor (**280**). It contrasts with the inefficient [4 + 2] cycloaddition of dienyl methyl ester (**277**; R = Me) in neat methacrolein, which showed no facial selectivity (entry 2).

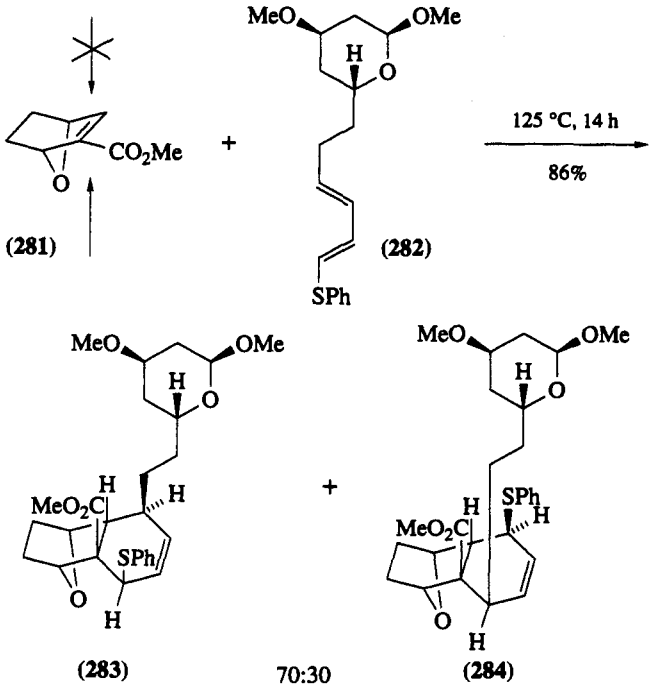


Scheme 66

Table 14 Diene with an Allylic Stereogenic Center: Medium-assisted Face Differentiation on Addition to Methacrolein (Scheme 66)

Entry	*R*	*Solvent*	*Temp.* (°C) *(time,* h)	*Yield* (%) *(278)* + *(279)*	*Ratio (278)/(279)*
1 **a**	Na	H_2O	55 (16)	85	18:82
2 **b**	Me	Methacrolein	55 (63)	10	50:50

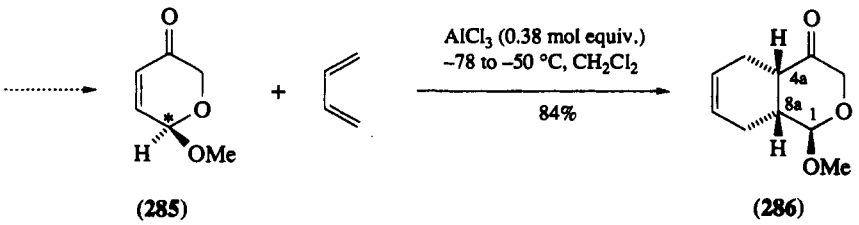
A synthesis of the hypocholesterolemic agent (+)-compactin centers around the Diels–Alder reaction of the chiral diene (**282**) with the chiral dienophile (**281**), which provided in a single operation the carbon framework of the target molecule (Scheme 67).[77] However, facial and regiochemical selectivities of the additions were only moderate, giving rise to the formation of two regioisomers (**283**) and (**284**); the major product (**283**) was transformed into (+)-compactin.



Scheme 67

4.1.5.2.2 Chiral dienophiles

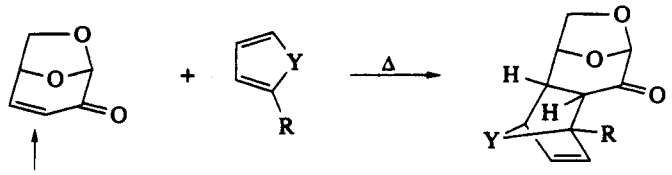
Cyclic enones carrying an endocyclic stereogenic center reliably undergo cycloadditions of 1,3-dienes to the sterically less-hindered face, as exemplified by the $AlCl_3$-catalyzed reaction of (**285**) with butadiene which yielded (**286**; 84%) as the sole cycloadduct (Scheme 68).[78]



Scheme 68

Levoglucosenone (**287**), readily available by the pyrolysis of cellulose, when heated with a variety of dienes in the absence of a Lewis acid provided exclusively products (**289**) resulting from cycloaddition to its convex face (Scheme 69, Table 15).[79]

$AlCl_3$-promoted Diels–Alder addition of butadiene to another sugar-derived dienophile (**290**) proceeded, as expected, only from the face opposite to the allylic ethoxy substituent, giving cycloadduct (**291**) (Scheme 70).[80]

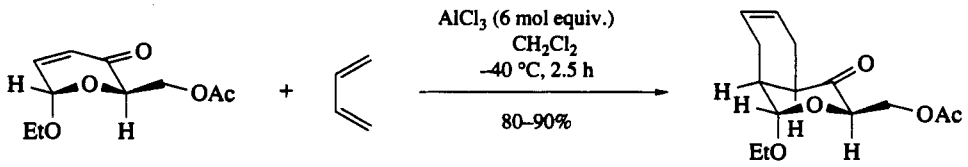


(287) (288) (289)

Scheme 69

Table 15 [4 + 2] Cycloadditions to Levoglucosenone (Scheme 69)

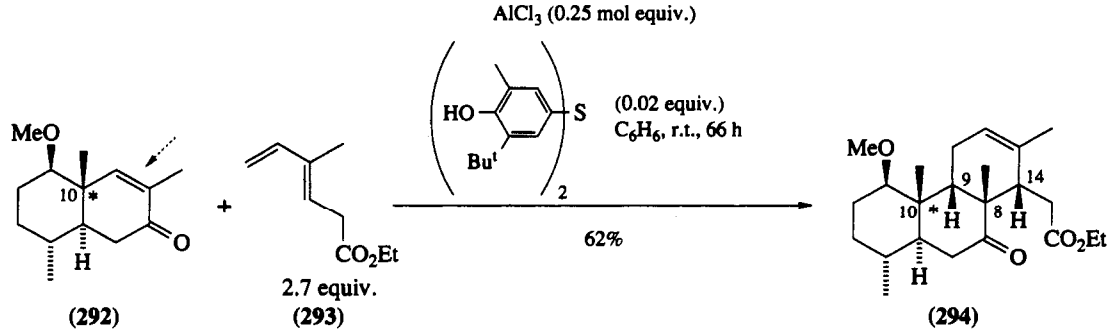
Entry	*Diene* Y	R	*Temp.* (°C) *(time,* h)	*Yield* (%) *(289)*
1 **a**	H_2	H	160 (3)	95
2 **b**	CH_2	H	168 (3)	48
3 **c**	$(CH_2)_2$	H	200 (3)	96
4 **d**	H_2	OAc	80 (7)	63



(290) (291)

Scheme 70

A synthesis of (±)-quassin relies on the $AlCl_3$-catalyzed Diels–Alder reaction (**292**) + (**293**) → (**294**), where the angular allylic methyl group of the dienophile directs the diene to its less-hindered face (Scheme 71).[81]

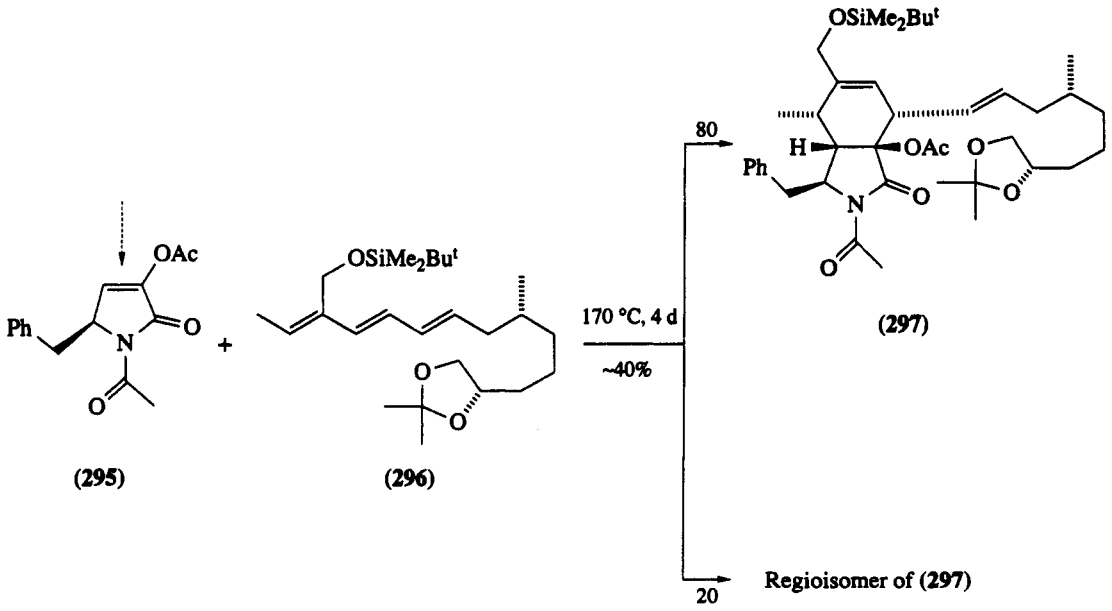


(292) (293) (294)

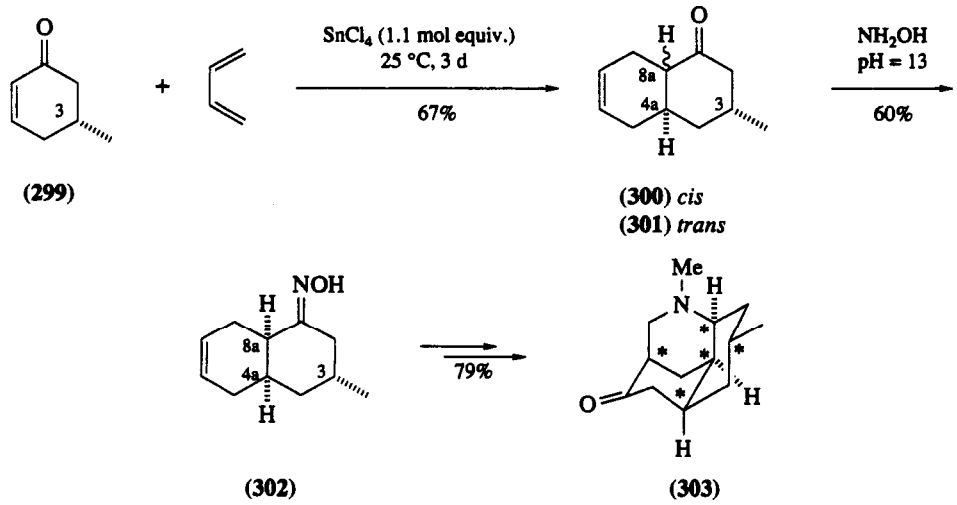
Scheme 71

The non-catalyzed [4 + 2] cycloaddition of the chiral pyrrolone (**295**) to triene (**296**) occurred with π-facial selection owing to the allylic benzyl substituent of dienophile (**295**) affording two regioisomers (Scheme 72).[82] The major product (**297**) is a key intermediate in a synthesis of cytochalasin B.

A particularly short and efficient synthesis of the lycopodium alkaloid (+)-luciduline (**303**) features as the first step the [4 + 2] cycloaddition of butadiene to optically pure cyclohexenone (**299**) opposite to the homoallylic methyl group (Scheme 73).[83] To achieve this excellent face discrimination the presence of $SnCl_4$ was required which, however, provoked an epimerization at C-8a yielding mainly the undesired *trans*-fused product (**301**). Oximation, under epimerizing conditions, easily rectified this problem by channelling both isomers (**300**) and (**301**) to a single *cis*-fused oxime (**302**) which was converted to the enantiomerically pure alkaloid (**303**).



Scheme 72



Scheme 73

4.1.6 STEREOFACE-SELECTIVE DIELS–ALDER REACTIONS WITH REMOVAL OF THE INDUCING MOIETY

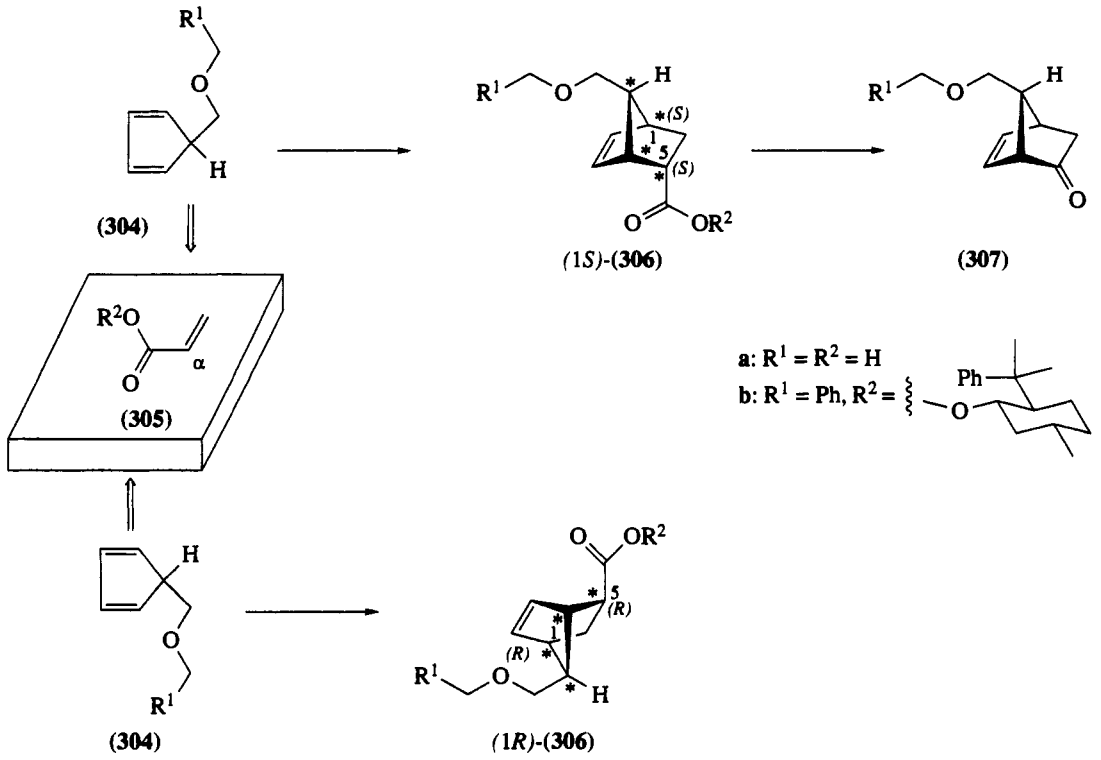
4.1.6.1 Background

Studies on the control of the absolute topicity of the Diels–Alder reaction started in 1961, but it is only during the last decade that substantial progress has been achieved. The development of this challenging field up to 1984 is the subject of several review articles.[84] A more specialized account on chiral enoate

dienophiles appeared in 1986.[85] Some of this 'earlier' work will stand the test of time; some of it laid the foundations for new methods and concepts and will be put into perspective with today's panorama of possibilities.

4.1.6.2 Covalently Bound Auxiliary Groups

The first use of an asymmetric Diels–Alder reaction in enantioselective synthesis, reported by Corey and Ensley (1975), involved both diene and dienophile face differentiations (Scheme 74).[86] Addition of 5-(methoxymethyl)cyclopentadiene (**304**) to acrylic acid (**305a**) proceeded *endo* selectively and *anti* with respect to the diene substituent. Consequently, the relative configuration of the four new chiral centers in (**306a**) was determined and, of four possible diastereoisomers, one was formed selectively.[72a] As expected, the diene added at the same rate to the two enantiotopic dienophile π-faces, affording a 1:1 mixture of the enantiomers (1*R*)-(**306a**) and (1*S*)-(**306a**).



Scheme 74

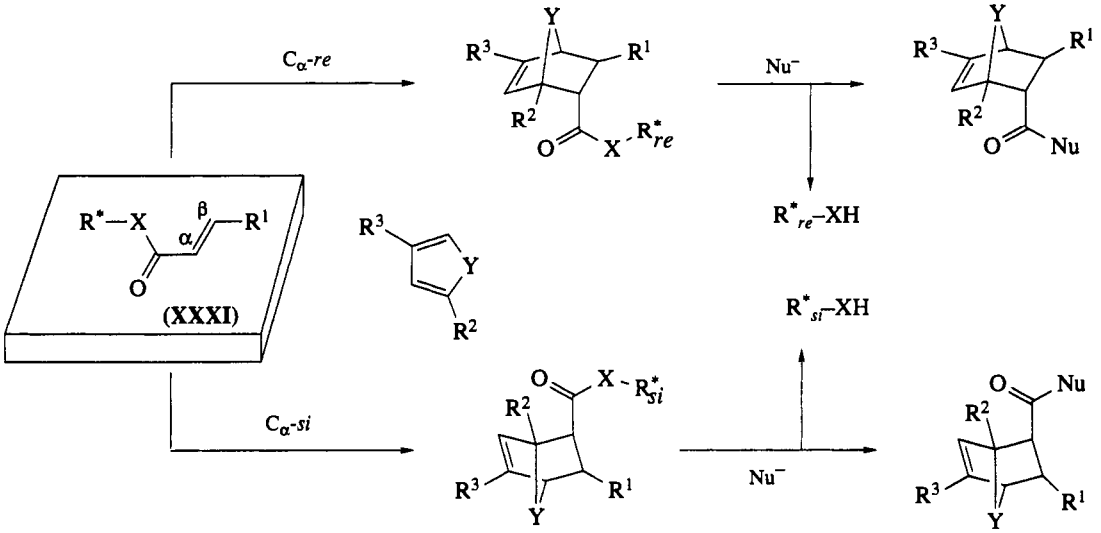
Since only the (1*S*)-enantiomer is suitable for the synthesis of prostaglandins, exclusive diene addition from the C_α *re*-face was required. Indeed, attachment of an appropriate chiral ester group R^2 to the dienophile caused steric shielding of the now diastereotopic C_α *si*-face of (**305b**), thereby directing the $AlCl_3$-promoted diene addition to the C_α *re*-face. As a result of the π-face differentiation, the desired (1*S*)-(**306b**) was obtained from (**305b**) in significant excess over the undesired (1*R*)-isomer. This mixture was then transformed into enantiomerically pure ketone (**307**) involving cleavage of the chiral control element R^2.[86]

The above example demonstrates the addition of a prochiral diene to a dienophile bearing a removable chiral auxiliary. Further options for π-topological differentiation in Diels–Alder reactions include the temporary attachment of a chiral control group to the diene or, more elegantly, the employment of a chiral catalyst. So far the stoichiometric use of covalently bound chiral control groups has proved to be more efficient and predictable. In practical terms, the ideal prosthetic group should meet the following criteria. (1) Provide a wide range of Diels–Alder adducts in high chemical yield with virtually quantitative and predictable π-face stereodifferentiation and a high *endo*/*exo* as well as regio-selectivity. (2) Both enantiomers or alternative topological counterparts should be readily available. (3) Be capable of effi-

cient attachment to the dienophile or diene and nondestructive removal from the adduct with complete retention of the induced configuration. (4) Permit direct facile and reliable assessment of induction by direct analysis of the reaction mixture (NMR, GC, HPLC). (5) Enable facile purification of the major cycloadduct to almost 100% *de*. (6) Impose crystallinity on intermediates and cycloaddition products.

4.1.6.2.1 Chiral dienophiles

The vast majority of work on asymmetric Diels–Alder reactions deals with additions of 1,3-dienes to α,β-alkenic carbonyl derivatives (**XXXI**) where the chirophore R* is attached to the carbonyl group either directly or *via* a heteroatom X, permitting subsequent removal of the auxiliary (*e.g.* by attack of a nucleophile Nu^-; Scheme 75).

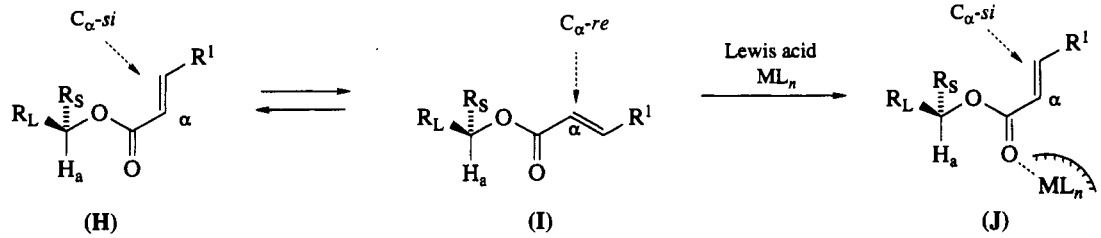


Scheme 75

The factors which direct the diene to the top (Cα *re*) or bottom face (Cα *si*) of dienophile (**XXXI**) may be of steric and/or stereoelectronic origin. Moreover, the overall stereofacial bias is intrinsically dependent on the conformation of (**XXXI**). Thus the rotational freedom around the single bonds which link the chiral and prochiral centers in (**XXXI**) needs to be restricted in a well-defined manner.

(i) Non-chelated Enoates Derived from Secondary Alcohols

In conjunction with the above arguments, the relevant conformers of acrylates derived from secondary alcohols are now discussed briefly (Scheme 76).[84a]

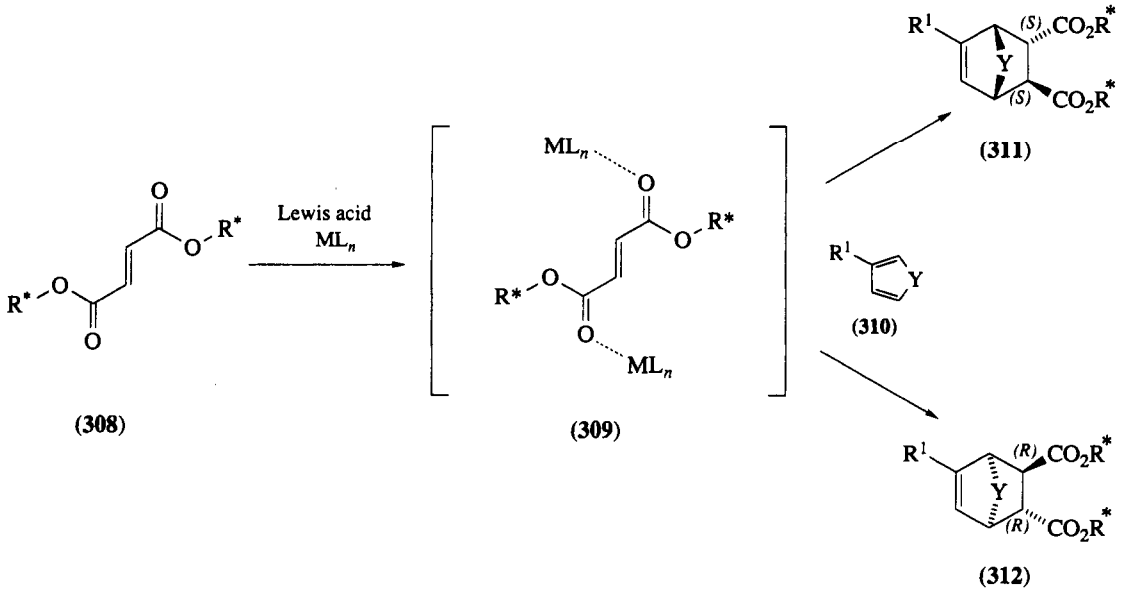


Scheme 76

According to X-ray data, such acrylates or (*E*)-Cβ-substituted enoates exhibit a synperiplanar C—Ha/C=O relationship in the solid state which also seems to predominate in solution. In solution, however, spectroscopic evidence indicates an equilibrium between conformers (**H**) and (**I**), where the

synplanar C=O/C=C disposition of the latter is disfavored by only $\Delta H = 0.32$ kcal mol^{-1}. If the diene adds exclusively to the π-face opposite the larger substituent, conformers (**H**) and (**I**) display a reversed topicity. Consistent with this element of unpredictability, no thermal Diels–Alder reactions of acrylates have ever surpassed a face selectivity of 80:20. However, the situation changes dramatically when the acrylate coordinates to a Lewis acid. Supported by the results of X-ray and spectroscopic studies, we assume predominant coordination of various Lewis acids (notably $TiCl_4$ and $SnCl_4$) with the carbonyl oxygen *anti* to the ester oxygen. This secures the C=O/C=C *s-trans* conformation (**J**). Moreover, Lewis acid coordination to acrylates increases the regio- and *endo*-selectivity as well as the rate of their [4 + 2] cycloaddition to 1,3-dienes. As a result of this advantageous coincidence of effects, most asymmetric Diels–Alder reactions are carried out at low temperatures in the presence of a Lewis acid.

In 1963, Walborsky and coworkers published the addition of bis(menthyl) fumarate (**308a**) to 1,3-butadiene promoted by Lewis acids, affording the cyclohexene derivative (**311a**) (Scheme 77, Table 16).[87a]



Scheme 77

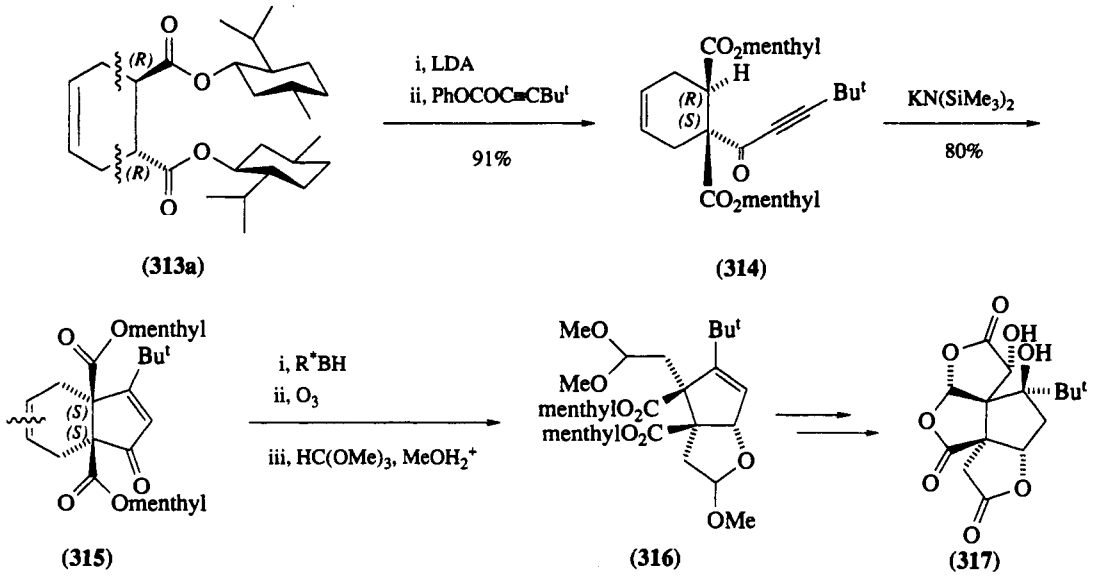
Table 16 Asymmetric Diels–Alder Additions of 1,3-Dienes to Fumarates Derived from Chiral Secondary Alcohols (Scheme 77)

Entry	*Dienophile* R^*	*Diene* Y	R^1	*Lewis acid* (mol equiv.)	*Solvent*	*Temp.* (°C)	*Yield (%)* (**311**) + (**312**)	*Ratio* (**311**)/(**312**)	*Ref.*
1 **a**	(1*R*)-Menthyl	H_2	H	$TiCl_4$ (1.0)	Toluene	25	80	89:11	87a
2 **a**	(1*R*)-Menthyl	H_2	H	Bu^i_2AlCl (2.0)	Hexane	–40	56	97.5:2.5	87b
3 **b**	(1*R*)-Menthyl	H_2	Me	Bu^i_2AlCl (1.0)	Hexane	–20	94	97.5:2.5	87b
4 **c**	(1*R*)-Menthyl	H_2	$OSiMe_3$	Et_2AlCl (2.0)	Toluene	–20	92	97:3	87b
5 **d**	(1*R*)-Menthyl	CH_2	H	Et_2AlCl (1.0)	Toluene	–78	100	99.5:0.5	87b
6 **e**	(*S*)-CH(Me)CO_2Et	H_2	H	None	Hexane	130	96	25:75	87c
7 **f**	(*S*)-CH(Me)CO_2Et	CH_2	H	None	Hexane/CCl_4	–54	99	2:98	87c
8 **g**	(*S*)-CH(Me)CO_2Et	$(CH_2)_2$	H	None	CCl_4	77	96	10:90	87c

Optimal results (product ratio (**311a**)/(**312a**) = 89:11, entry 1) were obtained using $TiCl_4$ (1 mol equiv.) in toluene at 25 °C. This relatively high induction is not surprising since fumarate (**309a**) profits from a cooperative influence of two chiral *O*-acyl groups which increase its dienophilicity and direct the diene to the π-face opposite of two large groups R_L in the coordinated dienophile (**309**). More recent studies showed improved π-face differentiations by the use of Bu^i_2AlCl and the more popular (*vide infra*) Et_2AlCl as the Lewis acid.[87b] Acyclic dienes furnished cyclohexenes (**311a**)–(**311c**) in ratios of (**311**)/(**312**) = 97.5:2.5 (entries 2–4, 56–94% yield) whereas addition of cyclopentadiene at –78 °C yielded quantitatively a 99.5:0.5 mixture of norbornenes (**311d**)/(**312d**). Furthermore, it appears that the two acyl groups stabilize the C=O/C=C *s-trans* conformation of the (*E*)-alkene (**308**) even in the ab-

sence of Lewis acids. Hence fumaric acid esters of the *re*-face-directing ethyl (*S*)-lactate gave [4 + 2] cycloaddition products (**311**) and (**312**) in 96–99% yield and in ratios which increase (25:75 → 2:98) with decreasing reaction temperature (130 → –54 °C, entries 6–8).[87c]

The utility of the asymmetric fumarate/butadiene addition in synthesis is highlighted by the conversion of the (*R,R*)-cyclohexene (**313a**) (derived from (+)-(1*S*)-menthol) to enantiomerically pure (–)-bilobalide (**317**) (Scheme 78).[88] This conversion involves particularly the annulation of a cyclopentenone ring to (**313a**) at the acylated centers which govern the topicity of the acylation (**313a**) → (**314**) and internal 'Michael reaction' (**314**) → (**315**). Ozonolysis of the cyclohexene moiety sets the stage for the formation of two γ-lactone rings.



(313a) (314) (315) (316) (317)

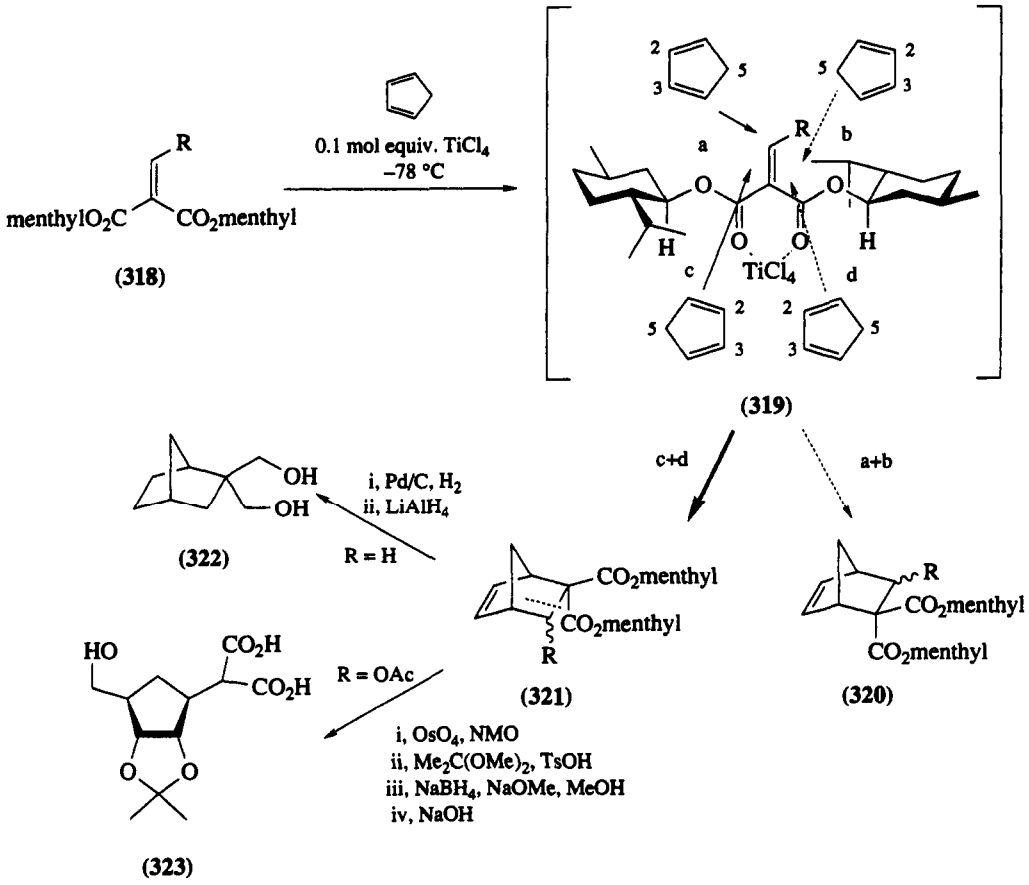
Scheme 78

Two menthyloxycarbonyl groups attached to the same alkenic terminal may also govern the topicity of diene additions, as exemplified by the $TiCl_4$-catalyzed (0.1 mol equiv., –78 °C) addition of cyclopentadiene to di-(1*R*)-menthyl methylenemalonates (**318**) (Scheme 79).[89] Under these conditions, (**318**; R = H) gave a <10:>90 mixture of norbornenes (**320**; R = H) and (**321**; R = H) in 93% yield. Crystallization of (**321**; R = H) followed by reductive cleavage ($LiAlH_4$) afforded enantiomerically pure diol (**322**). Analogous Diels–Alder reaction of (**318**; R = OAc) provided a 3:1 *endo/exo* mixture of (**321**; R = OAc) (83% yield, containing less than 5% of **320**; R = OAc), which was transformed into the optically pure *C*-nucleoside precursor (**323**) *via* a C–C bond cleavage by retroaldolization–reduction.

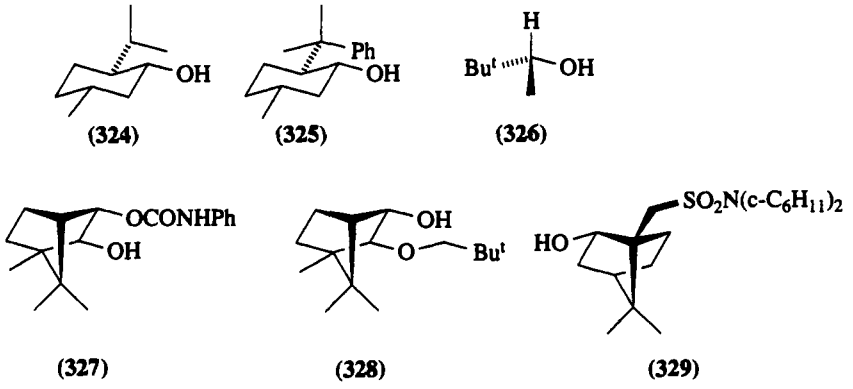
Comparison of Schemes 77 and 79 reveals that the topological interaction of the two menthyl ester groups is fundamentally different in [4 + 2] additions of fumarates (**308**) compared with those of methylenemalonates (**318**). In the latter, both ester auxiliaries cooperate in terms of activating the dienophile through formation of a stable chelate (**319**) but their individual stereoface biases in (**319**) are reversed. However, the observed π-face discrimination can be rationalized by assuming that the C-2,C-3 moiety of cyclopentadiene is more bulky than the 5-CH_2 group so that orientations c and d are favored over orientations a and b. Consistent with this hypothesis, no asymmetric induction could be achieved on addition of (**318**; R = H) to cyclohexadiene, which has comparably bulky C-2,C-3 and C-5,C-6 moieties.

The modest stereoface directing influence of one menthyl auxiliary in the addition of cyclopentadiene to the acrylate of (1*R*)-menthol (**324**) led to the development of improved alcohol auxiliaries, *e.g.* (**325**) to (**329**) (Scheme 80).

Without going into detail (see ref. 84), the use of neopentyl ether (**328**) is outlined here as a representative example (Scheme 81, Table 17).[90] Its acrylate (**330a**) underwent $TiCl_2(OPr^i)_2$-promoted addition of cyclopentadiene with >20:1 *endo/exo* selectivity and outstanding π-face discrimination to give norbornene (**331a**) in almost quantitative diastereoisomeric purity (entry 1); reductive cleavage regenerated the auxiliary (**328**) and afforded virtually pure alcohol (**332a**) in excellent overall yield. The less reactive butadiene required more stringent reaction conditions ($TiCl_4$, –8 °C, 112 h) but still proceeded with high chiral efficiency (entry 2). In contrast, crotonate (**330c**), deactivated by the C_β-positioned methyl group, failed to give the cyclopentadiene adduct (**331c**) in yields of >7% (entry 3).

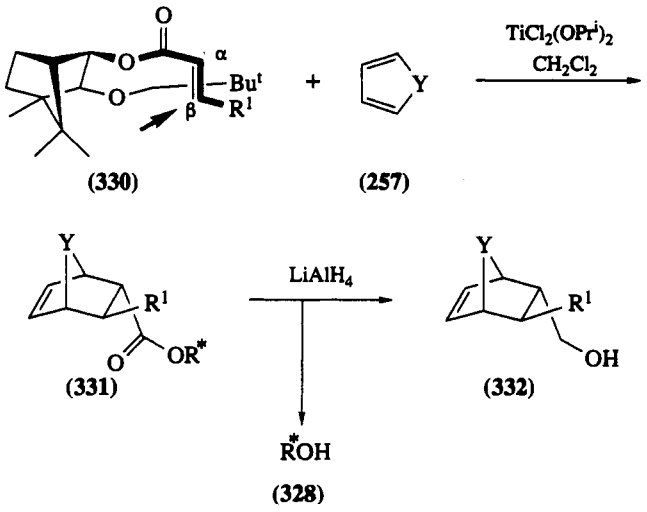


Scheme 79



Scheme 80

These observations are consistent with a steric shielding of the C_α,C_β-face in coordinated (**330**) by the Bu^t group which directs the diene to the opposite face. However, the addition process still suffers from steric hindrance due to the tetragonalization of the C_α and C_β centers, and slows down with crotonate (**330c**) to such an extent that polymerization predominates.

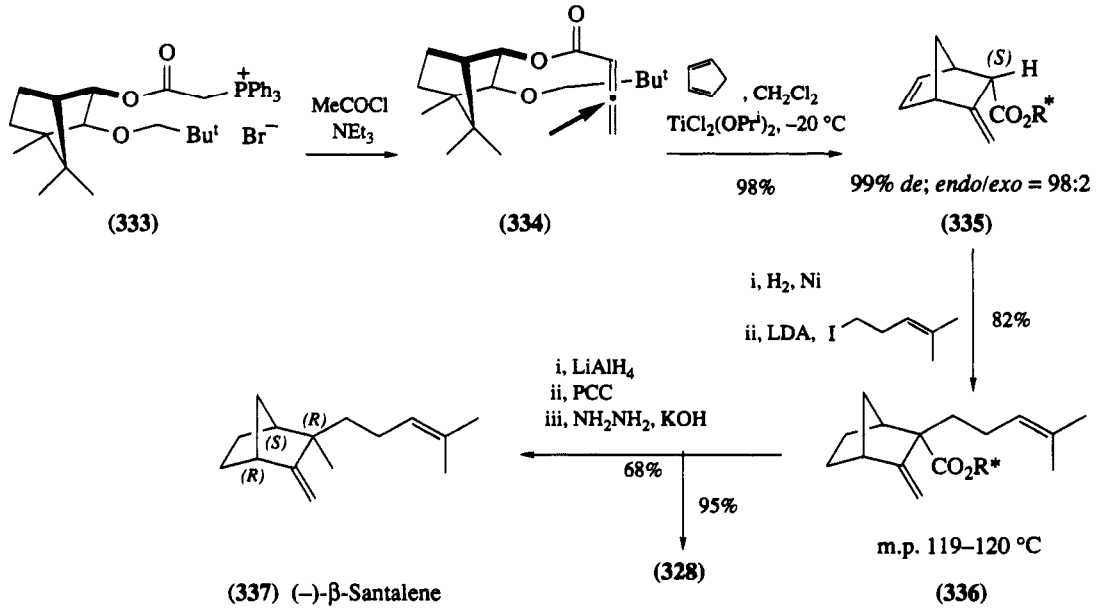


Scheme 81

Table 17 Asymmetric Diels–Alder Reactions of Neopentyl Ether Shielded Acrylates (Scheme 81)

Entry	*Dienophile* R^1	*Diene* *Y*	*Lewis acid*	*Temp. (°C)* *(time, h)*	*Yield (%)* *(331)*	*ee (%)* *(332)*
1 **a**	H	CH_2	$TiCl_2(OPr^i)_2$	–20 (4)	95	99.2
2 **b**	H	H_2	$TiCl_4$	–8 (112)	98	96
3 **c**	Me	CH_2	$TiCl_2(OPr^i)_2$ or $TiCl_4$	–20 to 20 (4–150)	<10	—

Allenic ester (**334**), nevertheless, displayed a sufficiently high dienophilicity towards cyclopentadiene to give, in the presence of $TiCl_2(OPr^i)_2$, *exo*-methylenenorbornene (**335**) in high yield and stereochemical purity (Scheme 82).[90b] The Diels–Alder process (**334**) → (**335**) served as the key step for a synthesis of enantiomerically pure (–)-β-santalene (**337**). The conversion of (**335**) into the natural product involved notably intermediate (**336**) which, owing to the attached auxiliary, could be efficiently purified by crystallization.

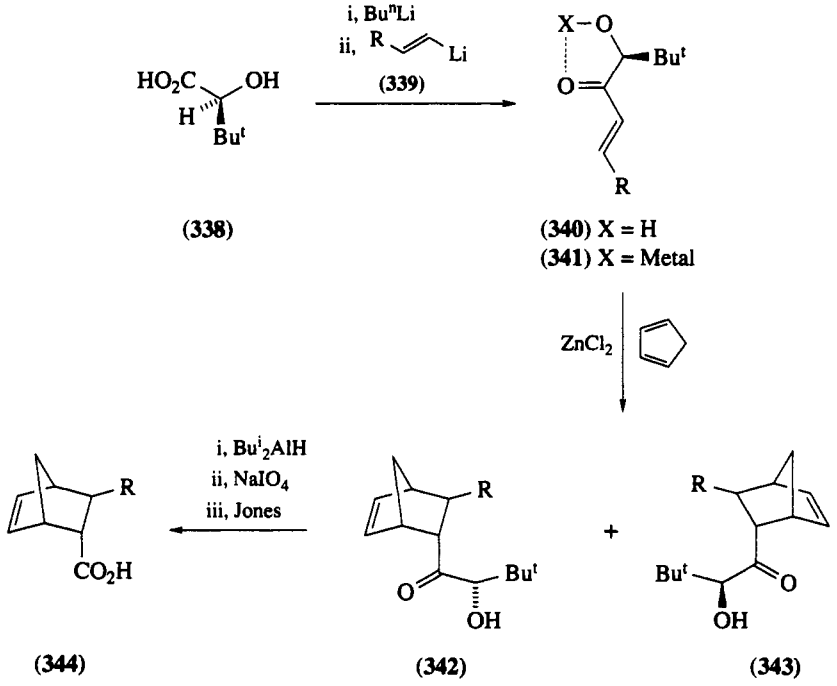


Scheme 82

In the following phase of development (*vide infra*) the scope of asymmetric Diels–Alder reactions was extended to include β-alkyl-substituted dienophiles and less-reactive dienes by means of 'activating' dienophile auxiliaries.

(ii) α,β-Unsaturated Hydroxy Ketones

The crucial role of chelation in terms of increasing rigidity and reactivity of chiral dienophiles was first demonstrated (1983) with α-hydroxy ketone derivatives (Scheme 83, Table 18).[91] Conjugated α-hydroxy ketones (**340**) and their enantiomers were prepared *via* separation of acid (**338**) from its enantiomer, followed by successive treatment with Bu^nLi and the appropriate vinyllithium reagent (**339**).



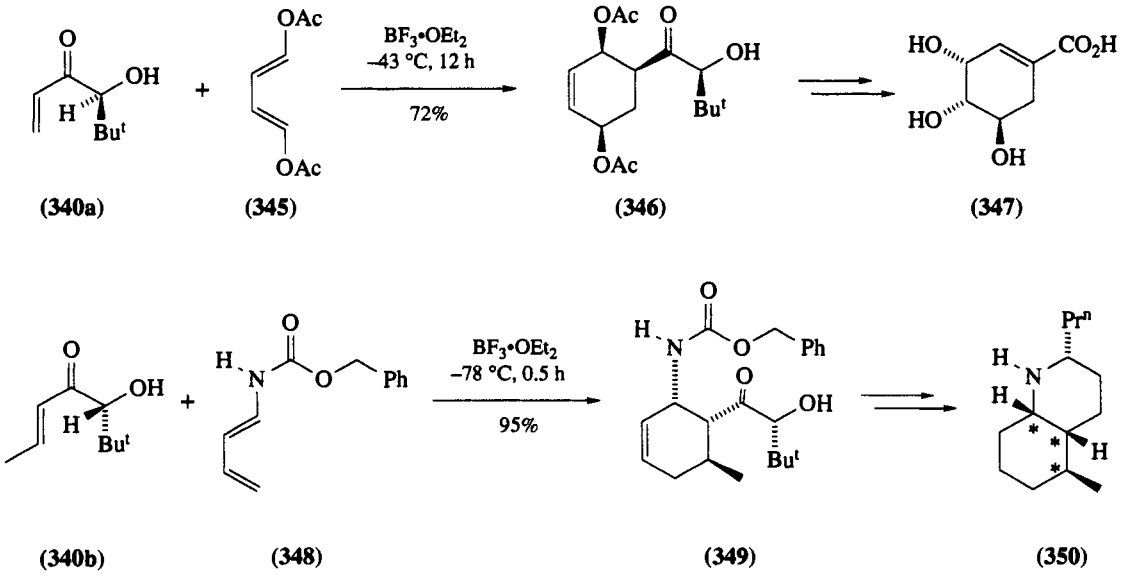
Scheme 83

Table 18 Diels–Alder Reactions of α,β-Unsaturated Hydroxy Ketones with Cyclopentadiene (Scheme 83)

Entry	*R*	*Lewis acid* (1 mol equiv.)	*Temp.* (°C) *(time,* h)	*Yield* (%)[a]	*endo/exo* *(C=O)*	*Ratio* *(342)/(343)*
1 **a**	H	—	–20 (24)	90	89:11	99:1
2 **a**	H	$ZnCl_2$	–43 (1)	95	94:6	>99:<1
3 **b**	Me	—	r.t. (72)	84	83:17	98.5:1.5
4 **b**	Me	$ZnCl_2$	–20 (16)	90	94:6	>99:<1

[a]Combined yield of *endo* and *exo* adducts.

Addition of cyclopentadiene to (**340a**) occurs readily at –20 °C even in the absence of a Lewis acid (Table 18, entry 1) to give adducts (**342a**) and (**343a**) in a ratio of 99:1. This high diastereotopic π-face differentiation undoubtedly derives from hydrogen bonding, which constrains the chiral center within a rigid five-membered ring. The bulky *t*-butyl group enforces the C=O/C=C *syn* conformation and directs the diene to the opposite enone face. The unusually high reaction rate can also be assigned to hydrogen bonding. In the presence of $ZnCl_2$ or $Ti(OPr^i)_4$, Diels–Alder additions to (**340**) proceed at even lower temperatures with improved *endo* and π-face selectivities (entries 2, 4). Apparently the dienophile system becomes more conformationally rigid and 'activated' in the chelate (**341**), permitting efficient asymmetric Diels–Alder addition of a less-reactive dienophile (entry 4) and of acyclic dienes, as exemplified by Scheme 84.



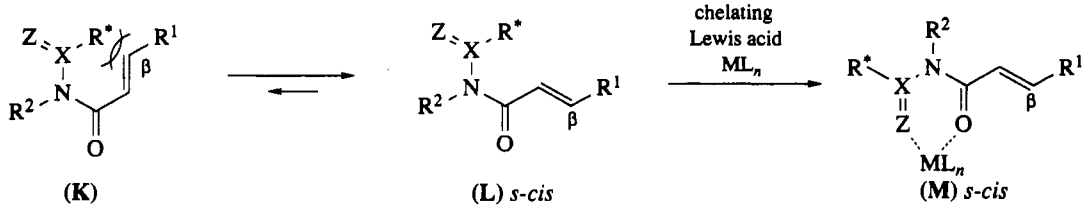
Scheme 84

Thus optically pure shikimic acid (**347**) has been synthesized *via* the addition of 1,4-diacetoxybutadiene (**345**) to (**340a**), whereas the Diels–Alder reaction of *N*-dienylcarbamate (**348**) to hydroxy enone (**340b**) served as the key step for a synthesis of the enantiomer (**350**) of naturally occurring pumiliotoxin C (**142**) (*cf.* Scheme 35).

Regardless of these impressive applications, the preparation of chiral dienophiles remains relatively laborious. A further shortcoming is the inevitable destruction of the valuable chiral auxiliary on oxidative removal, (**342**) → (**344**) (Scheme 83).

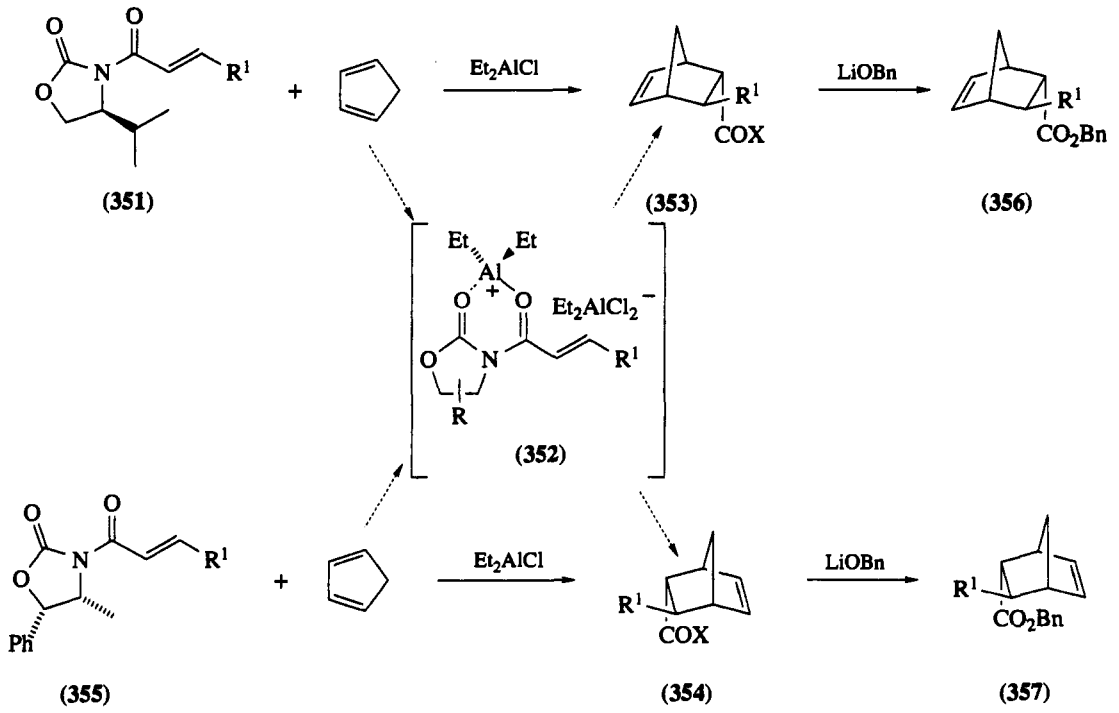
(iii) Chelated N-Acyl-N-enoyl Derivatives

In contrast to nonchelated enoates, α,β-alkenic amide derivatives prefer a C=O/$C_α$=$C_β$ *s-cis* arrangement (**L**) over (**K**) to avoid repulsions between $C_β$/XR* or $C_β$/R^2 (Scheme 85). This also holds for the chelated dienophiles (**M**) where rotation around the (C=O)—N and (X=Z)—N bonds is further inhibited. Such a chelation also increases the dienophilicity of (**M**), which contributes to the versatility of this concept.



Scheme 85

As an extension of the elegant applications of chiral *N*-acyloxazolidinones to asymmetric aldolizations and enolate alkylations, Diels–Alder reactions of the unsaturated derivatives (**351**) and (**355**) were first described in 1984 (Scheme 86, Table 19).[92]



Scheme 86

Table 19 Asymmetric Diels–Alder Additions of Cyclopentadiene to α,β-Unsaturated *N*-Acyloxazolidinones[a] (Scheme 86)

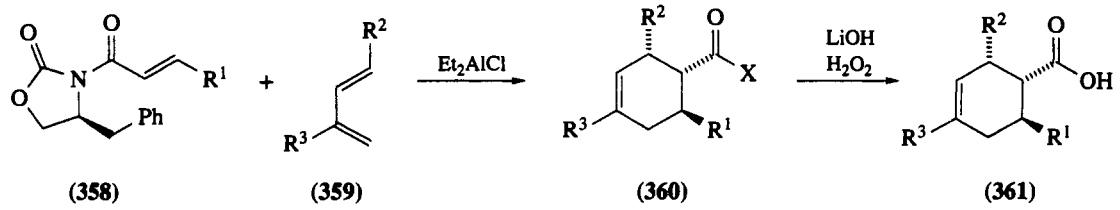
Entry	*Dienophile*	*R*[1]	*endo/exo (C=O)*	*Ratio*[b] *(353)/(354)*	*Purification*	*Pure product*[c]	*Yield (%)*
1 **a**	(**351**)	H	>100:1	93:7	Chrom.	(**353a**)	81
2 **b**	(**355**)	H	100:1	5:95	Chrom.	(**354b**)	82
3 **c**	(**351**)	Me	48:1	95:5	Cryst.	(**353c**)	82
4 **d**	(**355**)	Me	60:1	2:98	Chrom.	(**354d**)	88
5 **e**	(**351**)	Ph[d]	>50:1	93:7	Chrom.	(**353a**)	83

[a]Conditions: 1.4 mol equiv. of Et_2AlCl, CH_2Cl_2, −100 °C, 5 min. [b]Crude reaction mixture. [c]*ds* ≥99:1. [d]At −20 °C, 2.5 h.

Comparative studies of several Lewis acids revealed the essential advantage of using more than 1 equivalent of Et_2AlCl, whereas $TiCl_4$ or $SnCl_4$ gave poor inductions. Thus Et_2AlCl-induced (1.4 equivalent) additions of the valinol derivatives (**351**) to cyclopentadiene were complete within 2 min at −100 °C and gave, with 98–99% *endo* selection, norbornenes (**353**) and (**354**) in ratios of >93:<7 (entries 1, 3, 5). Inverse π-face topicity was displayed with similar efficacy by the norephedrine-derived dienophiles (**355**) (entries 2, 4). After recrystallization or chromatography the resulting major cycloadducts (**353**) or (**354**) were obtained in 81–88% yield and >98% diastereoisomeric purity. Nondestructive cleavage of the oxazolidinone auxiliaries from the adducts (**353**) and (**354**) by 'transesterification' with lithium benzyloxide furnished the benzyl esters (**356**) or their enantiomers (**357**). Sterically hindered addition products were preferably 'saponified' with LiOH/30% H_2O_2 in THF, *e.g.* (**360d**) → (**361d**) (Scheme 87).

The influence exerted by Et_2AlCl on the Diels–Alder additions of dienophiles (**351**) and (**355**) was ascribed to the intermediacy of the chelates (**352**) which exhibit C=C/C=O *syn* planarity. The electron deficiency and rigid structure of (**352**) account for the high reactivity and good π-face differentiation. Even less reactive acyclic dienes add smoothly to such chelated dienophiles (Scheme 87, Table 20). Interestingly, in this case the (*S*)-benzyl derivatives (**358**) displayed much higher diastereoselectivity than

the isopropyl derivatives (**351**). Good stereoface selectivities were achieved on additions to (*E*)-C_β-substituted *N*-enoyloxazolidinones at temperatures between –100 and 0 °C (Table 19, entries 3–5; Table 20, entries 2, 4). Additions to (*Z*)-*N*-crotonoyl or β,β-dimethylacryloyl dienophiles were less useful due to (*Z*/*E*) equilibration or insufficient reactivity. It is worth noting that the chiral oxazolidinone moiety also efficiently directed intramolecular Diels–Alder reactions of 2,7,9-decatrienoyl- and 2,8,10-undecatrienoyl derivatives.[92b]



(**358**) (**359**) (**360**) (**361**)

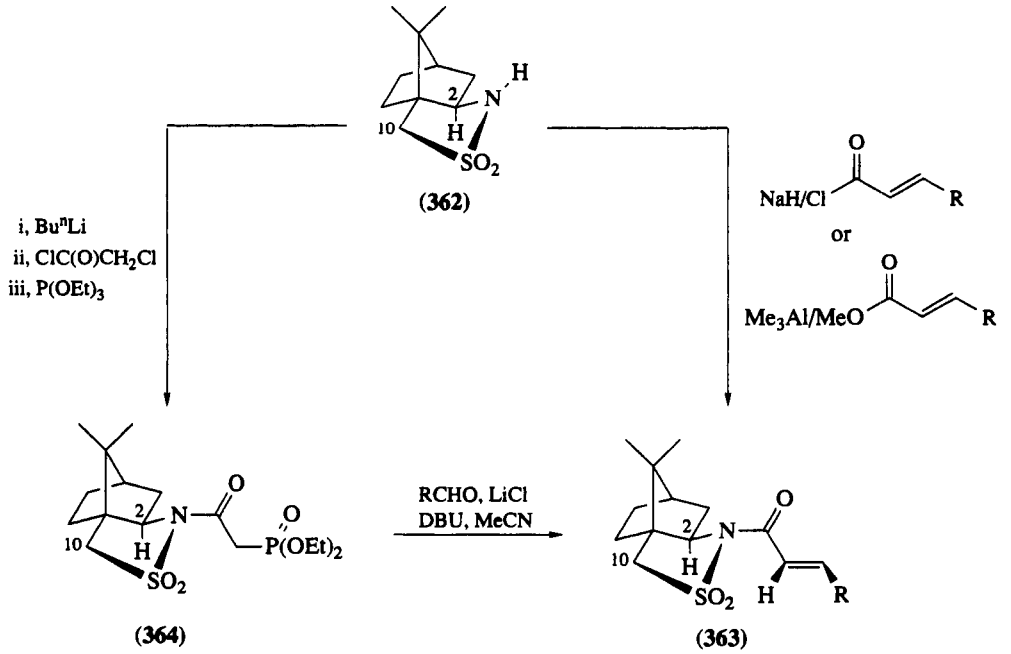
Scheme 87

Table 20 Asymmetric Diels–Alder Additions of Acyclic Dienes to α,β-Unsaturated *N*-Acyloxazolidinones[a] (Scheme 87)

Entry	*Dienophile* R^1	*Temp.* (°C) *(time,* h)	*Diene* R^2	R^3	*Purification*	*Yield* (%) *pure* (**360**)
1 **a**	H	–100 (0.3)	H	Me	Chrom.	85
2 **b**	Me	b	H	Me	Cryst.	83
3 **c**	H	–100 (0.3)	Me	H	Chrom.	84
4 **d**	Me	–30 (6)	Me	H	Cryst.	77

[a]Conditions: 1.4 mol equiv. of Et_2AlCl, CH_2Cl_2. [b]–40 °C, 10 h, then 0 °C, 0.5 h.

Bornane-10,2-sultam (**362**) and its antipode, accessible from inexpensive (+)- and (–)-camphorsulfonic acid in two simple operations, were introduced[93] in 1984 and rank today among the most practical auxiliaries (Scheme 88).[94] Both chirophore enantiomers are commercially available in kg quantities.[93f] Almost all of their *N*-acyl derivatives are stable and can be (1) readily purified by crystallization, (2) directly analyzed by ^1H NMR and/or GC to determine their stereochemical purity, and (3) cleaved (*e.g.* with $LiAlH_4$, LiOH, LiOOH, MeOMgI, *etc.*) under mild conditions without loss of the induced chirality and with excellent recovery of the auxiliary.

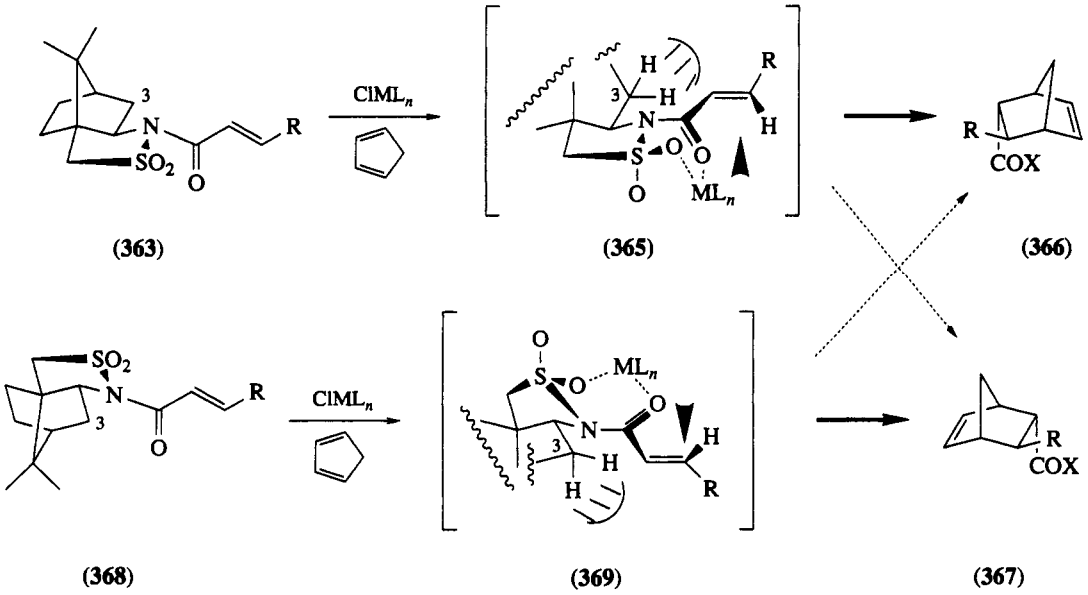


(**362**) (**364**) (**363**)

Scheme 88

The strongly dienophilic N-enoyl compounds (**363**) are readily prepared by direct *N*-acylation (NaH, RCOCl or Me_3Al, RCO_2Me)[94b] or *via* phosphonates (**364**)[93d] by means of a modified Wittig–Horner reaction.

In the presence of $TiCl_4$, $EtAlCl_2$, Et_2AlCl or Me_2AlCl, cyclopentadiene added smoothly to the acryloyl sultam (**363a**) at –130 °C and to the less reactive crotonoyl sultam (**363b**) at –78 °C (Scheme 89, Table 21).[93a,93b,93g] Adducts (**366**) were formed with excellent *endo* as well as π-face selectivities and obtained pure in good yields after crystallization.



Scheme 89

Table 21 Asymmetric Diels–Alder Additions of Cyclopentadiene to *N*-Enoylbornane 10,2-Sultams (Scheme 89)

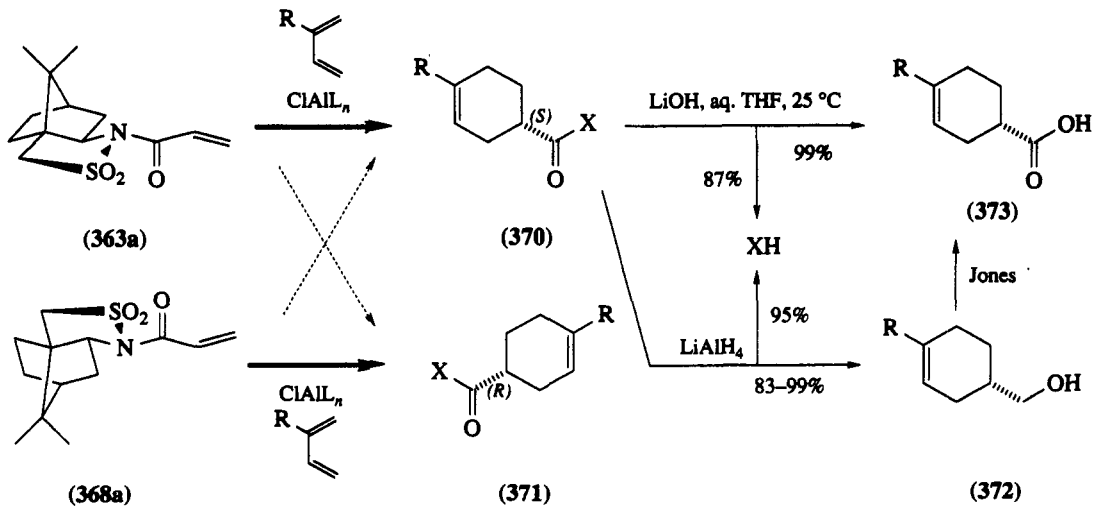
Entry	*Dienophile*	*R*	*Lewis acid* (mol equiv.)	*Temp.* (°C) *(time,* h)	*endo/exo (C=O)*	*Ratio*[a] *(366)/(367)*	*Purification*	*Pure product*[b]	*Yield (%)*
1 **a**	(**363**)	H	$EtAlCl_2$ (1.5)	–130 (6)	200:1	97.5:2.5	Cryst.	(**366a**)	83
2 **a**	(**363**)	H	$TiCl_4$ (0.5)	–130 (6)	25:1	97:3	—	—	—
3 **b**	(**363**)	Me	$TiCl_4$ (0.5)	–78 (1)	100:1	96.5:3.5	Cryst.	(**366b**)	83
4 **b**	(**363**)	Me	$EtAlCl_2$ (1.5)	–78 (18)	24:1	99:1	—	—	—
5 **b**	(**363**)	Me	Et_2AlCl (2)	–78 (18)	—	—	Cryst.	(**366b**)	80
6 **c**	(**368**)	Me	$TiCl_4$ (0.5)	–78 (20)	50:1	3:97	Cryst.	(**367c**)	>57
7 **c**	(**368**)	Me	$EtAlCl_2$ (1.5)	–78 (18)	50:1	3:97	—	—	—

[a]Mixtures of (**366**) + (**367**) obtained in 88–98% yield from dienophile. [b]Diastereomeric purity ≥99%.

$EtAlCl_2$- or Me_2AlCl-promoted Diels–Alder addition of butadiene or isoprene to (**363a**) also proceeded readily at –78 or –94 °C to give, after recrystallization, ~100% pure (*S*)-cyclohexenes (**370**) (Scheme 90, Table 22, entries 8–10). Reductive cleavage of the cycloadducts (**370**) with $LiAlH_4$ furnished the sultam (**362**) (89–95% after crystallization) and gave the pure alcohols (**372**) on simple bulb-to-bulb distillation. Alternatively, saponification of adduct (**370a**) with LiOH afforded acid (**373a**) (a potential precursor for a synthesis of (–)-shikimic acid, **347**) without epimerization.

The sense of asymmetric induction could be easily reversed (Schemes 89, 90; Tables 21, 22, entries 6, 7, 11) by exploiting the readily available enantiomeric dienophiles (**368**). It is worth noting that several of these sultam-controlled [4 + 2] cycloadditions were smoothly carried out with 10 g, 15 g and 112 g batches of dienophile (Tables 21, 22; entries 5,[93g] 10,[93h] 11,[93i] respectively).

Crystallized cyclopentadiene adduct (**367c**) was transformed into enantiomerically pure (–)-1-*O*-methylloganin aglucone (**378**) (Scheme 91).[93b] This synthesis illustrates the potential of asymmetric Diels–Alder reactions which in one step created four stereogenic centers of which all but C-1 (requiring C,O inversion) possess the desired absolute configuration. Extension of the sultam-directed bias to intra-



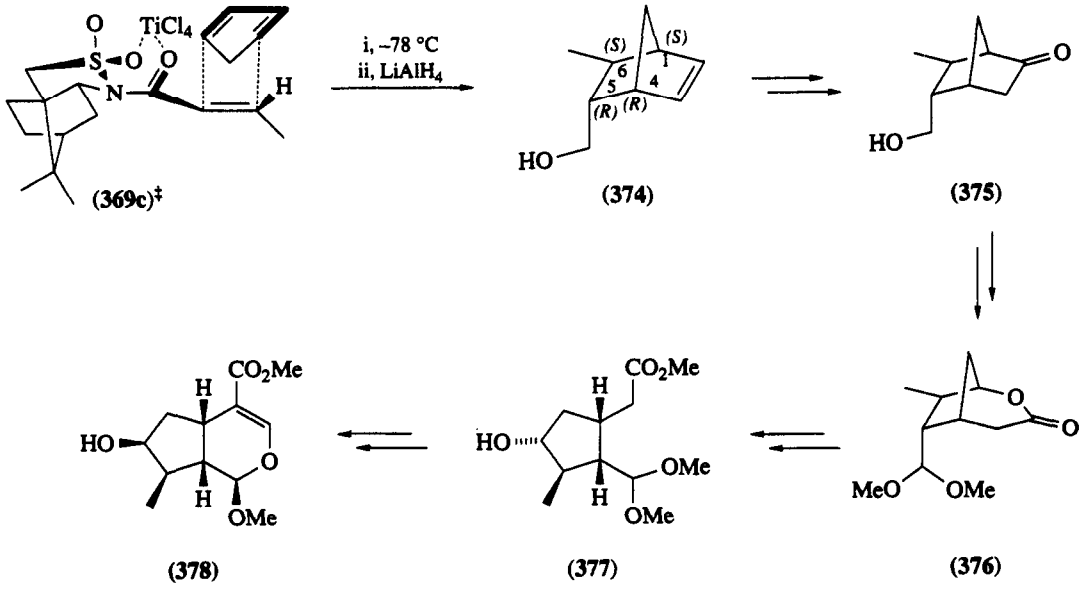
Scheme 90

Table 22 Asymmetric Diels–Alder Additions of Butadiene and Isoprene to *N*-Acryloylbornane 10,2-Sultams in CH_2Cl_2 (Scheme 90)

Entry	*Dienophile*	*Diene R*	*Lewis acid* (mol equiv.)	*Temp.* (°C) *(time,* h)	*Ratio* **(370)/(371)**	*Product cryst.*	*Yield (%)*
8 **a**	(**363a**)	H	$EtAlCl_2$ (1.5)	–78 (6)	98.5:1.5	(**370a**)	81[a]
9[b] **b**	(**363a**)	Me	$EtAlCl_2$ (1.5)	–94 (6)	97.2:2.8	(**370b**)	64[a]
10 **a**	(**363a**)	H	Me_2AlCl (1.5)	–78 (44)	95:5	(**370b**)	53–60[a]
11 **c**	(**368a**)	H	$EtAlCl_2$ (1.5)	–78 (—)	3.5:96.5	(**371a**)	95.9[c]

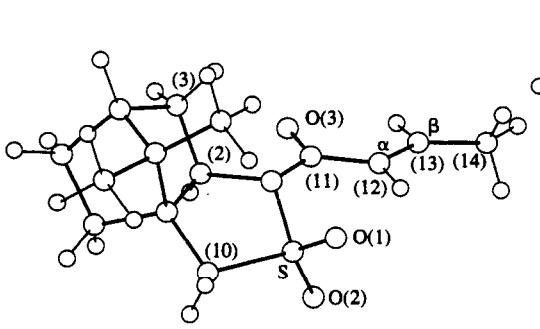
[a]Diastereomeric purity ≥99%. [b] Ref. 93j. [c] Not crystallized.

molecular Diels–Alder reactions proved equally successful[93c] and was exploited for the enantioselective total synthesis of the marine natural product (–)-pulo'upone.[93d]

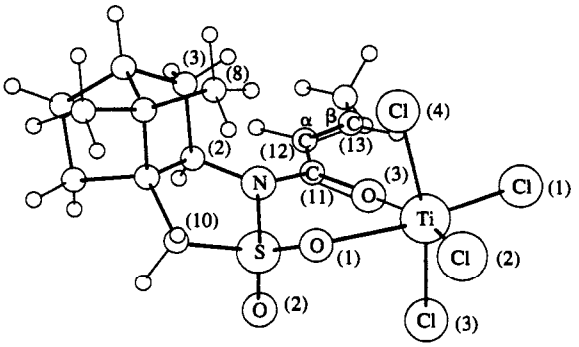


Scheme 91

The remarkable $TiCl_4$- and $EtAlCl_2$-enhanced rate and π-face differentiation of [4 + 2] cycloadditions to *N*-enoylsultams was rationalized in terms of chelates (**365**) and (**369**) (Scheme 89) involving the dicoordinating Lewis acid ML_n, the carbonyl O-atom and the upper sulfonyl O-atom which are attacked by dienes from the π-face opposite to the C-3 methylene group.[93a] Indeed, X-ray crystal-structure analyses of noncoordinated[93a] or $TiCl_4$-chelated *N*-crotonylsultam[93e] show in both cases *s-cis* disposed C═O/C_α═C_β bonds but an NSO_2/C═O *s-trans* arrangement of (**363b**) in the absence of $TiCl_4$ (Scheme 92).



(**363b**)



(**365b**) $ML_n = TiCl_4$

Scheme 92

In the $TiCl_4$ chelate (**365b**) the NSO_2 and C═O groups are locked into a rigid *s-cis* conformation where, compared with H_{exo} of C-3, the Cl atoms play only a minor role in blocking the C_α-*si* face (*cf.* Scheme 93).

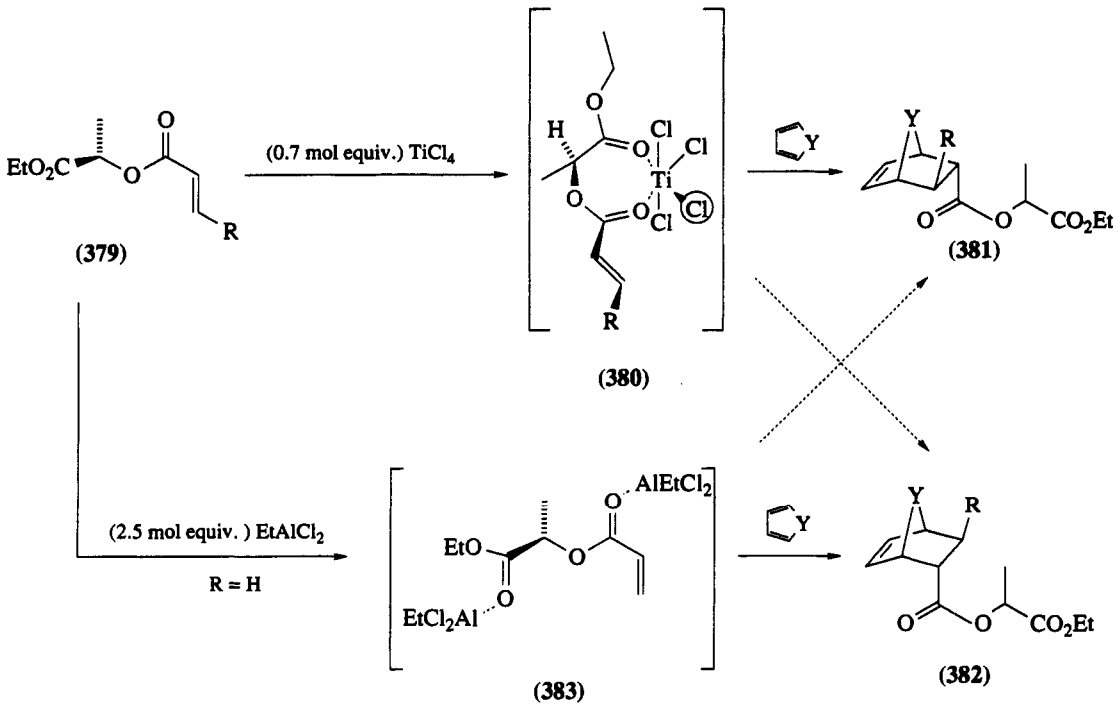
(iv) α,β-Unsaturated Chelated Esters and Amides

The concept of using an ester auxiliary which also contains a 'handle' suitable for chelation was first disclosed in 1984/1985.[95] Thus $TiCl_4$-promoted addition of cyclopentadiene to the acrylate of ethyl (*S*)-lactate (**379**) proceeded readily at –63 °C to give (with a 39:1 *endo/exo* preference) a 93:7 mixture of norbornenes (**381a**) and (**382a**), from which the major product (**381a**) was isolated by MPLC (Scheme 93, Table 23, entry 1). Mild saponification of adduct (**381a**) with LiOH in aqueous THF and purification *via* iodolactonization/elimination provided pure (1*R*,2*R*)-5-norbornene-2-carboxylic acid.

A highly significant X-ray crystal-structure analysis of the isolated $TiCl_4$ complex (**380a**) revealed the following features: chelation of the two ester carbonyl groups by the titanium atom with one of its chloride ligands shielding the C_α-*re* face of the alkenic bond which is *s-cis* relative to the adjacent C═O bond.[95b] It thus appears that during the Diels–Alder process the diene is directed to the C_α-*si* face of the chelated dienophile (**380a**) to avoid the steric bulk of the Cl ligand. Analogous reaction conditions but using $EtAlCl_2$ as a Lewis acid resulted in a similar *endo/exo* selectivity but a reversed face differentiation in favor of product (**382a**) (entry 2). A maximal ratio (**381a**)/(**382a**) = 22:78 attained with 2.5 mol equiv. of $EtAlCl_2$ indicates the 1:2 complex (**383**) to be the reactive species. The critical influence of $TiCl_4$ also shows on additions of 1,3-dienes to the (more reactive) fumarate of ethyl (*S*)-lactate.[87c] The dienes approach predominantly the *si* face of the dienophile in the presence of $TiCl_4$ (1.4–1.5 mol equiv.) (Table 23, entries 3–5), but the opposite *re* face in the absence of Lewis acids (Table 16, entries 6–8).

Prompted by the X-ray studies of the acryloyl lactate–$TiCl_4$ complex (**380a**), commercially available pantolactone was chosen as an auxiliary aiming to facilitate entropically the formation of a seven-membered titanium chelate (**385**). Indeed, using 0.1–0.75 mol equiv. of $TiCl_4$ the acrylate and crotonate of (*R*)-pantolactone (**384**) underwent smooth addition of cyclopentadiene, butadiene and isoprene to give adducts (**386**) and (**387**) in ratios of >93:<7 (Scheme 94, Table 24, entries a–d).[96a,96c] Opposite product ratios were obtained using dienophiles (**388**) derived from (*S*)-pantolactone (entry e)[96b] or (**390**) derived from the more readily available *N*-methyl-2-hydroxysuccinimide (entries f, g).[96c] The major products were purified by crystallization and saponified without epimerization (LiOH, THF/water, r.t.) to furnish the corresponding carboxylic acids.

In close relation to the work on acrylates derived from lactate, pantolactone and 2,5-disubstituted pyrrolidines (*vide infra*), *N*-acryloylproline benzyl ester (**391**) has been studied as a chiral dienophile



Scheme 93

Table 23 Lewis Acid Promoted Diels–Alder Additions of 1,3-Dienes to Acrylates and Fumarates Derived from Ethyl (*S*)-Lactate (Scheme 93)

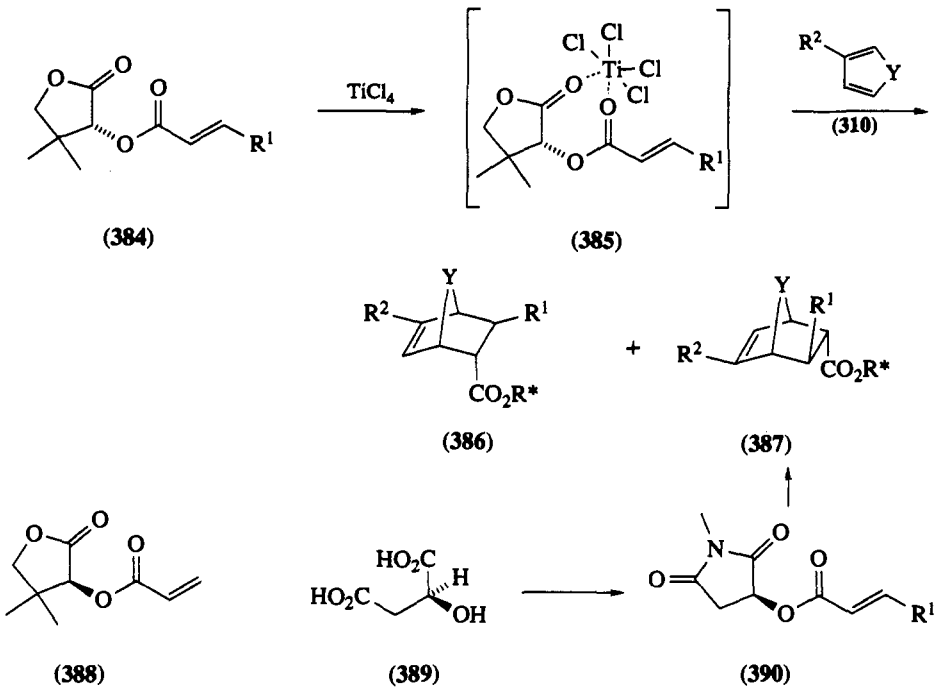
Entry	*R*	*Y*	*Lewis acid* (mol equiv.)	*Solvent*	*Temp.* (°C)	*Yield (%)* (**381**) + (**382**)	*Ratio* (**381**)/(**382**)
1 **a**	H	CH_2	$TiCl_4$ (0.75)	CH_2Cl_2/hexane	–63	88	93:7
2 **a**	H	CH_2	$AlEtCl_2$ (2.5)	CH_2Cl_2	–63	—[a]	22:78
3 **b**	(*S*)-$CO_2CH(Me)CO_2Et$	CH_2	$TiCl_4$ (1.5)	CH_2Cl_2	–40	99	95:5
4 **c**	(*S*)-$CO_2CH(Me)CO_2Et$	$(CH_2)_2$	$TiCl_4$ (1.4)	CH_2Cl_2/hexane	–24	97	92:8
5 **d**	(*S*)-$CO_2CH(Me)CO_2Et$	H_2	$TiCl_4$ (1.4)	CH_2Cl_2	–50	95	90:10

[a]Yield not reported.

(Scheme 95, Table 25).[97] Diels–Alder reaction of (**391**) with cyclopentadiene, mediated by $TiCl_4$ (1 mol equiv.) at 0 °C, gave adducts (**394a**) and (**395a**) in a ratio of 96.5:3.5 (85%, entry 1). Analogous to the reaction of the *O*-acryloyl lactate it is assumed that the diene adds preferentially from the C_α-*si* face of the complex (**392**) which is shielded at the C_α-*re* side by a chloride ligand. Again replacement of $TiCl_4$ by $EtAlCl_2$ resulted in a reversal of stereoface selection, yielding a 10:90 mixture of stereoisomers (**394a**) and (**395a**), attributed to the reaction of a monocoordinated dienophile (**396**) (entry 2). $TiCl_4$-promoted reaction of dienophile (**391**) with less reactive dienes (entries 3–7) had to be carried out at 20 °C but still gave products (**394**) + (**395**) (24–75%) in ratios of >90:<10. Comparing the $TiCl_4$-chelated *N*-acryloylproline (**392**) with the *O*-acryloyl analogs (**380**) and (**385**) shows that the amide derivative is less dienophilic but sufficiently rigid to permit good topological differentiation at a relatively high temperature. However, purification of the major product could only be achieved with (**394a**) (chromatography + crystallization) and cleavage of the amide bond required *O*-alkylation ($Me_3O^+BF_4^-$) prior to hydrolysis.

Similar, but less easily accessible, dienophiles (**397**) were reported to undergo preferential *si* face additions of cyclopentadiene at 0 °C when mediated by $AlCl_3$ or Et_2AlCl (Scheme 96, Table 26).[98] This diastereodifferentiation was most significant with $AlCl_3$-coordinated (**397c**) (entry 3) and still good, but much less *endo* selective, in the absence of $AlCl_3$ (entry 5). Treatment of *endo* products (**398**) with I_2 in aqueous DME and reduction of the iodolactone with Zn/MeOH furnished (1*R*,2*R*,4*R*)-5-norbornenecarboxylic acid (68%) and the recovered pyrrolidine auxiliary (63%).

Dienophiles carrying a sugar moiety as a face-directing element may also benefit from chelation. Two recent examples are depicted in Scheme 97.[99] Treatment of the 5-*O*,6-*O*-disilylated 3-*O*-acryloyl-1,2-*O*-isopropylidene-α-glucofuranose (**400**) with $TiCl_4$ gave a complex which was assigned chelate structure



Scheme 94

Table 24 $TiCl_4$-catalyzed Additions of 1,3-Dienes to *O*-Enoylpantolactone and *N*-Methyl-2-enoyloxysuccinimide (Scheme 95)

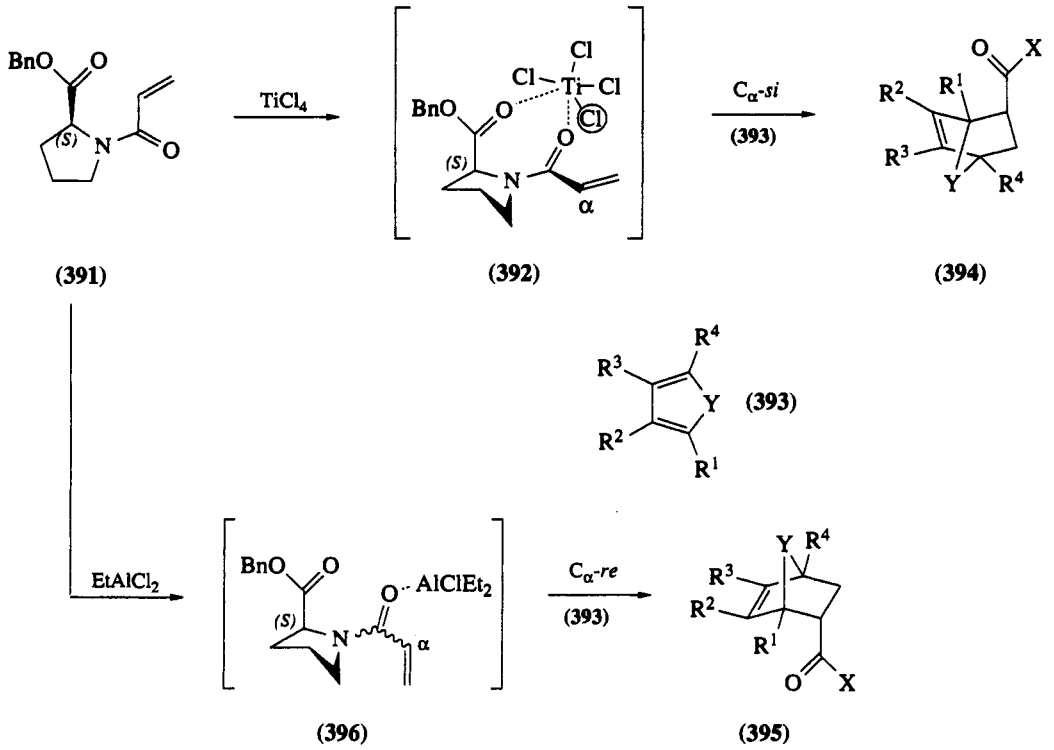
Entry	*Dienophile*	*Diene* R^2	*Diene* Y	*Temp.* (°C)	*Ratio* (386)/(387) *crude*	*Ratio* (386)/(387) *cryst.*	*Yield (%) major prod. cryst.*
a	(384) R^1 = H	H	CH_2	−10	97:3[a]	≥99.9:0.1	(386) 81
b	(384) R^1 = H	H	H_2	0	93:7	>99.5:0.5	(386) 73
c	(384) R^1 = H	Me	H_2	0	97:3	>99.5:0.5	(386) 76
d	(384) R^1 = Me	H	CH_2	−24	97.5:2.5[b]	>99:1	(386) 74
e	(388) —	H	H_2	−32	4.5:95.5	—	(387) >61[c]
f	(390) R^1 = H	H	CH_2	−10	3:97[a]	1:>99	(387) 86
g	(390) R^1 = Me	H	CH_2	−24	3:97[b]	1:>99	(387) 62

[a] *Endo/exo* = 20–52:1. [b] *Endo/exo* = 13–14:1. [c] Crystallized product after subsequent saponification/epoxidation/lactonization.

(**401**) featuring an *s-trans* C=O/C_α=C_β arrangement. Addition of cyclopentadiene at −78 °C gave exclusively the *endo* products (**402**; R = CH_2OH) and (**403**; R = CH_2OH) in a ratio of 93:7, which corresponds to a preferred diene attack from the less-hindered C_α-*si* face. Reactions of (**400**) with 1,3-cyclohexadiene, 1,3-butadiene and anthracene were less efficient (r.t., 12 d, yields <30%) and less diastereoselective. The analogous α-xylofuranose-derived complex (**405**) was expected to be more dienophilic. Cyclopentadiene reacted with (**404**) at −78 °C to afford (**402**; R = H) in 73% yield. No stereoisomeric product could be detected (^1H and ^{13}C NMR).

(v) α,β-Unsaturated Iron Acyl Complexes

Chiral iron acyl complexes [$(C_5H_5)Fe(CO)(PPh_3)COR$] undergo an impressive range of face-selective carbon–carbon bond-forming processes which also includes the $ZnCl_2$-mediated [4 + 2] addition of cyclopentadiene to the acryloyliron dienophile (**406**) (Scheme 98).[100] The *re*-face-directing bias of the auxiliary apparently relies on a predominant C=O/CO *s-trans* and a C=O/C_α=C_β *s-cis* disposition, resulting in a blocking of the C_α-*si* face by a phenyl substituent. The reaction mixture containing (**407**) and two minor products (84:12:4) was treated with ammonium cerium(IV) nitrate and then with $I_2/NaHCO_3$ to give iodolactone (**408**) in >95% *ee* (57% yield from **406**).

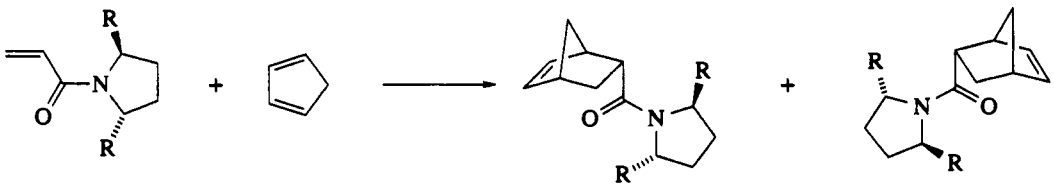


Scheme 95

Table 25 Lewis Acid Catalyzed Diels–Alder Reactions of Dienes to *N*-Acryloyl-(*S*)-proline Benzyl Ester (**391**) (Scheme 95)

Entry	*Diene (393)* R^1	R^2	R^3	R^4	*Y*	*Lewis acid*	*Temp.* (°C)	*Yield (%)*[a]	*Ratio (394)/(395)*	*Ratio endo/exo*
1 **a**	H	H	H	H	CH_2	$TiCl_4$	0	85	96.5:3.5	92:8
2 **a**	H	H	H	H	CH_2	$EtAlCl_2$	0	96	10:90	92:8
3 **b**	H	H	H	H	$(CH_2)_2$	$TiCl_4$	20	24	94:6	—[b]
4 **c**	Me	H	H	H	H_2	$TiCl_4$	20	41	89:6.5:2.7:1.8[c]	—
5 **d**	Me	H	H	Me	H_2	$TiCl_4$	20	42	90:10	—
6 **e**	H	H	Me	H	H_2	$TiCl_4$	20	72	92:8	—
7 **f**	H	Me	Me	H	H_2	$TiCl_4$	20	75	90:10	—

[a]Combined yield of *endo* and *exo* products. [b]*Endo/exo* ratio not reported. [c]Minor isomers not assigned.



(**397**) (**398**) (**399**)

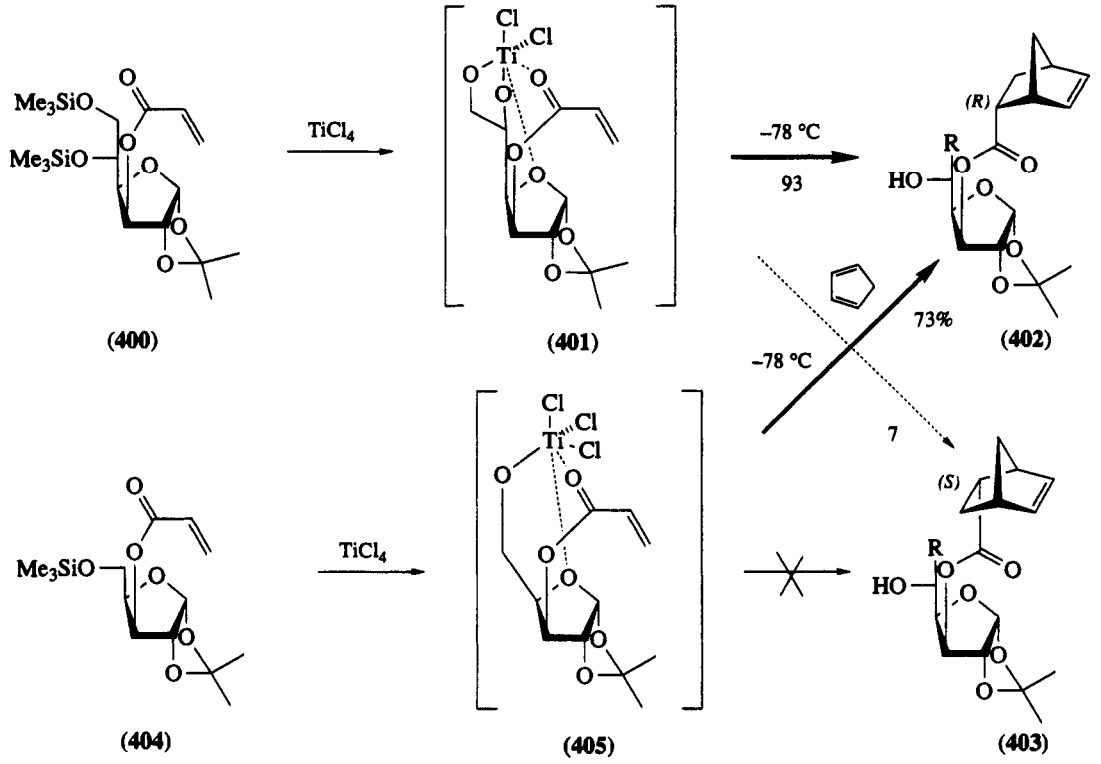
a: R = CO_2Me; **b**: R = CH_2OMe; **c**: R = CH_2OCH_2OMe

Scheme 96

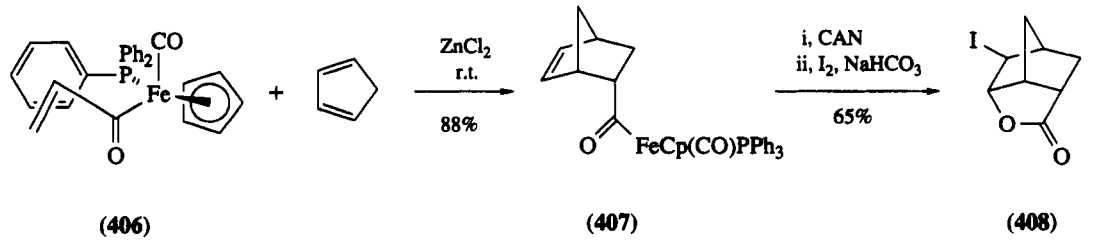
Table 26 Addition of Cyclopentadiene to *N*-Acryloyl *trans*-2,5-Disubstituted Pyrrolidines (**397**) (Scheme 96)

Entry	*R*	*Lewis acid*[a]	*Temp.* (°C) *(time,* h*)*	*Yield*[b]	*endo/exo*	*Ratio (398)/(399)*
1 **a**	CO_2Me	$AlCl_3$	0 (2)	85	87:13	97:3
2 **b**	CH_2OMe	$AlCl_3$	0 (1)	71	89:11	99:1
3 **c**	CH_2OCH_2OMe	$AlCl_3$	0 (1)	76	95:5	99:1
4 **c**	CH_2OCH_2OMe	Et_2AlCl	0 (1)	73	86:14	99:1
5 **c**	CH_2OCH_2OMe	None	r.t. (42)	75	69:31	95:5

[a]1.2 mol equiv. [b]Combined yield of *endo* and *exo* adducts.



Scheme 97



(406) (407) (408)

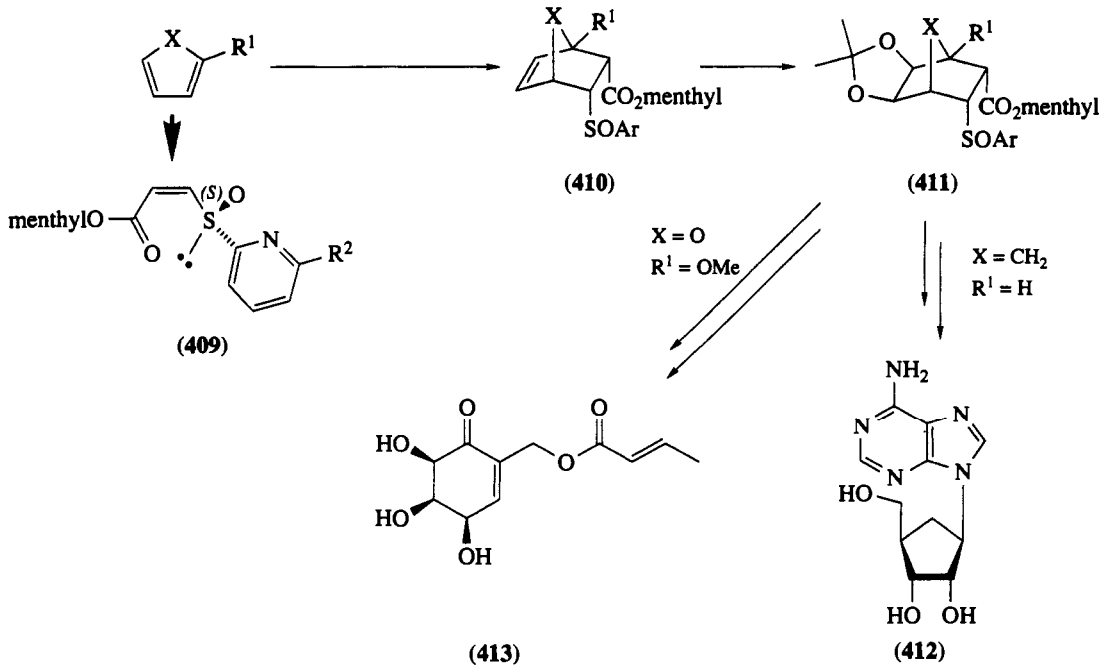
Scheme 98

(vi) Vinyl Sulfoxides

The chirality of a sulfoxide moiety may be also exploited for asymmetric [4 + 2] additions of 1,3-dienes to vinyl sulfoxides. However, the latter are poor dienophiles and thus require an additional 'activating' group.

Hence the menthyloxycarbonyl group in (**409**) facilitates the separation of its pure enantiomers as well as their *endo*-selective addition to 1,3-dienes.[101] (The *endo*-directing influence of (*E*)- or C-1-positioned carbalkoxycarbonyl substituents opposes that of the sulfoxide). The *cis*-related ester group, furthermore,

favors a conformation of (**409**) where the sulfur lone pair and the C=C bond are *syn* periplanar (Scheme 99, Table 27).[101a]



Scheme 99

Table 27 Sulfoxide Directed Asymmetric Diels–Alder Additions to (*Z*)-3-Arylsulfinylacrylates (Scheme 99)

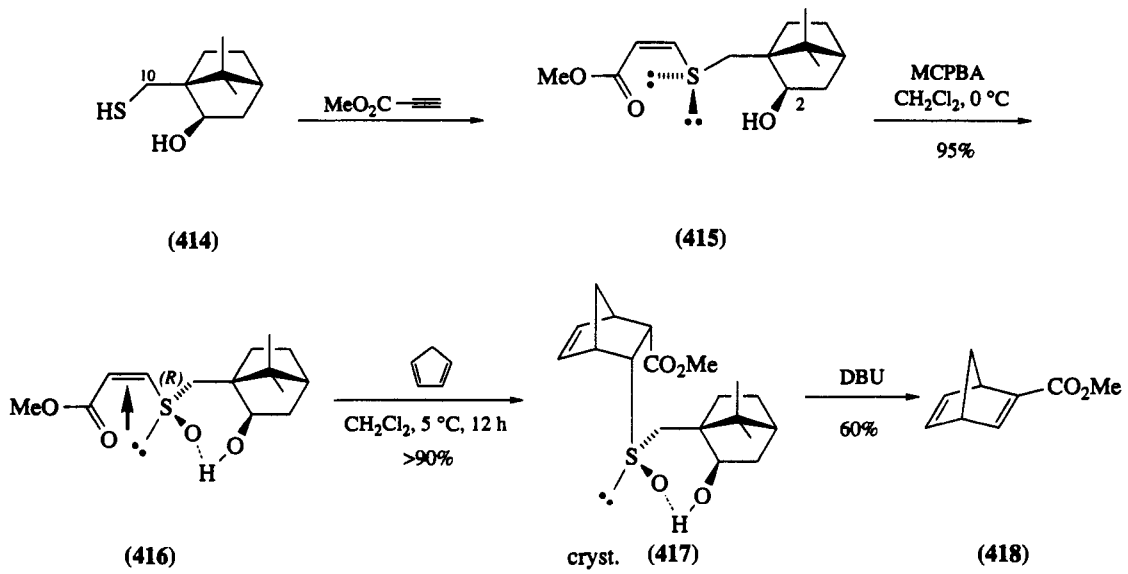
Entry	*Diene*		*Dienophile*	*Temp.* (°C)	*Lewis*	*Yield* (%)
	X	R^1	R^2	(*time*, h)	*acid*	(**410**)
1 **a**	CH_2	H	H	−78 (3)	Et_2AlCl	96
2[a] **b**	$(CH_2)_2$	H	H	r.t. (96)	$ZnBr_2$	~100
3 **c**	O	OMe	CF_3	0 (144)	None	>72

[a]Conditions: CH_2Cl_2, 1.1–1.2 equiv. Lewis acid.

Et_2AlCl-promoted reaction of (**409**; R^2 = H) with cyclopentadiene (−78 °C) gave almost exclusively the cycloadduct (**410a**) in 96% yield, consistent with a diene approach *syn* to the sulfoxide oxygen atom (entry 1). Transformation of the Diels–Alder product (**410a**) into the carbocyclic nucleoside (−)-aristeromycine (**412**) involved dihydroxylation of the alkenic bond, removal of the sulfur moiety by elimination, and ozonolysis of the resulting ester-conjugated double bond.[101b] [4 + 2] Cycloaddition of the less-reactive cyclohexa-1,3-diene to (**409**; R^2 = H) proceeded efficiently in the presence of $ZnBr_2$ (entry 2), providing product (**410b**) in quantitative yield.[101c] A synthesis of glyoxalase inhibitor I (**413**) relied on the analogous addition of 2-methoxyfuran which is incompatible with the presence of a Lewis acid. To this end the more reactive dienophile (**409**; $R^2 = CF_3$) was treated with 2-methoxyfuran under nonacidic conditions (0 °C, 6 d) to give (**410c**; X = O, R^1 = OMe) in high purity (entry 3).[101d] Conversion of the resulting crude product to acetal (**411**; X = O, R^1 = OMe) (72% from **409**; 98:2 stereoisomer mixture by HPLC) followed by crystallization provided pure (**411**; X = O, R^1 = OMe) which was transformed into the natural product (**413**).

Instead of preparing the sulfoxide chirophore *via* a separation of diastereoisomers, the diastereoselective oxidation of a sulfide offers an interesting alternative. Thus Michael addition of 10-mercaptoisoborneol (**414**) to methyl propiolate furnished (*Z*)-vinyl sulfide (**415**) which underwent a hydroxy-directed oxidation (MCPBA) to give the (sulfur-*R*)-vinyl sulfoxide (**416**) in a highly selective manner (Scheme 100).[102]

Diels–Alder addition of cyclopentadiene (1.3 mol equiv., CH_2Cl_2) to the purified dienophile (**416**) proceeded smoothly at 5 °C in a virtually quantitative *endo* fashion *syn* to the H-bonded sulfoxide oxygen atom (assuming that formula **416** depicts the reactive conformation). Stereoisomerically pure adduct



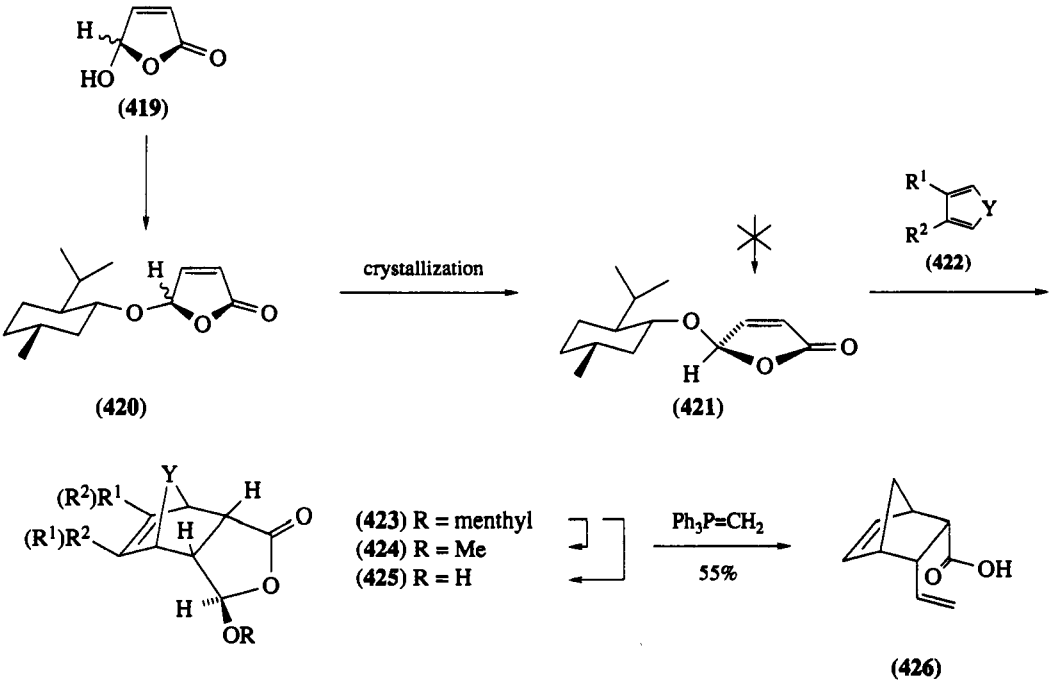
Scheme 100

(**417**) was subjected to DBU-induced elimination, affording norbornadiene (**418**) in high enantiomeric purity.[102]

(vii) Endocyclic Dienophiles

Covalent incorporation of the dienophile into a ring procures an additional rigidity and, as a consequence, the potential of *endo* and stereoface selective cycloadditions of 1,3-dienes in the absence of Lewis acids at high temperatures. On the other hand, this requires well-defined structural elements which are difficult to remove but can be put to advantage within a synthetic scheme.

Optically pure menthyloxybutyrolactone (**421**) was obtained by crystallizing a mixture of both epimers (**420**) (prepared from racemic **419**) under equilibrating conditions. Cycloadditions of dienes occurred at 110–120 °C exclusively to the much less hindered 'bottom' face of (**421**) with >97% *endo* selectivity to give adducts (**423**) (Scheme 101, Table 28).[103]



Scheme 101

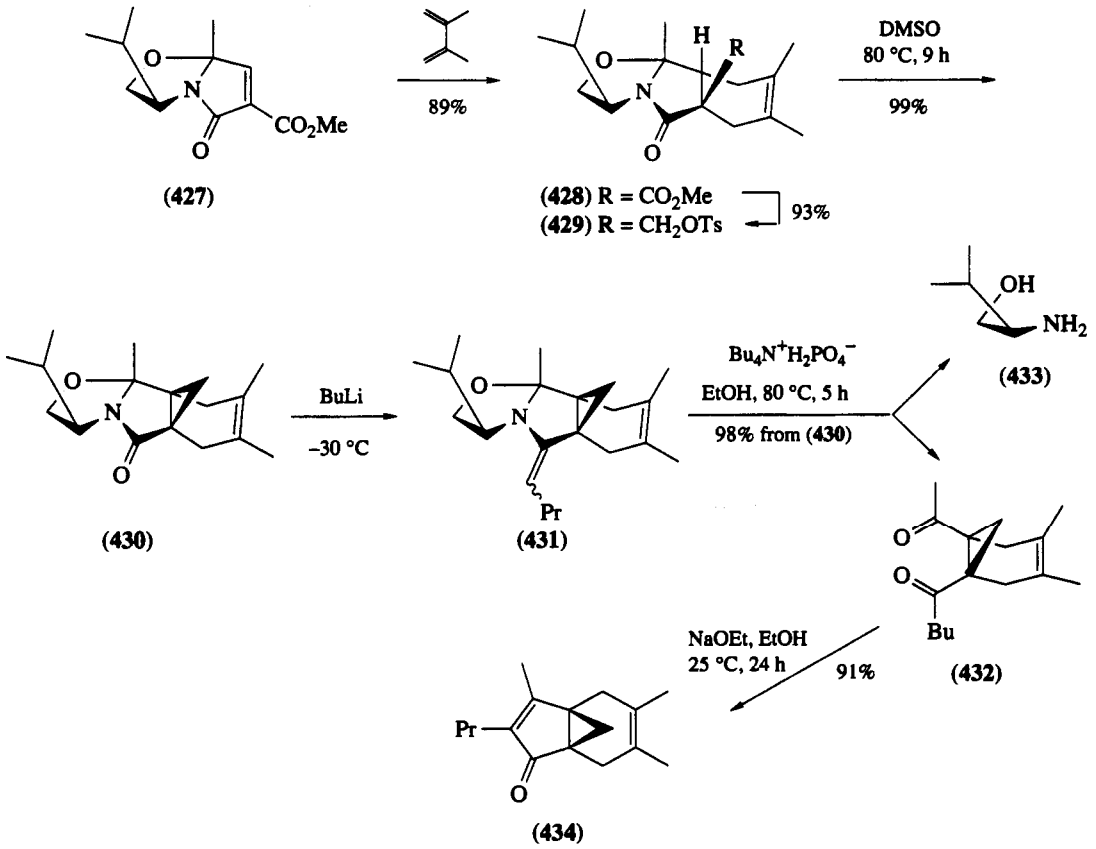
Table 28 Noncatalyzed Diels–Alder Reactions of 5-(Menthyloxy)-2(5*H*)-furanone with 1,3-Dienes (Scheme 101)

Entry	R^1	R^2	*Y*	*Temp.* (°C)	*Yield (%) of* (**423**)[a]
1 **a**	H	H	CH_2	110	65
2 **b**	H	H	$(CH_2)_2$	120	47
3 **c**	H	H	H_2	120	45
4 **d**	Me	H	H_2	120	56[b]
5 **e**	Me	Me	H_2	120	44

[a] 96% diastereomeric excess (^1H, ^{13}C NMR). [b] 50:50 mixture of regioisomers.

However, the addition of isoprene (entry 4) reveals a serious lack of regiochemical control under these noncatalyzed reaction conditions. Removal of menthol by methanolysis or hydrolysis (SiO_2, H_2O) afforded enantiomerically pure methoxy- or hydroxy-substituted lactones (**424**) or (**425**). Wittig reaction of (**425a**) provided carboxylic acid (**426**), a key intermediate for a synthesis of 6,7-dehydroaspidospermidine.

The versatile functionality pattern of bicyclic *N,O*-acetal-γ-lactams (found in conjunction with their π-face-selective alkylation) can also be applied to Diels–Alder reactions of the corresponding alkenic methoxycarbonyl-activated derivative (**427**) (Scheme 102).[104] Noncatalyzed addition of 2,3-dimethylbutadiene to dienophile (**427**) (60 °C, 8 h) proceeded exclusively from the π-face opposite the isopropyl substituent. The reactivities of the latent immonium and carbonyl groups in adduct (**428**) were exploited during transformation into [1,3,4]propellane (**434**).

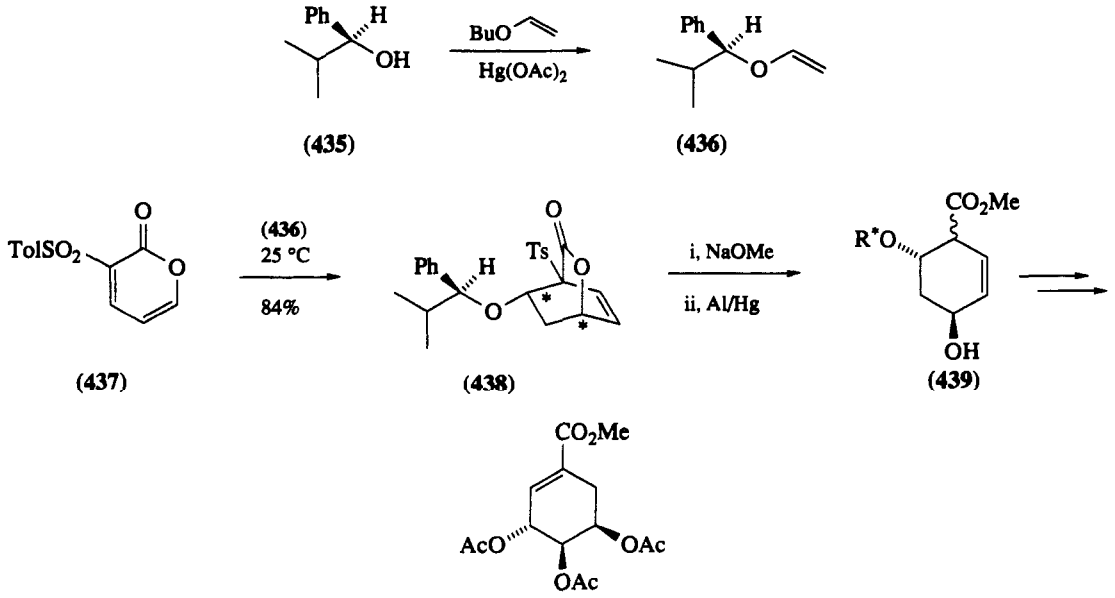


Scheme 102

(viii) Vinyl Ether

An interesting example of an asymmetric 'inverse-electron-demand' Diels–Alder reaction is the smooth addition of chiral vinyl ether (**436**) (readily accessible from **435**) to the electron-deficient 3-to-

luenesulfonyl pyrone (**437**) (Scheme 103).[105] The pure adduct (**438**), isolated by chromatography in 84% yield, was transformed into the (–)-4-epishikimic acid derivative (**440**) *via* cyclohexene intermediate (**439**).



Scheme 103

4.1.6.2.2 Chiral dienes

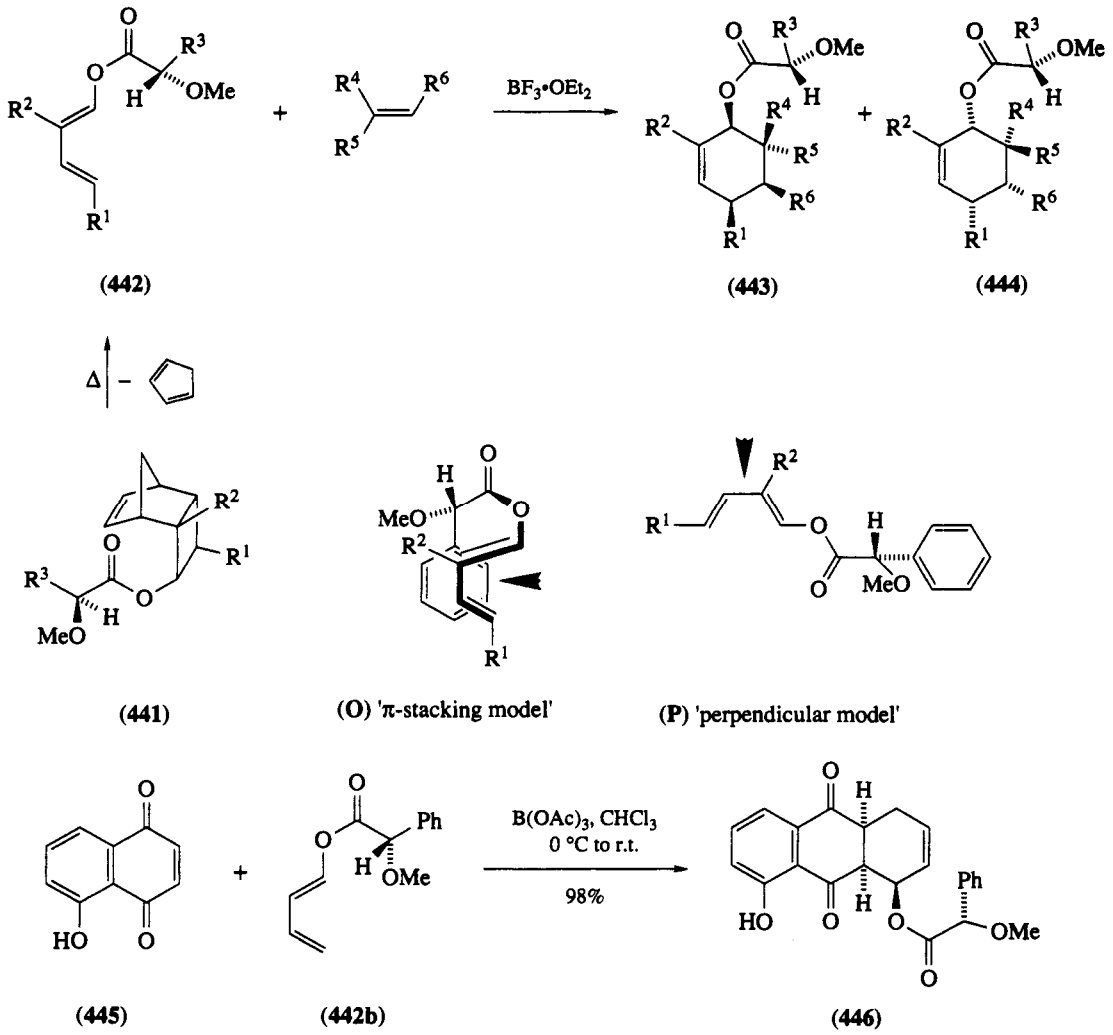
Asymmetric Diels–Alder reactions of dienes substituted with a removable chiral moiety with prochiral dienophiles have been much less extensively studied. The few successful examples involve ester or ether derivatives of 1,3-dienols.

(i) 1-(O-Methylmandeloxy)dienes

Dienyl esters (**442**; R^3 = Ph), available *via* a retro-Diels–Alder reaction of norbomene (**441**; R^3 = Ph), underwent $BF_3 \bullet Et_2O$-catalyzed additions of conjugated aldehydes, ketones and quinones (Scheme 104, Table 29).[106]

The π-face differentiation in favor of adducts (**443**) was more pronounced with increasing amounts of the Lewis acid and at lower reaction temperatures (*cf.* entries 3/4 and 8/9). The cooperative effect of chiral auxiliaries at the diene and at the dienophile units is exemplified by the double diastereoface selective addition presented in entry 2.[91] Particularly noteworthy is the outstanding π-face selectivity, observed in the [4 + 2] cycloaddition of juglone (**445**).[106b] Removal of the prosthetic group from adducts (**443**) was accomplished *via* hydrogenolysis or allylic displacement, as illustrated by the key step (**447**) → (**448**) of a synthesis of enantiomerically enriched (+)-ibogamine (Scheme 105).[106a]

This asymmetric induction was first rationalized in terms of a binding diene/aryl π-orbital overlap (Scheme 104).[106b] In this π-stacking model, methoxy/diene repulsion favors conformer (**O**) which undergoes preferential dienophile addition opposite to the phenyl-shielded diene face. More recently a different transition state conformation (**P**) was proposed based on X-ray studies of adducts (**443**).[106c] Distinctive characteristics of this model are a perpendicular disposition of phenyl and ester-carbonyl groups and a synperiplanarity of the latter with the methoxy substituent. A similar asymmetric induction was achieved with the diene (**442d**) (entry 5), where the phenyl is replaced by a cyclohexyl group, which indicates that π-stacking is not of major relevance here. A dienophile approach opposite to the sterically encumbering phenyl (or cyclohexyl), *i.e.* from the top face of (**P**), may be a reason for the observed topicities.



Scheme 104

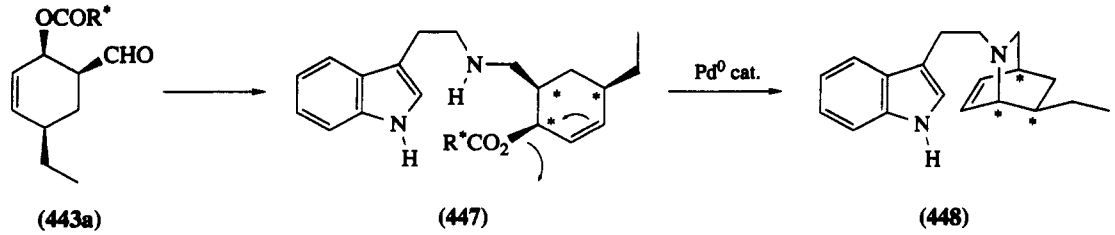
Table 29 Additions of Dienophiles to Chiral 1-Acyloxy-1,3-dienes (**442**)[a] (Scheme 104)

Entry	*Diene* R^1	R^2	R^3	*Dienophile*	*Mol equiv.* $BF_3{\cdot}OEt_2$	*Temp.* (°C)	*Ratio* (**443**)/(**444**)	*Ref.*
1 **a**	Et	H	Ph	$CH_2{=}CHCHO$	0.1	−10	80:20	106a
2 **b**	H	H	Ph	(*S*)-$CH_2{=}CHC(O)CH(OH)Bu^t$	0.3	−78 to −45	99.2:0.8	91
3 **c**	H	H	Ph	$CH_2{=}CHCHO$	0.15	−20	82:18	106c
4 **c**	H	H	Ph	$CH_2{=}CHCHO$	0.3	−78	94:6	106c
5 **d**	H	H	c-C_6H_{11}	$CH_2{=}CHCHO$	0.3	−78	89:11	106c
6 **e**	H	H	Ph	$CH_2{=}C(Me)CHO$	0.3	−78	98:2	106c
7 **f**	H	Me	Ph	$CH_2{=}CHCHO$	0.3	−78	97:3	106c
8 **g**	H	H	Ph	*p*-Benzoquinone	0.15	−78	96:4	106c
9 **h**	H	H	Ph	*p*-Benzoquinone	None	20	80:20	106c

[a]Yields of (**443**) + (**444**): 46–94%.

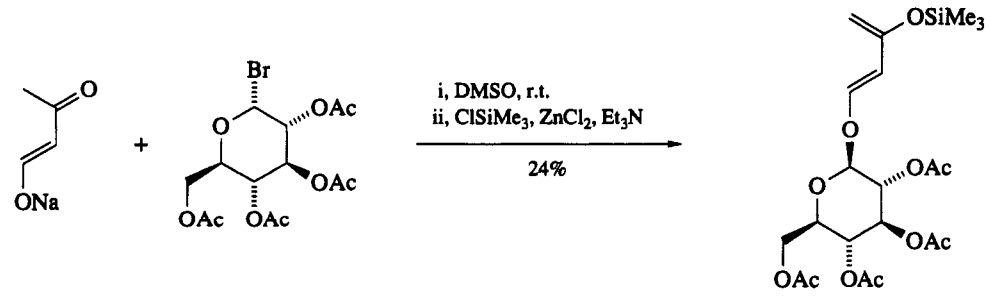
(ii) 1,3-Dienyl Tetraacetyl-β-glucopyranosides

Glucose-derived diene (**451**) displays a notable diastereofacial bias on addition to dienophiles.[107] Its preparation relies on the alkylation of tetraacetylglucopyranosyl bromide (**450**) with sodium salt (**449**) followed by *O*-silylation of the resulting enone (Scheme 106).[107a]



(443a) (447) (448)

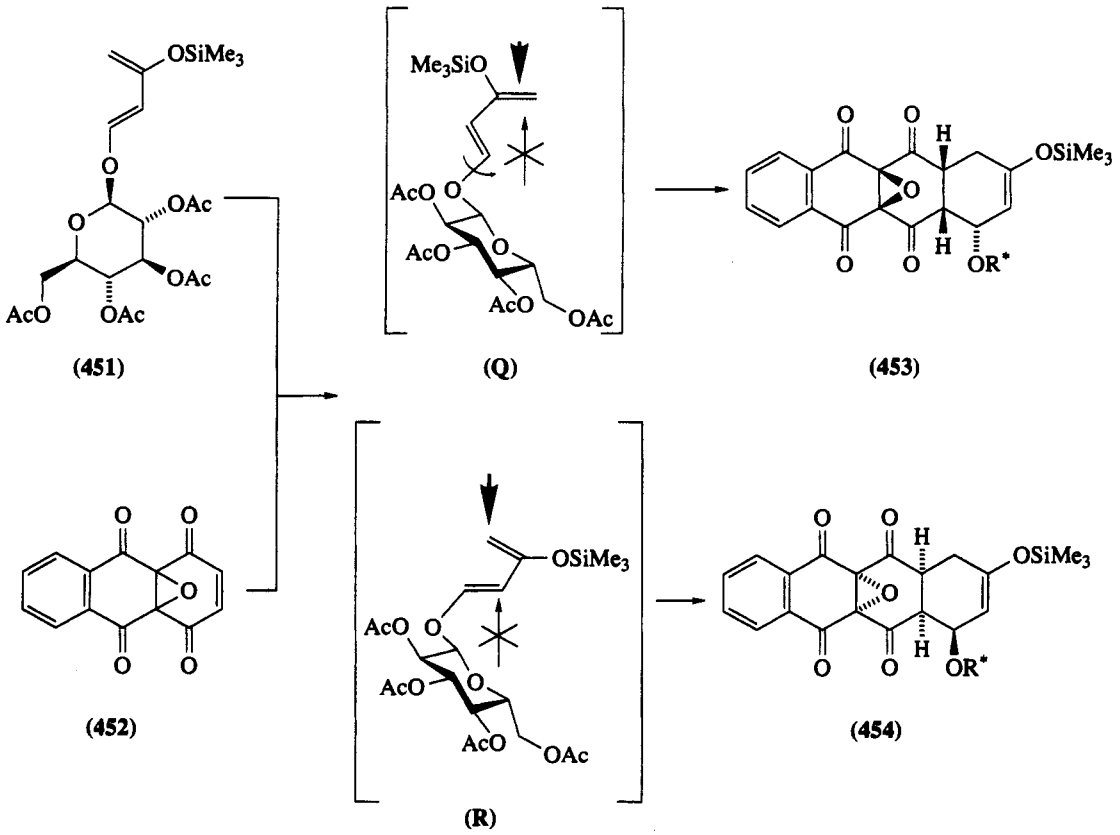
Scheme 105



(449) (450) (451)

Scheme 106

Serving as the key step for an anthracycline synthesis, addition of the epoxytetrone dienophile (**452**) to diene (**451**) gave a mixture of adducts (**453**) and (**454**) in ratios of 4:1 (C_6H_6, 5 °C) up to 7:1 (acetone, 5 °C) (Scheme 107). The major isomer (**453**), isolated by crystallization (74% yield from **451**), was then converted into (+)-4-demethoxydaunomycinone (**641**) (Scheme 142) *via* glycoside cleavage with 0.5N



(451) (Q) (453)

(452) (R) (454)

Scheme 107

HCl in EtOH/H_2O (1:1, reflux, 30 h). In agreement with X-ray and NOE measurements of (**451**) and consistent with the assumed operation of an *exo* anomeric effect, reactive diene conformations (**Q**) and (**R**) were proposed.[107b] It was therefore inferred that the major cycloaddition pathway involves attack of the dienophile (**452**) at the least-hindered 'top face' of conformer (**Q**).

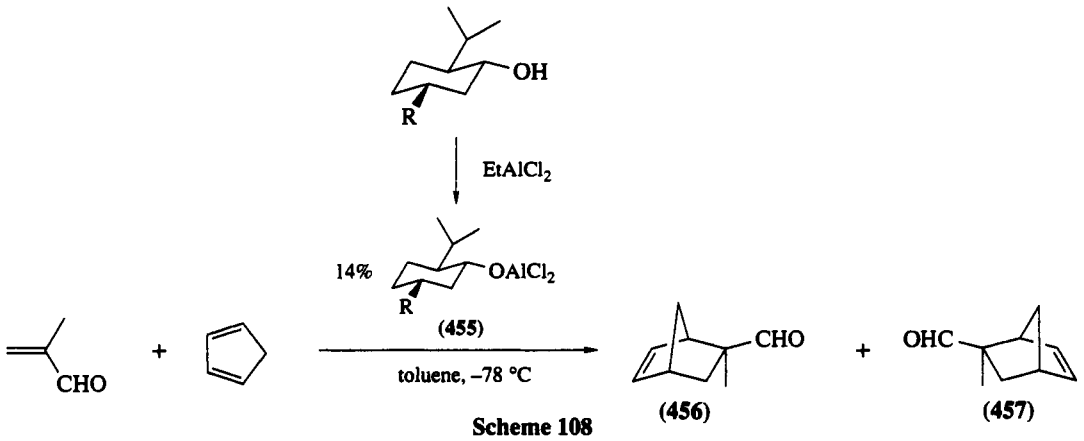
4.1.6.3 Chiral Catalysts

At first sight, the use of a chiral catalyst appears to be the potentially most attractive method to achieve asymmetric Diels–Alder reactions of prochiral dienes and dienophiles. Compared to the stoichiometric use of a covalently attached auxiliary, two synthetic steps would be avoided. However, analysis of the resulting enantiomer mixture and purification of the major product may be more laborious.

4.1.6.3.1 Chiral alkoxyaluminum dichlorides

As early as 1979 it was reported that addition of cyclopentadiene to methacrolein, catalyzed by (–)-menthyloxyaluminum dichloride (**455**; R = Me) (0.14 mol equiv., –78 °C, 3 h) furnished[108a] a mixture of enantiomeric adducts (**456**) and (**457**) (56%) in a ratio of 86:14 which was subsequently corrected to a more modest value of 78.5:21.5 (Scheme 108).[84a,108b]

This isolated report encouraged preparation of a host of chiral Lewis acids throughout the world to test their capacity to induce asymmetric Diels–Alder reactions catalytically. However, until very recently (*vide infra*) only disappointing face selectivities (<50%) were found on [4 + 2] cycloadditions of alkenic diene and dienophile partners.



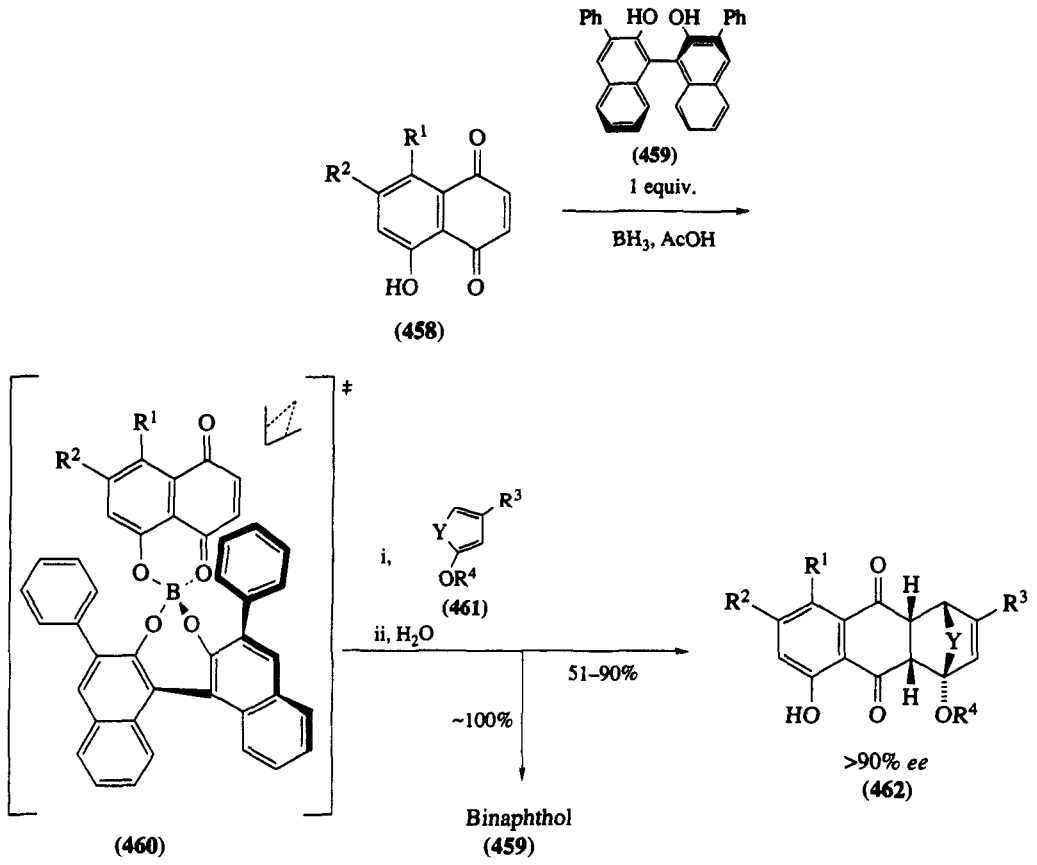
Scheme 108

4.1.6.3.2 Chelation of prochiral dienophiles by chiral boron, aluminum and titanium Lewis acids

In view of previous positive experience with chelated chiral dienophiles (Section 4.1.6.2.1 (iii)), it was plausible to expect that nonchiral dienophiles would also profit from chelation in terms of increased reactivity and decreased conformational mobility. This would enhance the π-face directing influence of a chiral ligand attached to the same chelating metal.

Successive treatment of (*S*)-binaphthol (**459**) with equimolar amounts of BH_3·THF and AcOH gave a non-isolated Lewis acid. Reaction of the latter with juglone (**458a**) provided a complex, assigned structure (**460a**), in which one phenyl substituent shields the top face of the dienophilic bond (Scheme 109, Table 30).[109] Indeed, a fast and efficient addition of 1-methoxycyclohexa-1,3-diene to the complex (**460a**) provided adduct (**462a**) as the only enantiomer within the limits of detection (entry 1). Analogous 'bottom face' additions to complexes (**460**) were observed with 2-methyl-4-trimethylsilyloxybuta-1,3-diene (entry 2) and 1-acetoxybuta-1,3-diene (entry 3).[109] It appears that the initially formed adducts remain strongly chelated, which prevents dissociation of the binaphthoxyboron Lewis acid and necessitates its stoichiometric application.

Chiral titanium and aluminum Lewis acids (**465**), prepared *in situ* from (**463**) or (**464**), promote the addition of cyclopentadiene to *N*-acryolyl- and *N*-crotonoyl-oxazolidinones (**466**) (Scheme 110, Table



Scheme 109

Table 30 Diels–Alder Reactions of *peri*-Hydroxyquinones: Asymmetric Induction by Chiral Lewis Acid (Scheme 109)

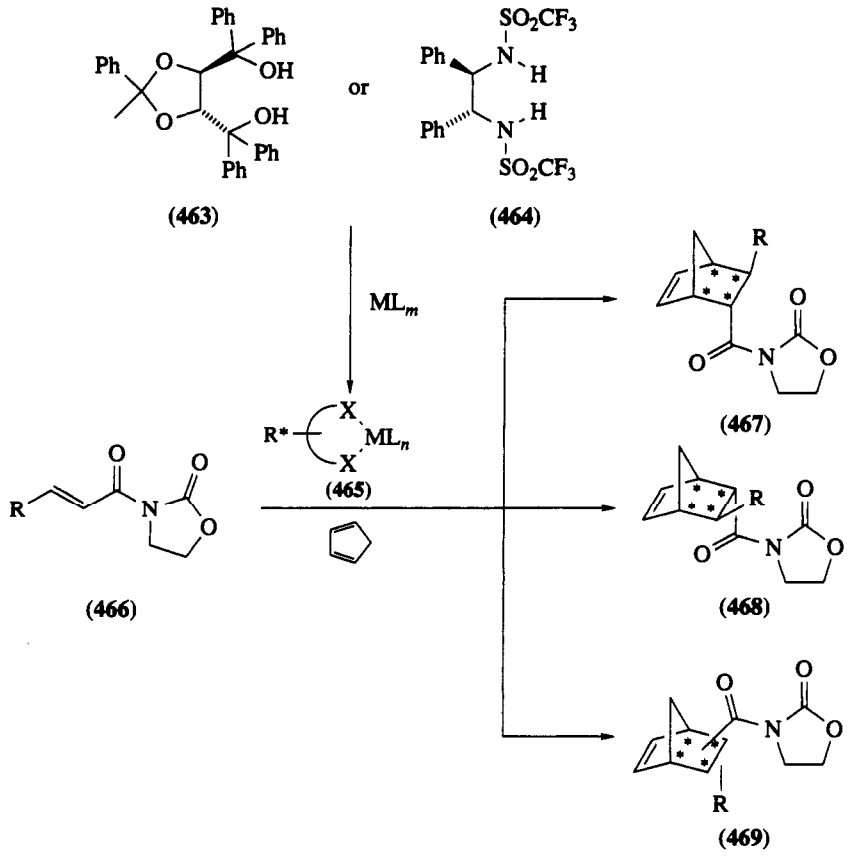
Entry	*Dienophile* R^1	R^2	R^3	*Diene* R^4	Y	*Temp.* (°C)	*Yield (%)* (**462**)	*ee (%)* (**462**)
1 **a**	H	H	H	Me	$(CH_2)_2$	−78	70–90	>98
2 **b**	O—CPh_2—O		Me	$SiMe_3$	H_2	20	>51	>90
3 **c**	H	H	H	C(O)Me	H_2	20	>68	>98

31).[110] The titanium Lewis acid derived from diol (**463**) could be employed in catalytic amounts (0.1 mol equiv.) when molecular sieves were present (entries 2, 3). Under these conditions, cycloaddition of the crotonoyl dienophile was significantly more enantioselective compared with that of the acryloyl analog. On the other hand, both adducts (**467a**) as well as (**467b**) were obtained in ≥92% *ee* using the Lewis acid (**465**) (0.1–0.2 mol equiv.), prepared *in situ* from bis-sulfonamide (**464**) and $AlMe_3$ (entries 4, 5).[110b]

4.1.6.3.3 Tartrate-derived chiral acyloxyborane catalysts

So far the most promising chiral 'Diels–Alder catalyst' has been obtained *in situ* by treatment of monoacylated tartaric acid (**470**) with BH_3·THF (1 mol equiv.).[111] The resulting non-isolated acyloxyborane was assumed to feature a five-membered ring derived from the α-hydroxy acid moiety of (**470**) with the boron atom bound to the carboxylate and C_α-positioned oxygen atoms (*cf.* formula **471**) (Scheme 111, Table 32).

It is remarkable that 0.1 mol equiv. of this chiral acyloxyborane complex induced fast (−78 °C) and highly enantioselective Diels–Alder reactions of cyclic or acyclic 1,3-dienes with simple acrylic acid (entry 1),[111a] or α,β-unsaturated aldehydes (entries 2–9).[111b] Table 32 reveals a striking stereodirecting



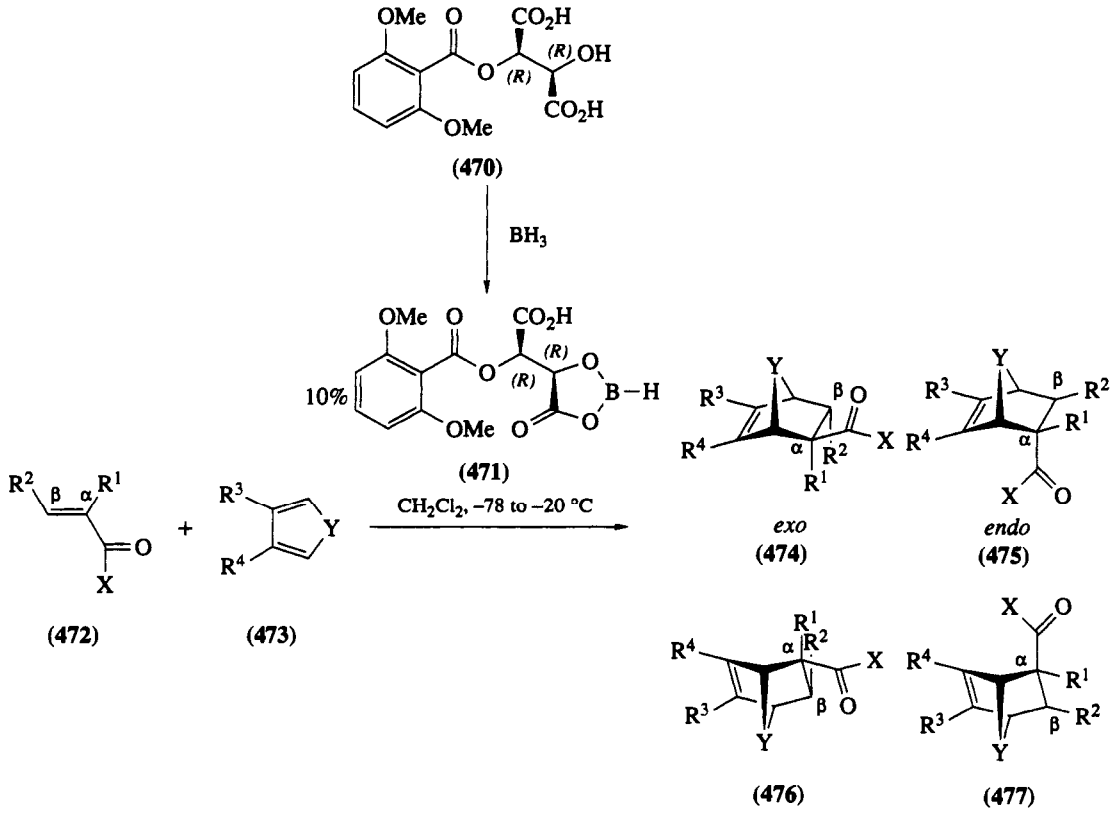
Scheme 110

Table 31 Asymmetric Diels–Alder Reactions of Cyclopentadiene and *N*-Enoyloxazolidinones Mediated by Chiral Lewis Acids (Scheme 110)

Entry	*Dienophile* *R*	*Lewis acid precursors* *ligand* (mol equiv.)	*ML*m (mol equiv.)	*Molecular sieves*	*Temp.* (°C)	*Yield* (%)[a]	*Ratio* (**467**) + (**468**) /(**469**) = *endo*/*exo*	*Ratio* (**467**)/(**468**)	*Ref.*
1 **a**	Me	(**463**) (2.2)	$TiCl_2(OPr^i)_2$ (1)	None	–15	93	90:10	96:4	110a
2 **a**	Me	(**463**) (0.1)	$TiCl_2(OPr^i)_2$ (0.1)	4 Å	0	87	92:8	95.5:4.5	110a
3 **b**	H	(**463**) (0.1)	$TiCl_2(OPr^i)_2$ (0.1)	4 Å	–40	93	96:4	82:18	110a
4 **a**	Me	(**464**) (0.2)	$AlMe_3$ (0.1)	None	–78	88	96:4	97:3	110b
5 **b**	H	(**464**) (0.1)	$AlMe_3$ (0.2)	None	–78	92	>98:2	95.5:4.5	110b

[a]Combined yield of *endo* and *exo* products.

influence of C_α and C_β substituents in the enal dienophiles. Hence, acrolein gave specifically products (**477**; $R^1 = R^2 = H$) with an *endo* positioned CHO unit and in high enantiomeric purity resulting from diene additions to the C_α-*si* face (entries 2, 3). Methacrolein carrying a C_α-methyl group selectively provided products (**474**; $R^1 = Me$, $R^2 = H$) which again reflect a predominant C_α-*si* face attack to the enal but an *exo*-oriented aldehyde group in the transition state (entry 6). The C_β substituent of crotonaldehyde does not interfere with the 'CHO-*endo* preference' but dramatically decreases the face differentiation of the addition process (entry 5). In the case of (*E*)-2-methyl-2-butenal, having substituents at both C_α and C_β positions, high CHO-*exo* as well as C_α-*si* face selectivities were observed (entry 9); thus the effect of the C_α-methyl overcomes that of the C_β-methyl moiety. As expected, transformation of methacrolein to (**476**; $R^1 = R^2 = H$) was equally efficient and selective when catalyzed by the readily available enantiomer of (**471**). However, it should be noted that the absolute configuration of several cycloadducts is only tentatively assigned (entries 4, 5, 7–9). Further understanding, extensions and applications of this principle may attract substantial interest in the future.



Scheme 111

Table 32 Asymmetric Diels–Alder Reaction of Acrylic Acid and of Conjugated Aldehydes Catalyzed by a Chiral Acyloxyborane (Scheme 111)

Entry	*Dienophile*			*Diene*			*Temp.* (°C) *(time,* h)	*Yield*[a] *(%)*	*Ratio endo/exo (C=O)*	*Major adduct*	*ee (%)*
	R^1	R^2	X	R^3	R^4	Y					
1 **a**	H	H	OH	H	H	CH_2	–78 (24)	93	96:4	(**477**)	78
2 **b**	H	H	H	H	H	CH_2	–78 (14.5)	90	88:12	(**477**)	84
3 **c**	H	H	H	H	H	$(CH_2)_2$	–78 (10)	46	>99:<1	(**477**)	80
4 **d**	H	H	H	Me	Me	H_2	–78 (10.5)	53	—	(**477**)	84[c]
5 **e**	H	Me	H	H	H	CH_2	–78 (10)	53	90:10	(**477**)	2[c]
6 **f**	Me	H	H	H	H	CH_2	–78 (6)	85	11:89	(**474**)	96
7 **g**	Me	H	H	Me	Me	H_2	–78 (7.5)	61	—	(**474**)	97[c]
8 **h**	Me	H	H	Me	H	H_2	–40 (10.5)	65[b]	—	(**474**)	91[c]
9 **i**	Me	Me	H	H	H	CH_2	–78 (9.5)	91	3:97	(**474**)	90[c]

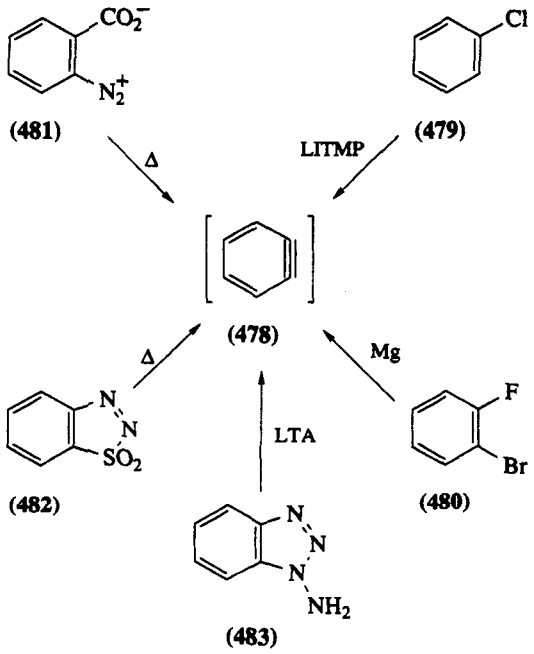
[a]Combined yield of *endo* and *exo* adducts. [b]Contains 2% of the '*meta*' regioisomer. [c] Absolute configuration not reported

4.1.7 BENZYNES AS DIENOPHILES

4.1.7.1 Background and Preparation

The chemistry of benzyne (dehydrobenzene), pioneered by Wittig and coworkers, was reviewed between 1967 and 1981.[112] Benzyne (**478**) (Scheme 112) is a 'high-energy', extremely reactive species and oligomerizes rapidly in the absence of other reaction partners.

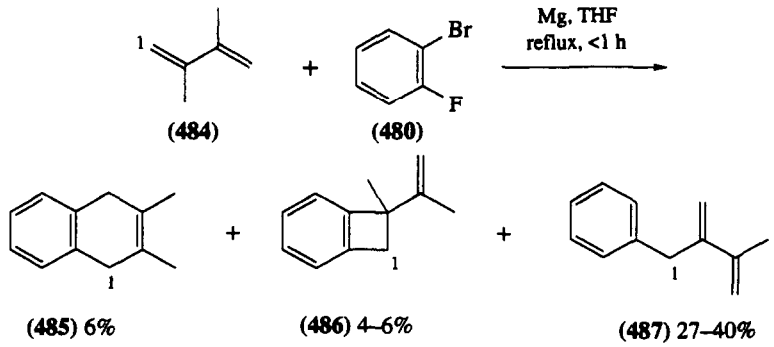
To apply (**478**) as a dienophile in Diels–Alder reactions it is, therefore, prepared *in situ* in the presence of a suitable diene, while maintaining its stationary concentration as low as possible. The most popular methods of preparation (Scheme 112) include dehydrohalogenations of halobenzenes, *e.g.* (**479**),[113a] metallation of *o*-dihalobenzenes, *e.g.* (**480**),[113b] as well as thermal decompositions of benzenediazonium-2-



Scheme 112

carboxylate (**481**)[113c] and 1,2,3-benzothiadiazole 1,1-dioxide (**482**).[113d] Precursors (**481**) and (**482**) are explosive and are best prepared *in situ*. Oxidation of 1-aminobenzotriazole (**483**) with lead tetraacetate provides another relatively safe access to (**478**).[113e]

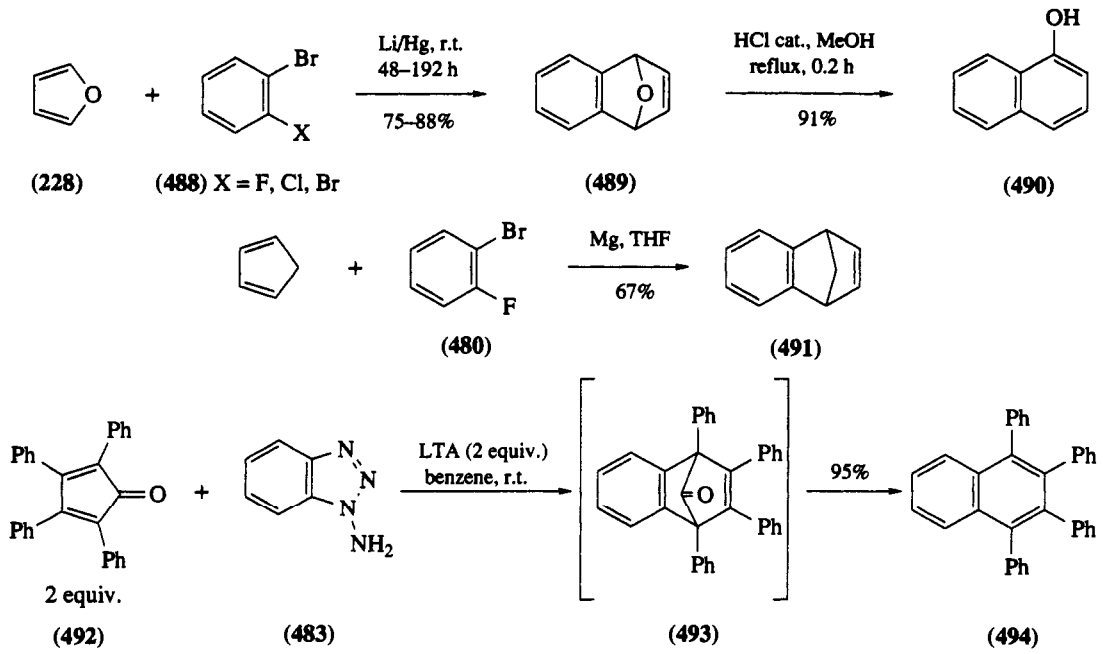
Reaction of benzynes with acyclic dienes generally gives Diels–Alder products in poor yields because of competitive [2 + 2] cycloadditions and ene-type processes (Scheme 113). The product distribution, obtained from 2,3-dimethyl-1,3-butadiene (**484**),[114] is more characteristic of a two-step mechanism than of a concerted addition. Without pursuing this argument, it appears that the extremely poor yield of [4 + 2] cycloadduct (**485**) results from the very fast reaction of benzyne with the 'transoid' diene (**484**). Bond formation at C-1 coupled with a hydrogen transfer (→ **487**) or cyclobutane ring closure (→ **486**) seems to occur rapidly before diene (**484**) can adopt the *s-cis* conformation.



Scheme 113

4.1.7.2 Reactions with Cyclopentadiene and Furan Derivatives

Cyclic 1,3-dienes (with an inherent *s-cis* conformation) can react with benzyne to afford Diels–Alder adducts in high yields (Scheme 114). The addition to furan (**228**), reported by Wittig and Pohmer in 1955,[115] is so efficient that it has become a diagnostic test for the formation of benzyne. Cyclopentadiene[113b] and tetracyclone (**492**)[113e] also serve as standard assay reagents.



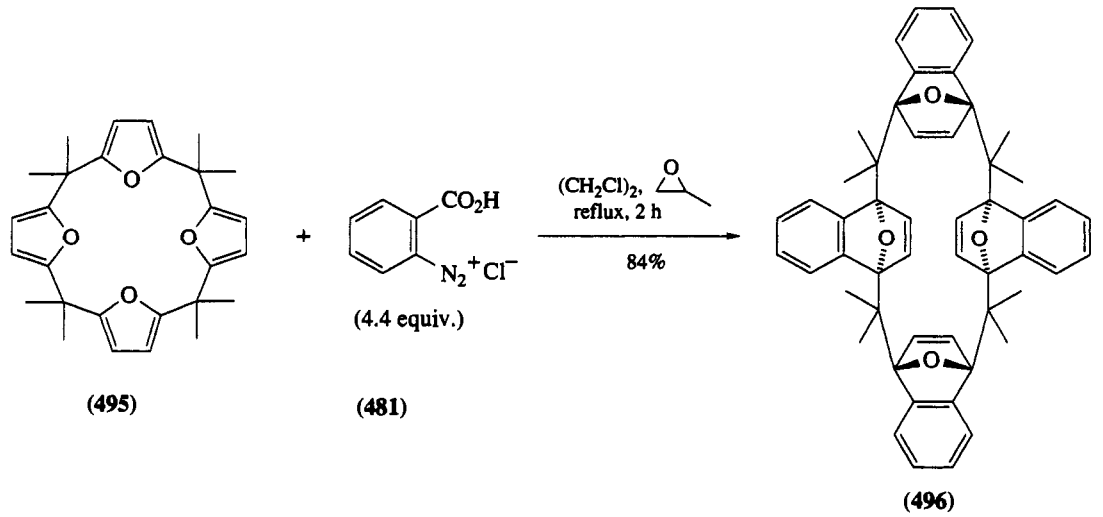
(228) (488) X = F, Cl, Br (489) (490)

(480) (491)

(492) (483) (493) (494)

Scheme 114

The propensity of furans for benzyne cycloadditions is illustrated by its fourfold application to the four furan units of (**495**), providing the unusual macrocycle (**496**) in 84% yield in one synthetic operation (Scheme 115).[116] The benzyne/furan adducts are also useful precursors for naphthalene derivatives. For example, adduct (**489**) (Scheme 114) was readily converted into α-naphthol (**490**) by treatment with acid.[115]

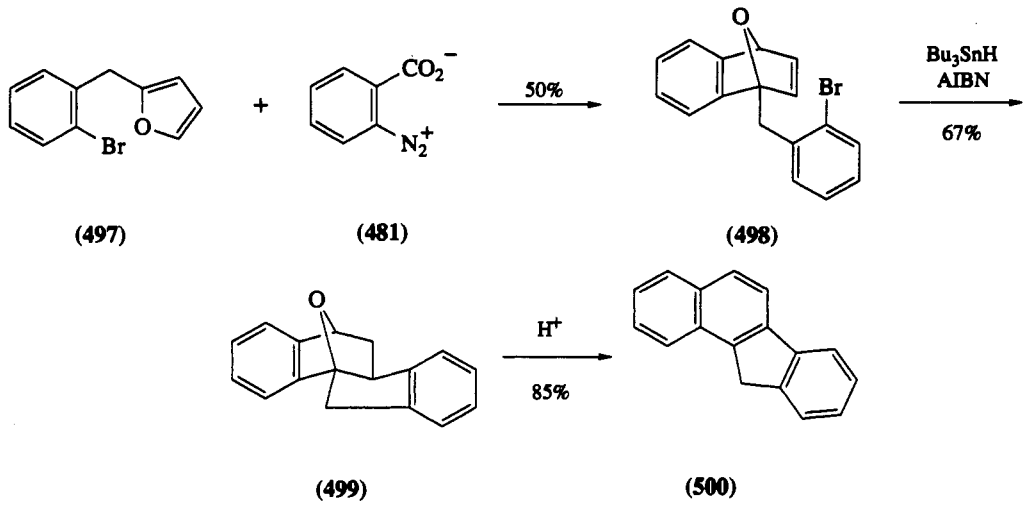


(495) (481) (496)

Scheme 115

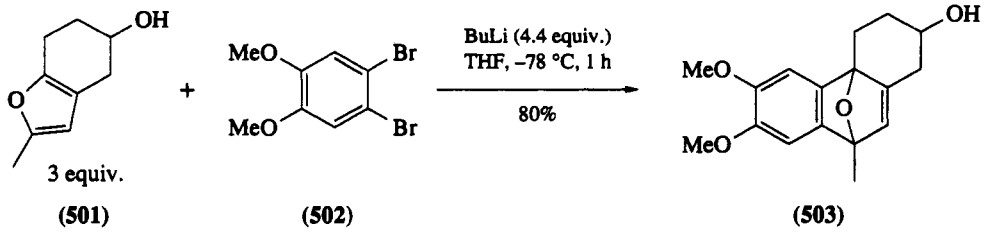
Additions of (**478**) to furans which contain an appropriately placed aryl or vinyl bromide unit permit the construction of polycyclic systems by a Diels–Alder/radical cyclization/aromatization sequence (Scheme 116).[117]

A route to partially hydrogenated phenanthrenes relies on the Diels–Alder reaction of a benzyne to an annulated furan, *e.g.* (**501**) → (**503**) (Scheme 117).[118] However, regiochemistry 'raises its ugly head' when both the furan and the benzyne are nonsymmetrically substituted (Scheme 118). Hence, the [4 + 2] cycloaddition of 3-methylbenzyne with 2-substituted furans (**504**) gave the *anti* and *syn* adducts (**506**)

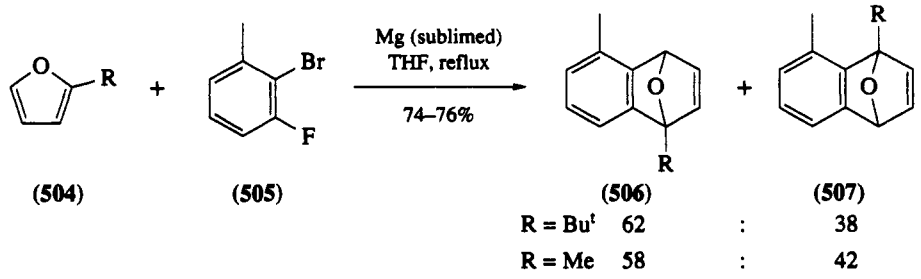


Scheme 116

and (**507**) in comparable proportions, irrespective of the size of R and irrespective of the method of benzyne generation.[119a] Analogous addition of the more polarized 3-fluorobenzyne to 2-*t*-butylfuran gave preferentially (90:10) the corresponding, more crowded, *syn* product.[119b]



Scheme 117

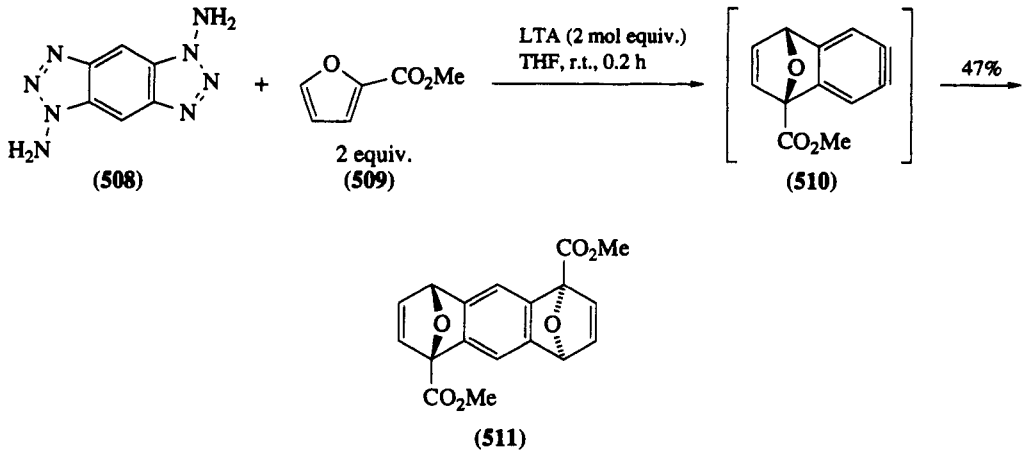


Scheme 118

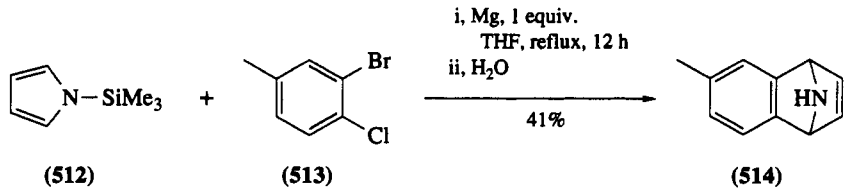
Bistriazole (**508**) served as a formal 1,4-benzadiyne equivalent in a sequence of two Diels–Alder additions to 2-methoxycarbonylfuran (**509**), which yielded (**511**) as the sole regio- and (tentatively assigned) stereo-isomer (Scheme 119).[120] It appears, therefore, that the CO_2Me group, in the transient monoadduct (**510**), controls the orientation in the second step.

Pyrroles have also been subjected to [4 + 2] cycloadditions of benzynes. *N*-Trimethylsilylpyrrole (**512**) is particularly suitable for such additions; subsequent mild desilylation furnished 1,4-dihydronaphthalen-1,4-imines, *e.g.* (**514**), in yields ranging from 30 to 53% (Scheme 120).[121]

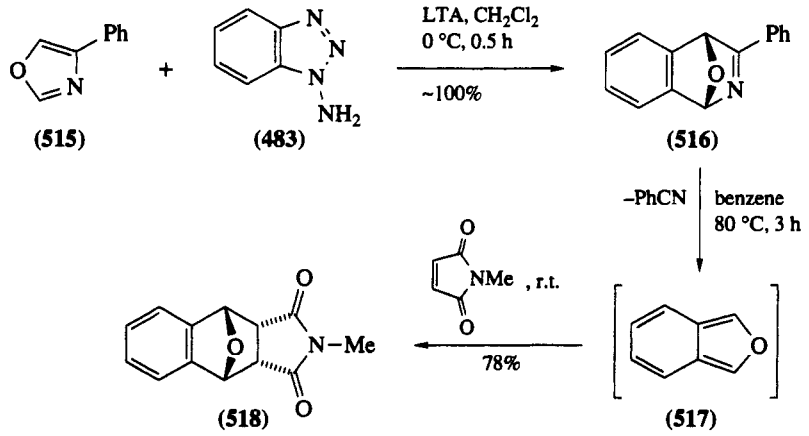
Oxazoles are another class of heteroaromatic dienes which readily undergo Diels–Alder reactions with benzynes. For example, slow, simultaneous injection of solutions of triazole (**483**) and lead tetraacetate to a solution of oxazole (**515**) in CH_2Cl_2 at 0 °C afforded cycloadduct (**516**) in essentially quantitative yield.[122] The latter is a convenient source for the unstable isobenzofuran (**517**), which can be trapped by [4 + 2] cycloaddition to a variety of dienophiles, *e.g.* by *N*-methylmaleimide (Scheme 121).



Scheme 119



Scheme 120

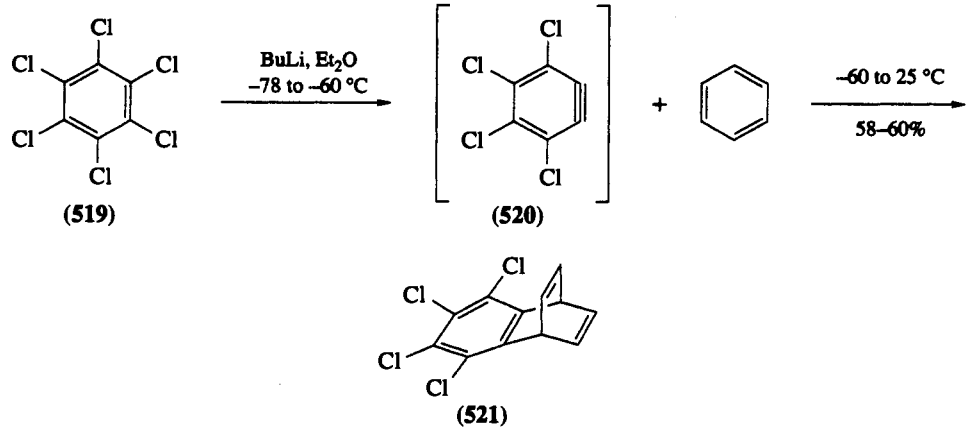


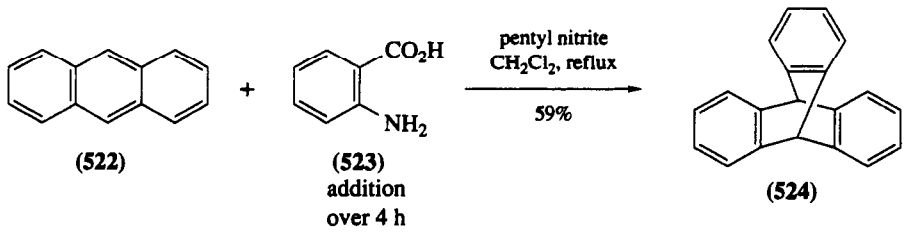
Scheme 121

4.1.7.3 Reactions with Benzenes and Anthracenes

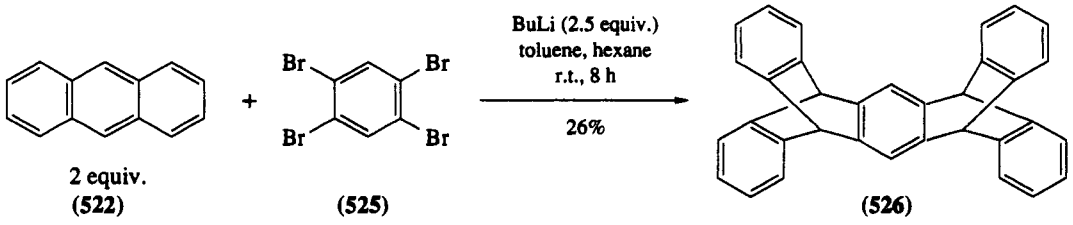
The outstanding dienophilicity of benzynes is highlighted by their Diels–Alder additions to benzenes. Tetrachlorobenzyne (**520**), easily generated by lithiation of hexachlorobenzene (**519**), smoothly reacted with benzene to afford tetrachlorobenzobarrelene (**521**) in ~60% yield (Scheme 122).[123] The parent benzyne (**478**) underwent similar addition to benzene, although not so efficiently.[112]

[4 + 2] Cycloaddition of benzyne (**478**) to (the less aromatic) anthracene provides a well-known approach to triptycene (**524**).[124] More recently, this type of reaction was extended to elegant syntheses of iptycenes, *e.g.* (**526**), using 1,2,4,5-tetrabromobenzene (**525**) as a 1,4-benzadiyne equivalent (Scheme 123).[125]





Scheme 122



Scheme 123

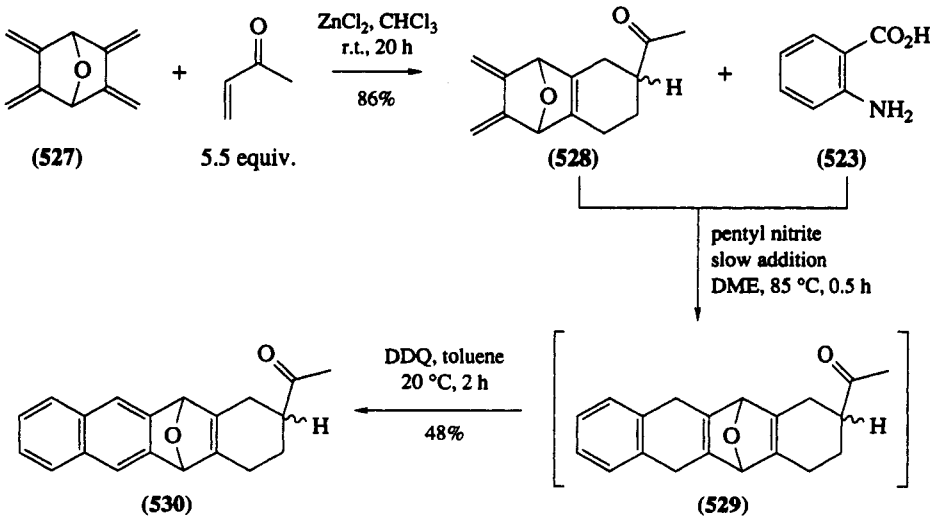
4.1.7.4 Reactions with Exocyclic or Partially Cyclic 'Cisoid' Dienes

The tetrakis(methylidene)-7-oxabicyclo[2.2.1]heptane (**527**) offers an interesting route to linear polyannulated ring systems, e.g. 4-demethoxydaunomycinone (**641**), *via* a sequence of two Diels–Alder reactions (Scheme 124). Monoadduct (**528**) could be isolated and subjected to the [4 + 2] cycloaddition of benzyne.[126a] An alternative synthesis of anthracyclinone analogs starts with the Diels–Alder addition of 3-methoxybenzyne to a derivative of the 'bis-cisoid' tetraene (**527**).[126b]

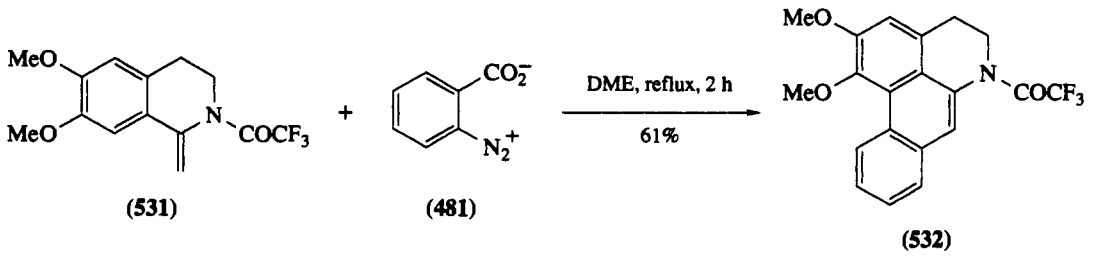
A synthetic approach to the class of aporphine alkaloids centers on [4 + 2] cycloadditions of benzynes to the 'cisoid' 1,3-diene (**531**), which contains one double bond as part of a benzene ring (Scheme 125).[127]

4.1.7.5 3,4-Pyridyne as a Dienophile

Hetarynes (dehydroaromatic heterocycles) can also act as dienophiles in Diels–Alder reactions.[112] This capacity and the inherent regiochemical problems are illustrated by two syntheses of the alkaloid ellipticine, which both feature a [4 + 2] cycloaddition of 3,4-pyridyne (**533**) (Scheme 126).[128] The first approach used the triazenylcarboxylic acid (**534**) as a precursor for hetaryne (**533**), which then underwent an addition to pyranoindolone (**535**); spontaneous CO_2 extrusion of the initial cycloadducts (**536**; X = N, Y = CH) and (**536**; X = CH, Y = N) gave directly a 50:50 mixture of ellipticine (**537**) and its undesired regioisomer (**538**).[128a]



Scheme 124



Scheme 125

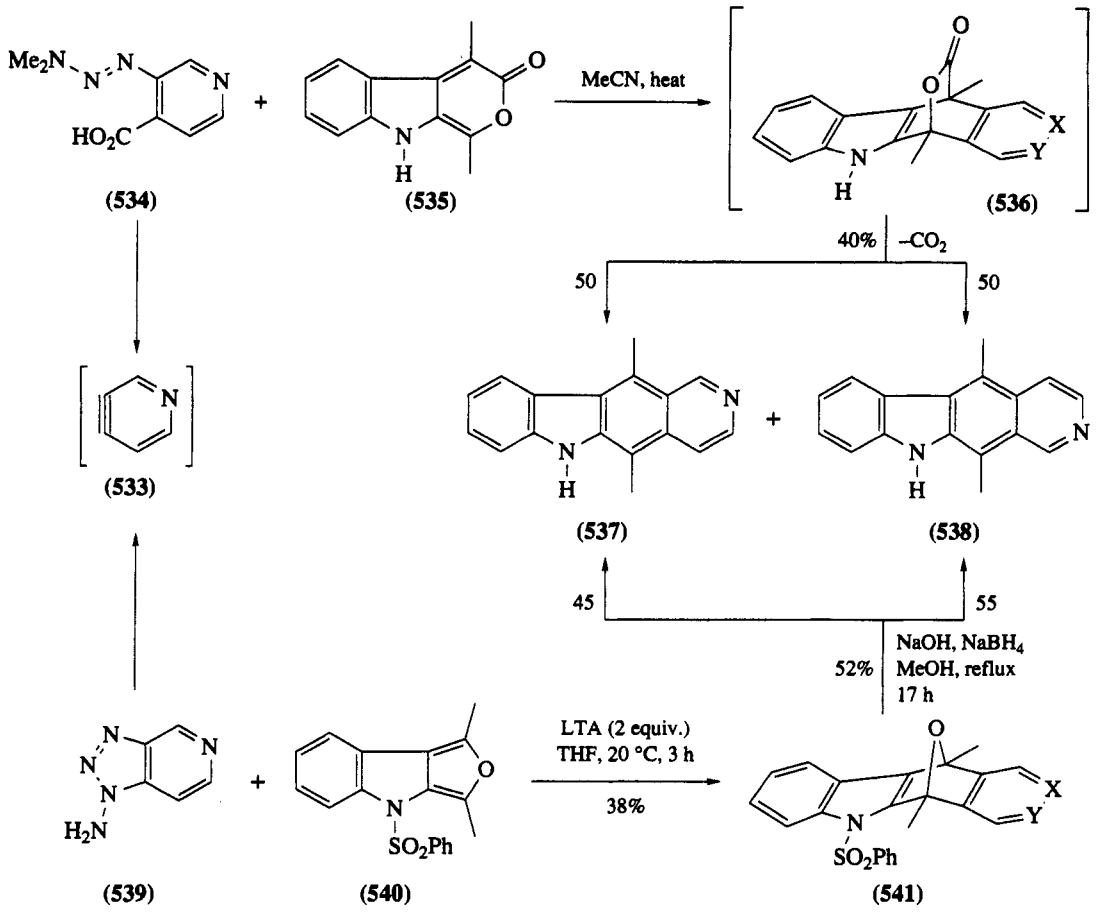
A similar lack of regiochemical control also hampers the [4 + 2] cycloaddition of pyridyne (**533**) (prepared from **539**) to furoindole (**540**). Desulfonylation and 'deoxygenation' of the cycloadduct mixture of (**541**; X = N, Y = CH) and (**541**; X = CH, Y = N) afforded ellipticine (**537**) and isoellipticine (**538**) in a 45:55 ratio.[128b]

4.1.8 *ORTHO*-QUINODIMETHANES AS DIENE COMPONENTS

4.1.8.1 Background

ortho-Quinodimethanes (*o*-xylylenes), represented by the prototype (**542**), are very reactive dienes. When generated in the presence of a dienophile they afford [4 + 2] cycloadducts, *e.g.* (**543**), with a concomitant restoration of aromaticity (Scheme 127). In fact, species (**542**) and its derivatives were first recognized by Cava and coworkers[129a,c,d] and, independently, by Jensen and Coleman[129b] (1957–1959) *via* trapping by maleic anhydride or *N*-phenylmaleimide, and identification of cycloadducts (**543**).

Several reviews have dealt with Diels–Alder reactions of *o*-quinodimethanes,[130] emphasizing the more powerful, selective and thus extensively used intramolecular versions (*cf.* Scheme 135) introduced in 1971.[131] The most recent survey also tackled the issue of asymmetric induction by means of a chiral auxiliary group attached to the *o*-quinodimethane precursor.[130i] This section aims at a complementary coverage of intermolecular Diels–Alder reactions of *o*-quinodimethanes, underlining synthetically relevant aspects.



Scheme 126

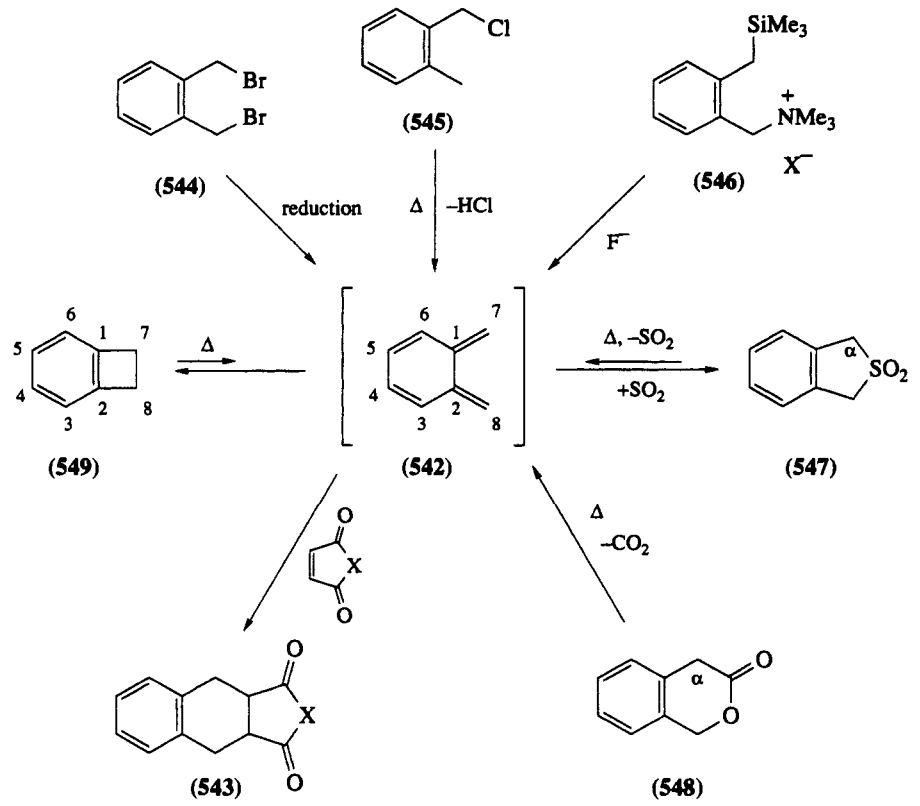
4.1.8.2 Preparation

The preparation of this class of dienes has received considerable attention during the last few years. Scheme 127 depicts the current approaches, such as 1,4-eliminations of *o*-xylene derivatives *via* reduction (**544**) → (**542**),[132] thermal dehydrohalogenation (**545**) → (**542**),[133] and fluoride-induced desilylation (**546**) → (**542**).[134] The last procedure is particularly noteworthy because of the mild reaction conditions, which are compatible with various functional groups. The chelotropic, thermal elimination of sulfur dioxide, (**547**) → (**542**), one of the oldest routes to *o*-quinodimethanes,[129c] remains attractive owing to the easy functionalization of (**547**) at C_α.[130c,135] This advantage also holds for 3-isochromanones (**548**), which provide (**542**) on Diels–Alder cycloreversion with loss of carbon dioxide.[130c] Without doubt, the most established source of *o*-quinodimethanes are the derivatives of benzocyclobutene (bicyclo[4.2.0]octa-1,3,5-triene) (**549**), which on heating undergo a clean and reversible electrocyclic ring opening (**549**) ⇌ (**542**).[129b] Consequently, when *o*-quinodimethanes are generated by an independent route, in the absence of a reaction partner, benzocyclobutenes can be obtained in high yields (*vide infra*).

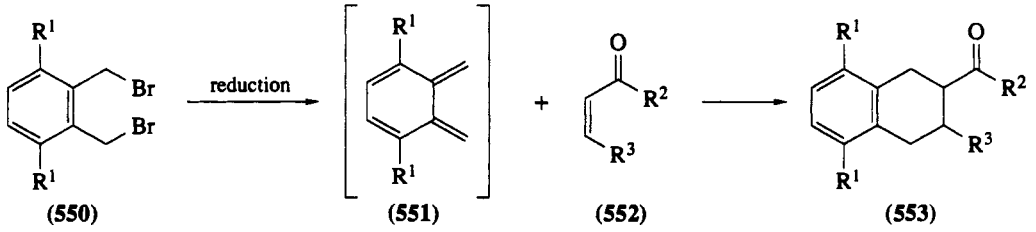
Recently, the occasionally capricious reduction of α,α′-dibromo-*o*-xylenes (**550**) has been improved by the use of Zn/ultrasound, zinc/silver couple, reactive nickel (0) or $CrCl_2$, as assayed by *in situ* trapping of (**551**) with typical dienophiles (Scheme 128, Table 33).[132]

These methods still show limitations. The reduction of (**550a**) with activated nickel in the presence of diethyl maleate gave a 50:50 mixture of *cis* and *trans* adducts (entry 4), probably due to a nickel-promoted *cis/trans* isomerization of the dienophile prior to cycloaddition. Homogeneous reduction using $CrCl_2$ failed with a dibromide precursor containing a quinone moiety.[132d]

The preparatively attractive approach to benzocyclobutenes by flash pyrolytic 1,4-dehydrohalogenation, (**545**) → (**542**) → (**549**),[133a] was extended to the even more remarkable conversion of *o*-methylbenzal chlorides to 1-chlorobenzocyclobutenes e.g. (**554**) → (**555**) (Scheme 129).[133b]



Scheme 127

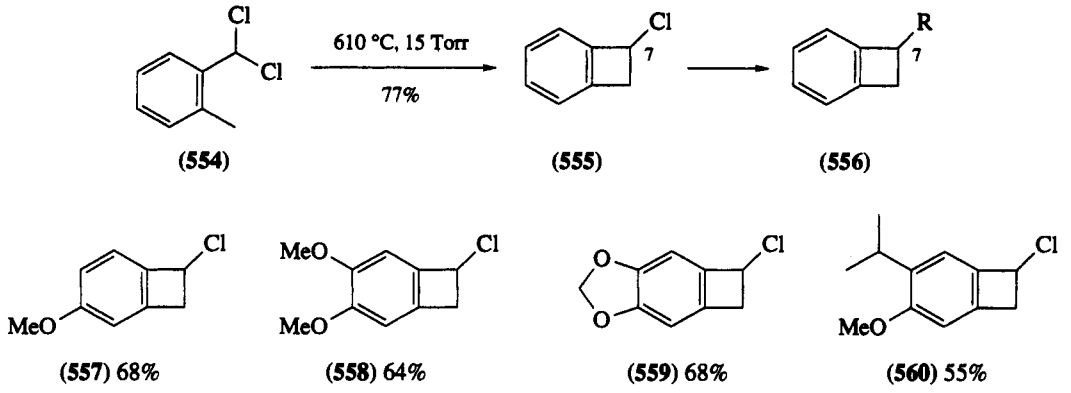


Scheme 128

Table 33 Reduction of α,α′-Dibromo-*o*-xylenes and Diels–Alder Reactions of the Resulting *o*-Quinodimethane Intermediates (Scheme 128)

Entry	R^1	R^2	R^3	*Reduction method*	*Yield (%) of (553)*	*Ref.*
1 a	H	Me	H	Zn/ultrasound[a]	87	132a
2 b	Me	Me	H	Zn/Ag[b]	74	132b
3 a	H	OMe	H	Ni[d]	67	132c
4 a	H	OEt	CO_2Et	Ni[d]	90[e]	132c
5 a	H	OEt	H	$CrCl_2$[c]	84	132d
6 c	OMe	Me	H	$CrCl_2$[c]	85	132d

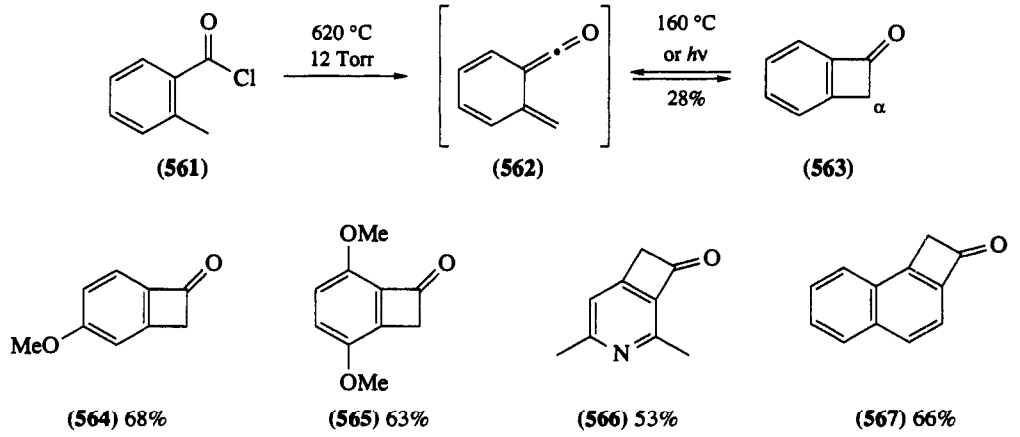
[a]Activated zinc (2.3 equiv.), dioxane, ultrasound, N_2, 20–25 °C, 12 h. [b]Zn(Ag) (2 equiv.), DMF, stirring, N_2, r.t., 6 h. [c]Addition of dibromide + dienophile (3–5 equiv.) to $CrCl_2$ (3–5 equiv.) in THF/HMPA, N_2, 20 °C, 0.5 h. [d](i) NiI_2 (1.25 equiv.), Li (3 equiv.), naphthalene (0.13 equiv.), r.t., 12 h; (ii) dienophile (2 equiv.), slow addition of dibromide, r.t., 7 h. [e]50:50 mixture of *cis/trans* products.



Scheme 129

Treatment of *o*-tolualdehyde with PCl_5, followed by thermal HCl elimination, afforded (**555**) in 77% overall yield. The halogen in (**555**) can be replaced by substitution with nucleophiles and, *via* the Grignard reagent, with electrophiles, providing an easy access to variously 7-substituted benzocyclobutenes (**556**). This sequence is compatible with aromatic substituents, as exemplified by the range of useful building blocks (**557**)–(**560**), obtained in good yields.

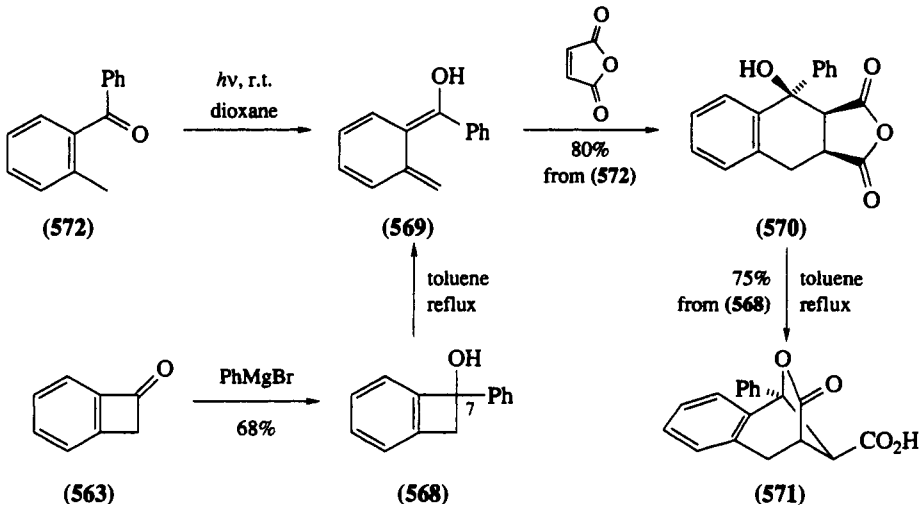
Similar flash vacuum pyrolysis of *o*-toluic acid chloride (**561**) lends itself to the easy preparation of benzocyclobutenone (**563**) (76% at a laboratory scale of 250 g).[133b] Variations of the aromatic nucleus are easy, as demonstrated by the preparation of derivatives (**564**)–(**567**) (Scheme 130).



Scheme 130

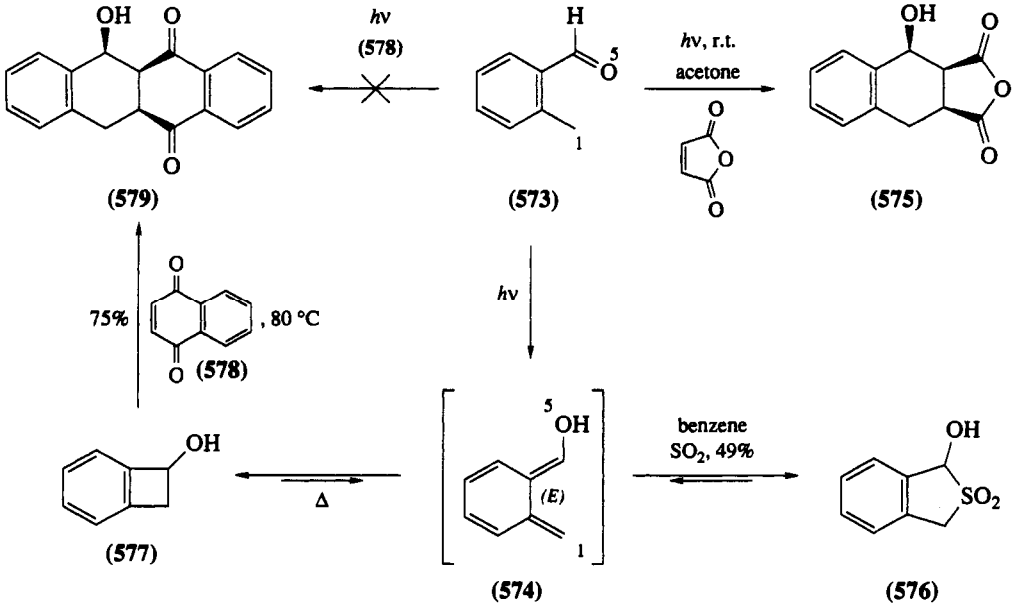
As to the underlying reaction mechanism, it appears that vacuum thermolysis of (**545**), (**554**) and (**561**) generates in each case, initially, a transient *o*-quinodimethane which cyclizes in the highly dilute gas phase. *o*-Quinoid vinylketene intermediate (**562**) could be regenerated in solution from the isolated benzocyclobutenone (**563**) on heating or irradiation and trapped by electron-poor dienophiles, *e.g.* (**632**) (Scheme 141).[133c,146] Alternatively, benzocyclobutenones can be easily functionalized at the carbonyl group or at C_α, affording further *o*-quinodimethane precursors.

For example, 7-phenylbenzocyclobuten-7-ol (**568**) (obtained from **563**) when heated with maleic anhydride in toluene gave acid lactone (**571**) in 75% yield (Scheme 131).[136] This result is consistent with an *endo*-[4 + 2] cycloaddition of the dienophile to the (*E*)-dienol (**569**) followed by lactonization of cycloadduct (**570**). The cycloadduct (**570**) was, furthermore, obtained in 80% yield by the 'photoenolization' of *o*-methylbenzophenone (**572**) in the presence of maleic anhydride at room temperature.[137] It follows that the photoinduced 1,5-hydrogen shift of (**572**) must have generated the same (*E*)-dienol (**569**) as that obtained by the thermal ring opening of (**568**). This and other aspects of 'photoenolization' have been reviewed.[136]



Scheme 131

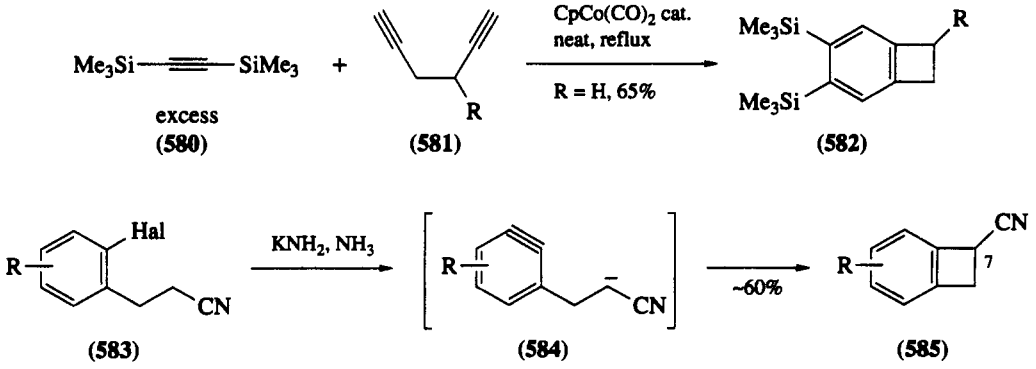
Analogous irradiation of *o*-tolualdehyde forms apparently (*E*)-dienol (**574**), which was trapped directly with maleic anhydride (→ **575**)[136] or SO_2 (→ **576**) (Scheme 132).[138] α-Hydroxysulfones such as (**576**) could be transformed into α-methoxy and α-acetoxy sulfones and then used, *per se*, as *o*-quinodimethane precursors.[138] The advantage of thermal benzocyclobutenol ring opening (**577** → **574**) over photoenolization (**573** → **574**) is illustrated by the efficient formation of Diels–Alder product (**579**) on heating (**577**) with (**578**).[136] The corresponding photogeneration/trapping technique failed due to the photosensitivity of the quinone dienophile (**578**). Another drawback of *in situ* photoenolizations is the facile light-induced *cis/trans* isomerization of acyclic dienophiles.



Scheme 132

A relatively new route to benzocyclobutenes, without the involvement of *o*-quinodimethanes, is the cobalt-catalyzed co-oligomerization of bis(trimethylsilyl)acetylene with 1,5-hexadiynes, (**580**) + (**581**) → (**582**) (Scheme 133).[139] Despite its elegance, and the potential to modify the silyl groups, this method suffers from limitations in providing benzocyclobutenes with well-defined substitution patterns. In this

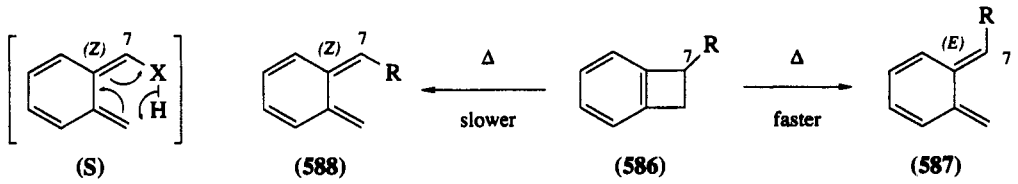
respect, it is the 'older', more general, base-induced cyclization of *o*-halodihydrocinnamonitriles (or esters), *e.g.* (**583**) → (**585**), which currently enjoys much wider practical use.[140]



Scheme 133

4.1.8.3 Regio- and Stereo-chemistry

It thus follows that benzocyclobutenes are readily accessible, relatively inert and reliable 'masked' *o*-quinodimethane equivalents. With 7-substituted derivatives (**586**), thermal 'unmasking' takes place at a rate which varies widely with the nature of the substituent R (Scheme 134, Table 34).[130a]



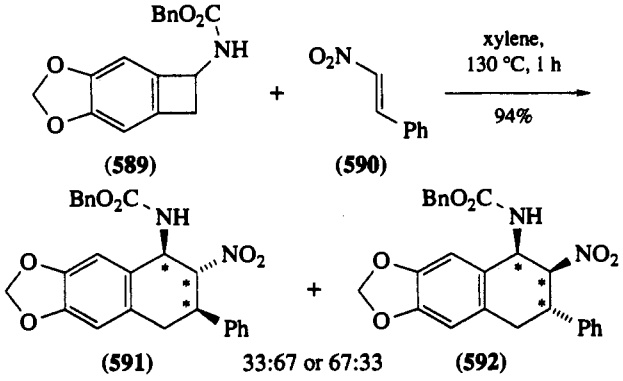
Scheme 134

Table 34 Approximate Temperature for Complete Ring Opening of 7-Substituted Benzocyclobutenes[a] (Scheme 134)

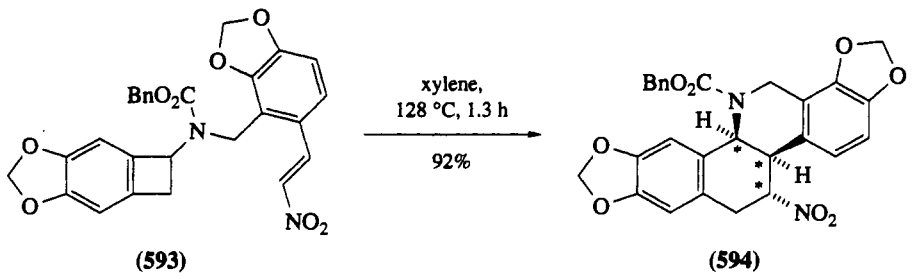
Substituent R	NH_2	OH	NH(C=O)R′	C=O	CH_2	H
Temp. (°C)	25	80	111	150	180	200

[a]Reaction time: 18 h.

This thermal ring opening favors the formation of (*E*)-*o*-quinodimethanes (**587**) over that of (*Z*)-dienes (**588**) which, when the substituent R bears a hydrogen atom (R = XH), undergo a 1,5-H shift. For this and other reasons, the (*E*)-configuration of terminally substituted *o*-quinodimethanes is relevant for their use in Diels–Alder reactions.[130a]



Scheme 135



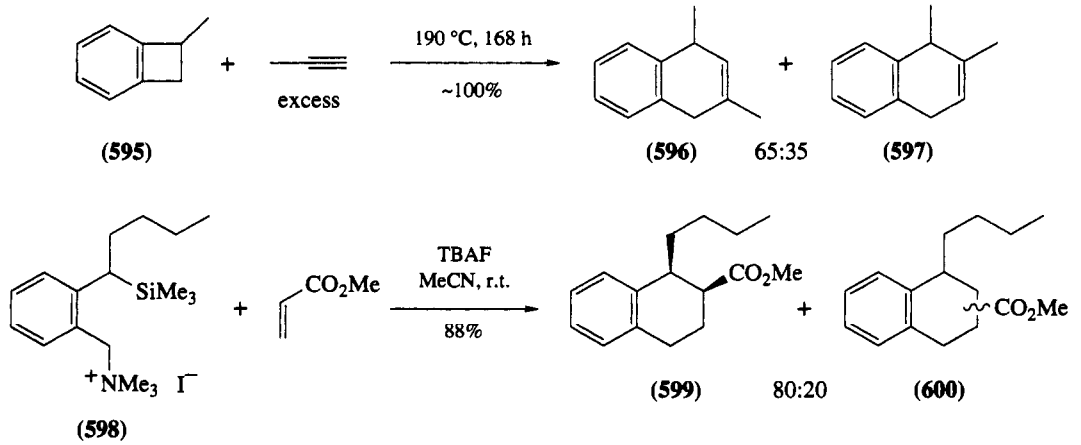
(593) (594)

Scheme 135 ***(continued)***

Hence, no 1,5-hydrogen shift was observed on heating benzocyclobutenylcarbamate (**589**) with nitrostyrene (**590**) at 130 °C, which furnished cycloadducts (**591**) + (**592**) in 94% yield (Scheme 135).[141] The strong regio-directing effects of the *N*-CO_2Bn (diene) and NO_2 groups (dienophile) secured their 'ortho' disposition in the products. However, the observed product ratio (**591**)/(**592**) reflects a stereospecific, but only poorly *endo*/*exo*-selective, [4 + 2] cycloaddition step.

This result contrasts sharply with that of the intramolecular transformation (**593**) → (**594**) (a key step in a synthesis of chelidonine). The exclusive formation of (**594**) (isolated in 92% yield) shows here an opposite regiochemical control and a strong preference for an *exo*-oriented nitro group in the transition state, dictated by the constraints of intramolecularity.[141]

Intermolecular thermal addition of 7-methylbenzocyclobutene (**595**) to propyne (→ **596** + **597**) displayed only modest regioselectivity (Scheme 136).[142] [4 + 2] Cycloadditions of the more polarized methyl acrylate to 7-*n*-butyl-*o*-quinodimethane, generated from (**598**) at room temperature *via* the desilylation technique, was more selective, giving the '*ortho*'/'*endo*' isomer (**599**) as the major product.[134] A methoxy substituent or a nitrogen atom as part of the developing aromatic ring has virtually no regiodirecting influence, as demonstrated by the corresponding reactions of (**601**) and (**604**).[134]



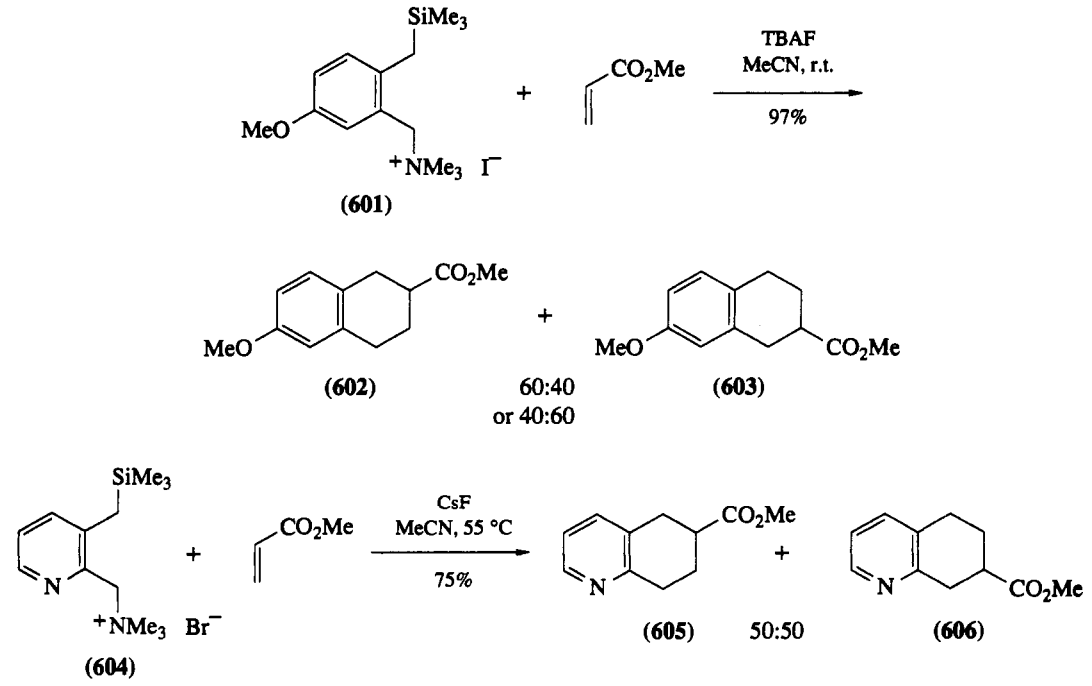
(595) (596) (597)

(598) (599) (600)

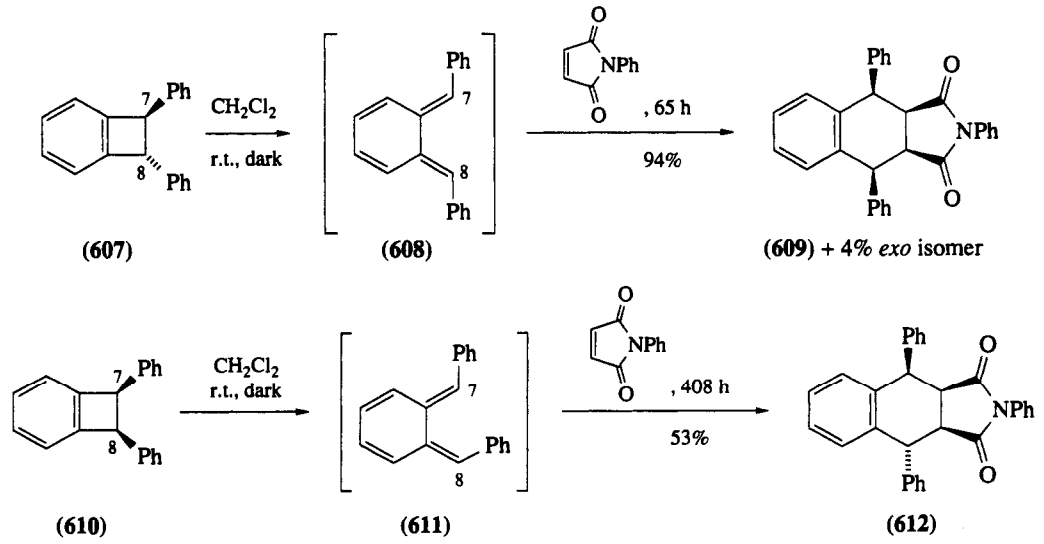
Scheme 136

Several stereochemical facets show up on Diels–Alder reactions of 7,8-disubstituted *o*-quinodimethanes. A seminal study of addition reactions of 7,8-diphenylbenzocyclobutenes provided strong evidence for a conrotatory opening of the four-membered ring, followed by a supra-supra-facial *endo*-selective Diels–Alder reaction with *N*-phenylmaleimide, as exemplified by the transformation (**607**) → (**609**) (Scheme 137).[143] Based on this result, it is now generally agreed that the *trans* relation of substituents at C-7 and C-8 in benzocyclobutenes translates, *via* the transient (*E*,*E*)-*o*-quinodimethanes, *e.g.* (**608**), into the *cis* disposition in the corresponding cycloadducts.

The corresponding transformation of *cis*-benzocyclobutene (**610**) to (**612**) proceeded slower (by a factor of 27), in keeping with the involvement of an (*E*,*Z*)-intermediate (**611**).[143] Attempts to generalize the latter type of stereochemistry met with only limited success due to the propensity of (*E*,*Z*)-*o*-quinodimethanes for 1,5-shifts (*e.g.* **S**, Scheme 134) and cyclizations.



Scheme 136 *(continued)*

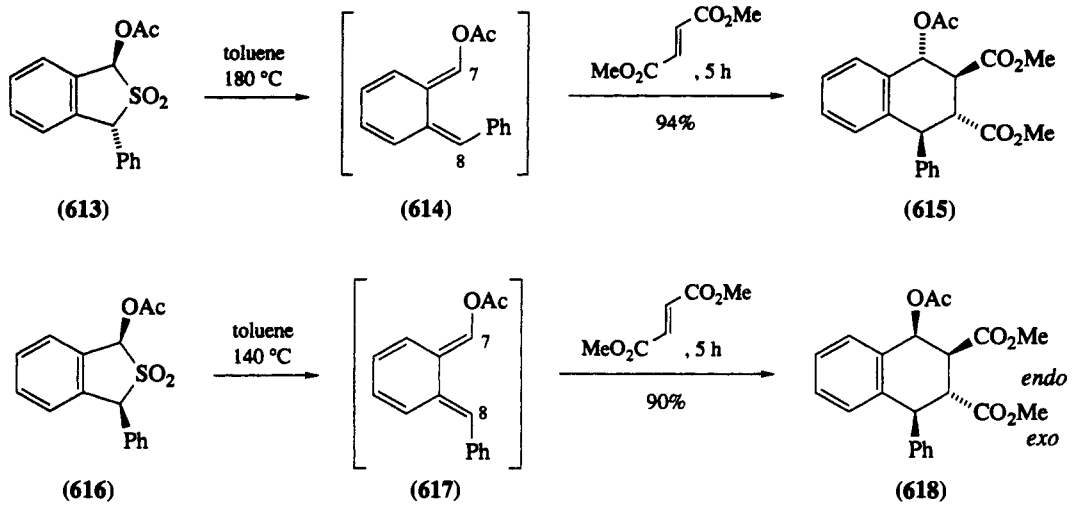


Scheme 137

One reported exception is the thermal stereospecific SO_2 extrusion of *trans*-acetoxyphenyl sulfone (**613**), coupled with the Diels–Alder reaction of the postulated (*E,Z*)-diene (**614**) to dimethyl fumarate, yielding (**615**; 94%) (Scheme 138).[138b]

As expected, *cis*-sulfone (**616**) afforded fumarate adduct (**618**; 90%) under milder conditions. Both examples display a complete 'retention' of diene and dienophile configurations in the cycloadducts. Moreover, each product (**615**) and (**618**) shows a *trans* disposition of the phenyl and adjacent ('*ortho*') methoxycarbonyl groups; the latter is apparently *exo* oriented on addition to (*E,E*)-diene (**617**).[138b]

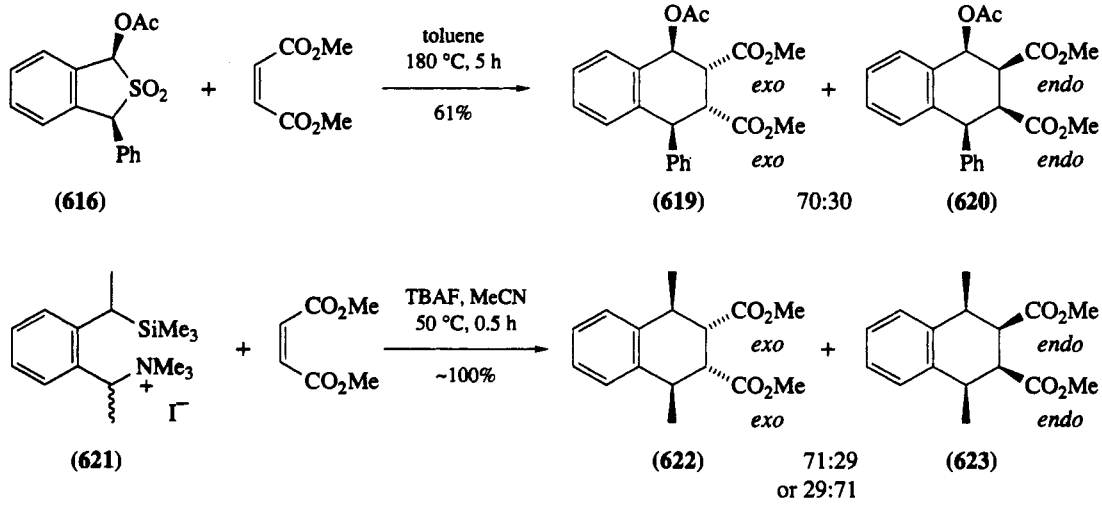
[4 + 2] Cycloadditions of dimethyl maleate to (*E,E*)-*o*-quinodimethanes exhibit only modest *endo*/*exo* selectivities (in contrast to maleic anhydride) (Scheme 139).[134,138b]



(613) (614) (615)

(616) (617) (618)

Scheme 138



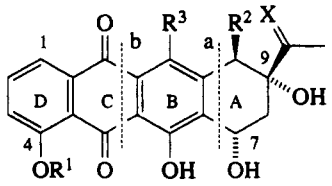
(616) (619) 70:30 (620)

(621) (622) 71:29 or 29:71 (623)

Scheme 139

4.1.8.4 Applications in Synthesis

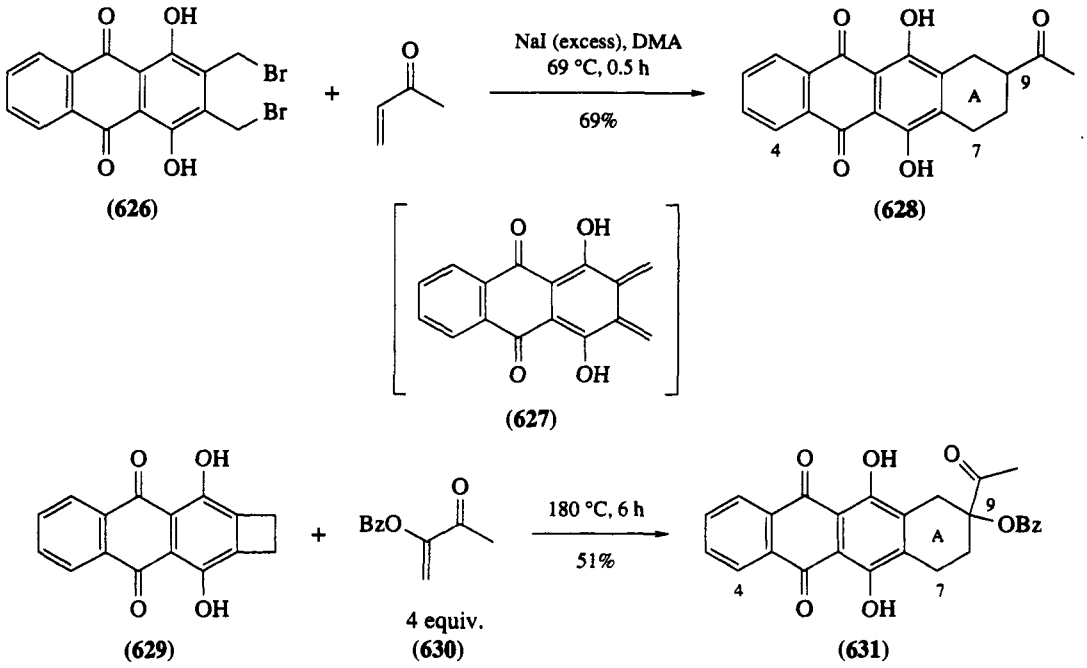
Diels–Alder reactions have played an eminent role (*cf.* Schemes 25, 26, 45, 53, 107, 109 and 124) in the synthesis of analogs of daunomycinone (**624**) and aklavinone (**625**), two representative aglycones of the tumor-inhibiting anthracyclines (Scheme 140).[144]



(**624**) R^1 = Me, R^2 = H, R^3 = OH, X = O Daunomycinone

(**625**) R^1 = H, R^2 = CO_2Me, R^3 = H, X = H_2 Aklavinone

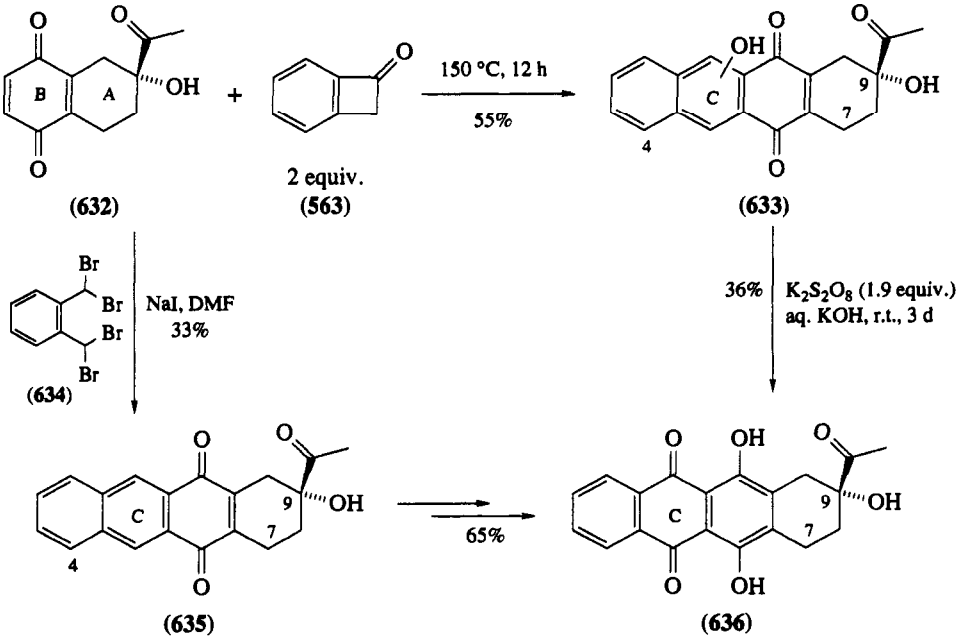
Several approaches to this linearly annulated ring system make use of *o*-quinodimethanes to form either ring A ('disconnection' a) or ring C ('disconnection' b). The first strategy is illustrated by the treatment of bis(bromomethyl)anthraquinone (**626**) with NaI in DMA and trapping of transient diene (**627**) with methyl vinyl ketone, which gave tetracyclic ketone (**628**) (Scheme 140).[145a] The generation of the same diene (**627**) by heating benzocyclobutene (**629**) is more efficient and compatible with the less-reactive dienophile (**630**) to afford the 9-oxygenated product (**631**) in one step.[145b]



(626) (627) (628) (629) (630) (631)

Scheme 140

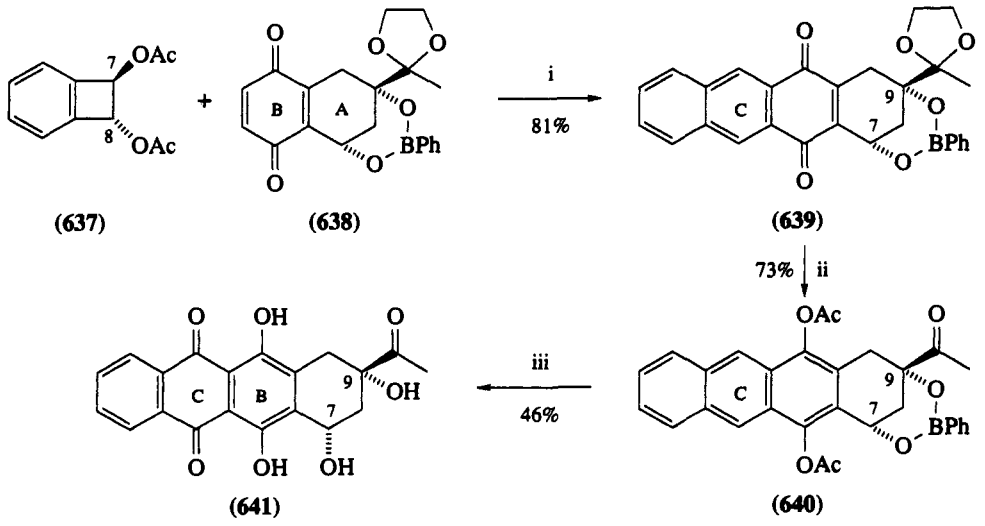
Formation of ring C ('disconnection' b) was readily accomplished by addition of *o*-quinodimethane intermediates, e.g. (**562**)[146] or 7,8-dibromo-*o*-quinodimethane,[147] to tetrahydronaphthoquinones such as racemic or enantiomerically pure (**632**) (Scheme 141).



(632) (563) (633) (634) (635) (636)

Scheme 141

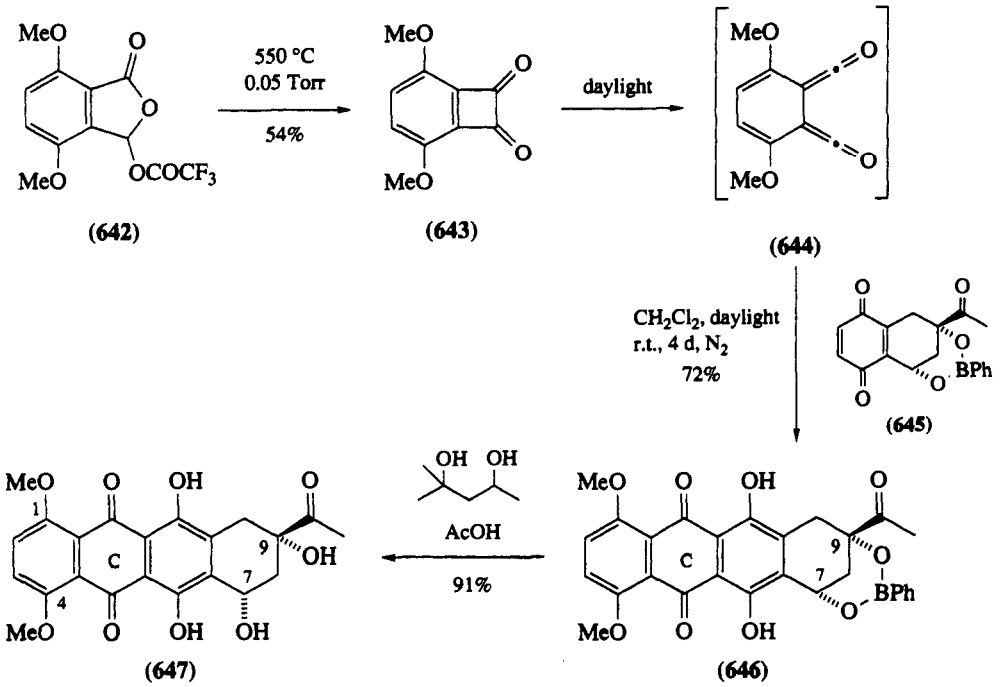
Resulting adducts (**633**) and (**635**) require further manipulation involving oxidation of ring C and introduction of a hydroxy group at C-7. The latter problem was elegantly solved by using enantiomerically pure, fully functionalized, phenylboronate (**638**) as an '$_{A,B}$-dienophile' (Scheme 142).[148] Thermal generation and cycloaddition of (*E,E*)-diacetoxy-*o*-quinodimethane furnished adduct (**639**) in 81% yield. The remaining five steps served mainly to adjust the oxidation levels of rings B and C.



i, xylene, reflux, 3 h; ii, 6 N HCl, dioxane, 25 °C, 4 h; H_2, Pd/C; Ac_2O, pyridine, 25 °C, 0.7 h; iii, CrO_3, Ac_2O, AcOH, 25 °C, 20 h; BCl_3, CH_2Cl_2, –70 to 10 °C, 1.5 h; $Me_2C(OH)CH_2CH(OH)Me$, AcOH, CH_2Cl_2, 25 °C

Scheme 142

This approach was dramatically shortened (from six to two operations) by providing the required oxidation level *via* the *o*-quinodimethane partner (Scheme 143).[146] Benzocyclobutenedione (**643**), readily available through flash vacuum pyrolysis of phthalide (**642**), furnished 'divinylketene' (**644**) on photo-



Scheme 143

lytic ring opening. Transient species (**644**) underwent a smooth addition to enantiomerically pure quinone (**645**) to give adduct (**646**) which, on simple deprotection, yielded (+)-1-methoxydaunomycinone (**647**) in 66% overall yield.

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4.2
Heterodienophile Additions to Dienes

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4.2.1 INTRODUCTION

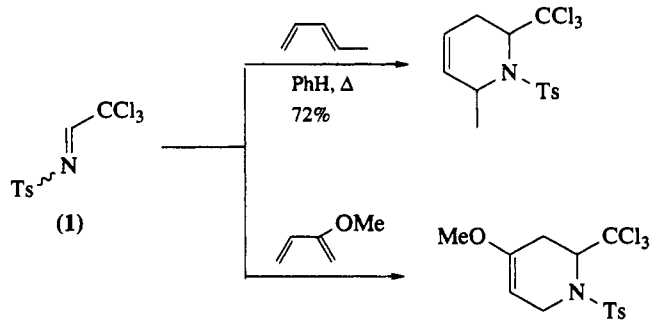
Diels–Alder reactions of heterodienophiles have been known for decades, but only recently has this methodology become widely accepted by the synthetic community. There is enormous diversity in the structural types of compounds which can act as heterodienophiles, and a wide array of heterocyclic adducts can be prepared *via* these [4 + 2] cycloadditions. It seems clear that hetero Diels–Alder reactions span a range of mechanism from concerted to stepwise ionic processes. In many instances, mechanistic information is totally lacking. The discussion below therefore classifies heterodienophiles by structural rather than mechanistic class. Only the major types of synthetically useful heterodienophiles have been included. Moreover, the significant regio- and stereo-chemical features of the reactions have been exemplified as much as possible using recently reported cases. Other more comprehensive and more specialized reviews[1] should be consulted for older material and more obscure hetero Diels–Alder cycloadditions.

4.2.2 IMINO DIENOPHILES

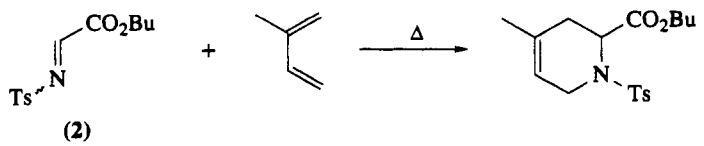
The initial report of an imine acting as a heterodienophile was briefly mentioned by Alder almost five decades ago.[2] Since that time an ever increasing number of examples of this type of cycloaddition have appeared. The large preponderance of imino Diels–Alder reactions have utilized electron-deficient imines, although a few cases of inverse electron demand cyclizations exist. Detailed reviews of this subject have previously been published.[1]

4.2.2.1 *N*-Sulfonyl Imines

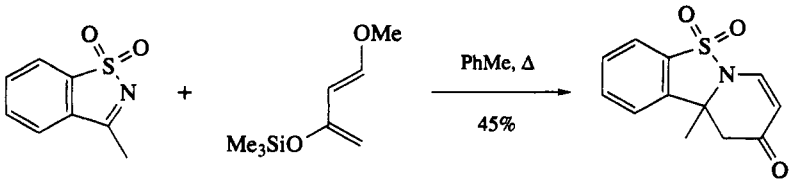
Although some of the earliest reported examples of imino Diels–Alder reactions have involved *N*-sulfonyl imines,[1d,3] these dienophiles have not been widely utilized in synthesis. These cycloadditions appear to be generally efficient and show excellent regiochemical control.[4] For example, imine (**1**) derived from chloral adds to unsymmetrical dienes to give single regioisomeric products as shown in Scheme 1.[4,5] Similarly, glyoxylate-derived imine (**2**) shows good regioselectivity in its cycloadditions (equation 1),[3b] as does cyclic *N*-sulfonyl imine (**3**) (equation 2).[6]



Scheme 1



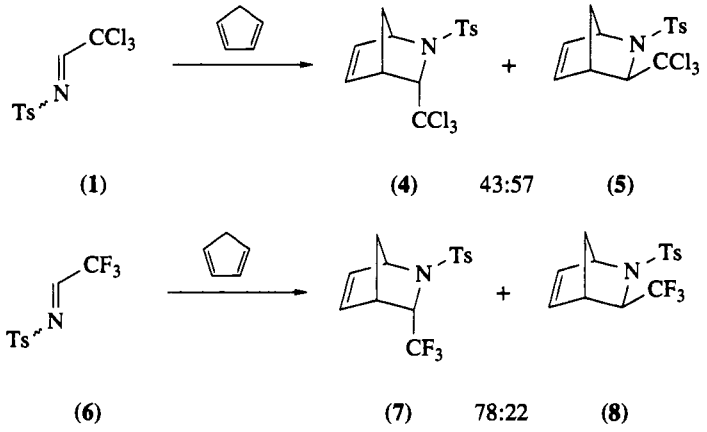
(1)



(3) (2)

It has been suggested that the regioselectivity observed in these cycloadditions is due to a reaction mechanism involving concerted bond forming and breaking in an unsymmetrical, highly polarized transition state.[1,4] Such a postulate seems reasonable, but at present there is little supporting evidence for it.

Krow *et al.* have investigated the stereochemistry of the addition of imines (**1**) and (**2**) to various cyclic dienes.[7] With cyclopentadiene, dienophile (**1**) produces a kinetic 43:57 mixture of *endo* (**4**)/*exo* (**5**) adducts (Scheme 2). Interestingly, fluorinated dienophile (**6**) gives a 78:22 mixture of *endo* (**7**)/*exo* (**8**) as the kinetic cycloaddition products. The observed stereochemical results may be largely due to steric factors, although ambiguities in interpretation arise since one cannot ascertain the reacting geometry (*E* or *Z*) of these dienophiles.

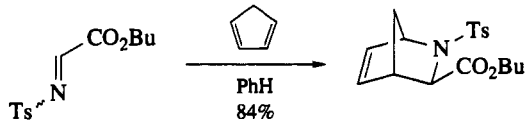


(**1**) (**4**) 43:57 (**5**)

(**6**) (**7**) 78:22 (**8**)

Scheme 2

The carboxyl-substituted dienophile (**2**) shows excellent stereoselectivity with cyclopentadiene, affording solely *exo* adduct (**9**) (equation 3).[8] This somewhat surprising result can be rationalized if one assumes that the cycloaddition involves an (*E*)-imine which reacts *via* a transition state having the bulky tosyl group *endo* to avoid steric interactions with the methylene bridge of the diene. Such a transition state, however, precludes secondary orbital interactions of the carbonyl group with the diene.

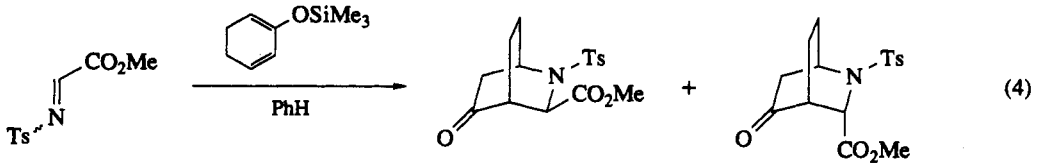


(**2**) (**9**) (3)

Some results described by Holmes and coworkers are consistent with the stereochemical outcome of equation (3).[9] Cycloaddition of imine (**10**) with 2-trimethylsiloxy-1,3-cyclohexadiene afforded a mixture of adducts (**11**) and (**12**) with the *exo* isomer predominating (equation 4). In this example, only a single regioisomer was detected.

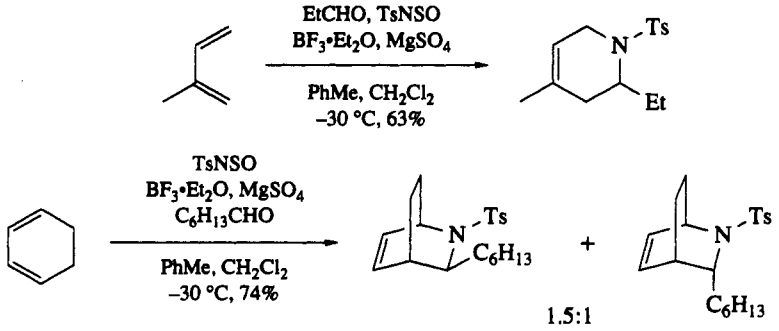
Recently, Sisko and Weinreb have developed a new, *in situ* procedure for effecting *N*-sulfonyl imine Diels–Alder reactions.[10] The method consists of treating an aldehyde with an *N*-sulfinyl sulfonamide/boron trifluoride etherate in the presence of a diene (Scheme 3). Under these conditions the *N*-sulfinyl sulfonamide reacts with the aldehyde to produce an *N*-sulfonyl imine. This reaction, developed by Kresze,[3b,11] has been used previously for preparing imines from simple, non-enolizable aldehydes (*cf.* **1,2**), but had not been applied to more complex aldehydes. As can be seen from the scheme, the cycload-

dition is effective with a variety of aldehyde precursors and 1,3-dienes. The process shows the usual high regioselectivity associated with [4 + 2] cycloadditions of *N*-sulfonyl imines (*vide supra*) but proceeds with only marginal stereoselectivity.



(4)

(10) (11) 57%:24% (12)



Scheme 3

4.2.2.2 *N*-Acyl Imines

Since the initial report in 1962 by Merten and Muller of the cycloaddition of an *N*-acyl imine with a conjugated diene,[12] a number of examples of this type of reaction have appeared.[1] In general, *N*-acyl imines are highly reactive, unstable species which are rarely isolated,[13] but rather are generated *in situ* from stable precursors. Depending upon the method of formation of the particular dienophile and the reaction conditions, a neutral *N*-acyl imine or a protonated (or Lewis acid complexed) *N*-acyl immonium ion may be involved in the Diels–Alder reaction.

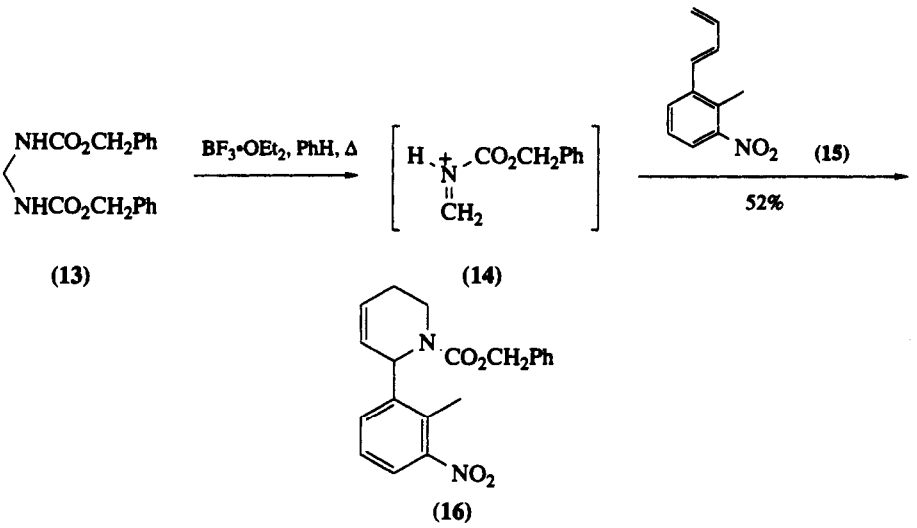
4.2.2.2.1 Acyclic dienophiles

As a rule, cycloadditions with acyclic *N*-acyl imino dienophiles are useful synthetic reactions which demonstrate excellent regio- and stereo-selectivity. A commonly used source of *N*-acyl immonium dienophiles are bis-urethanes[12,14–17] such as (**13**) (equation 5), which upon treatment with a Lewis acid and a diene afford Diels–Alder adducts. In this case, (**13**) reacts with boron trifluoride etherate to afford immonium ion (**14**) which adds to diene (**15**), yielding tetrahydropyridine (**16**).[17]

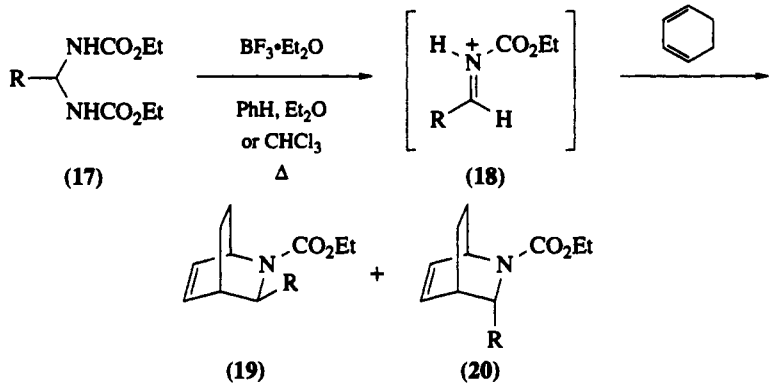
Krow has in fact studied the involvement of immonium intermediates like (**14**) in these reactions and has made important contributions in understanding the mechanism of the process.[7,18] The available data are consistent with a concerted cycloaddition mechanism, perhaps involving a polarized transition state. With substituted bis-carbamates such as (**17**) (Scheme 4), a protonated (*E*)-*N*-acyl immonium dienophile (**18**) is probably the reactive species. Krow has investigated the cycloaddition of various substituted dienophiles (**18**) with 1,3-cyclohexadiene and the stereochemical results are summarized in Scheme 4.[18] It was found that in most cases there is about a 3–4:1 preference for *exo* (**19**)/*endo* (**20**) cycloadducts. Thus immonium ion (**18**) generally reacts *via* a transition state in which the *N*-acyl group is *endo* to the diene. The exceptions to this rule occur when group R is very bulky and/or α-branched, leading to an increase in isomeric adduct (**20**). In these cases, R in (**18**) prefers an *endo* orientation to avoid severe steric interactions with the ethano bridge of the diene.

A few instances of neutral acyclic *N*-acyl imino dienophiles have been reported.[8b,19,20] Some of these imines can be prepared and isolated, but often they are generated *in situ*. For example, Wittig chemistry

has been used to synthesize *N*-acyl imines of glyoxylate and mesoxylate which can be trapped regioselectively by dienes to give Diels–Alder adducts (Scheme 5).[19]



(5)

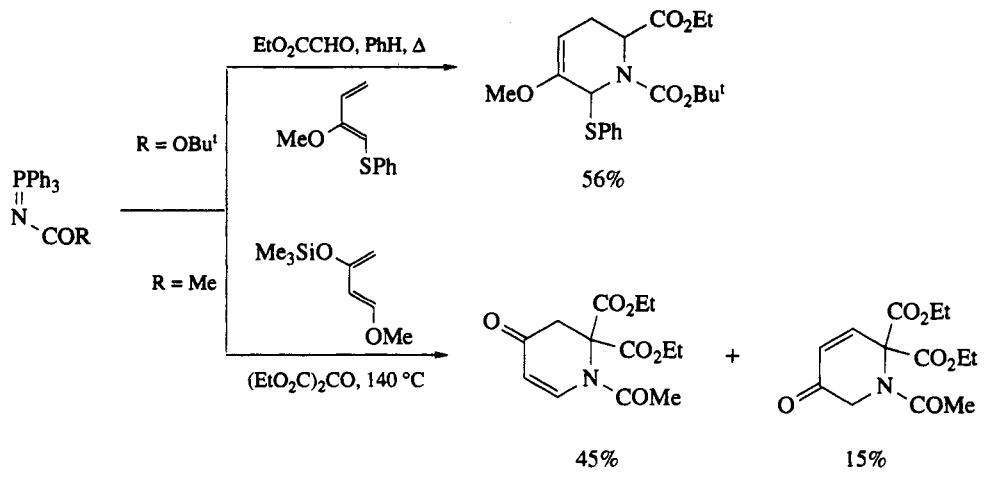


R =	CO_2Et	70%	30%
	CO_2Me	80%	20%
	Ph	80%	20%
	COMe	67%	33%
	Me	82%	18%
	Et	81%	19%
	Pr	81%	19%
	Bu^i	79%	21%
	Pr^i	36%	64%
	CCl_3	38%	62%
	cyclohexyl	54%	46%

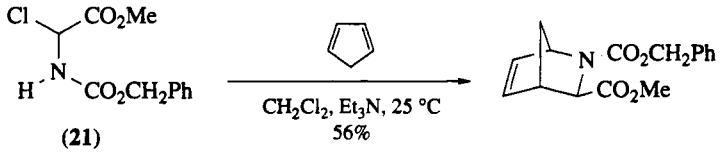
Scheme 4

Alternatively, an α-chlorocarbamate (**21**) has been used to produce an imine which cycloadds to cyclopentadiene (equation 6).[20] Interestingly, only the *exo* adduct was formed.

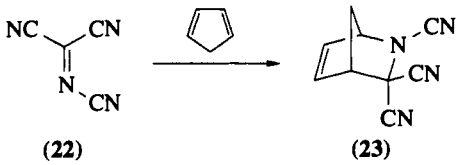
In some related work, trinitrile (**22**) (equation 7) has been prepared and was found to react with cyclopentadiene to afford (**23**) in unspecified yield.[21] No other examples of cyanamid-derived imino dienophiles seem to have been reported to date.



Scheme 5



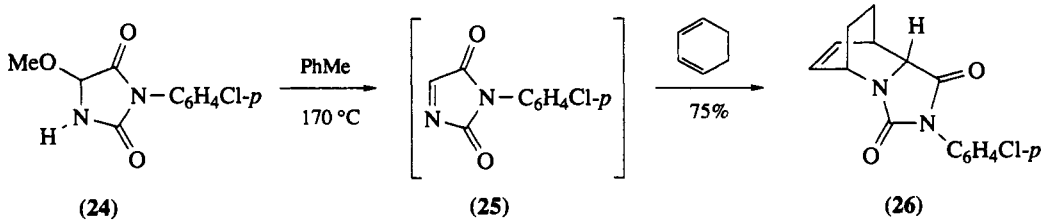
(6)



(7)

4.2.2.2.2 Cyclic dienophiles

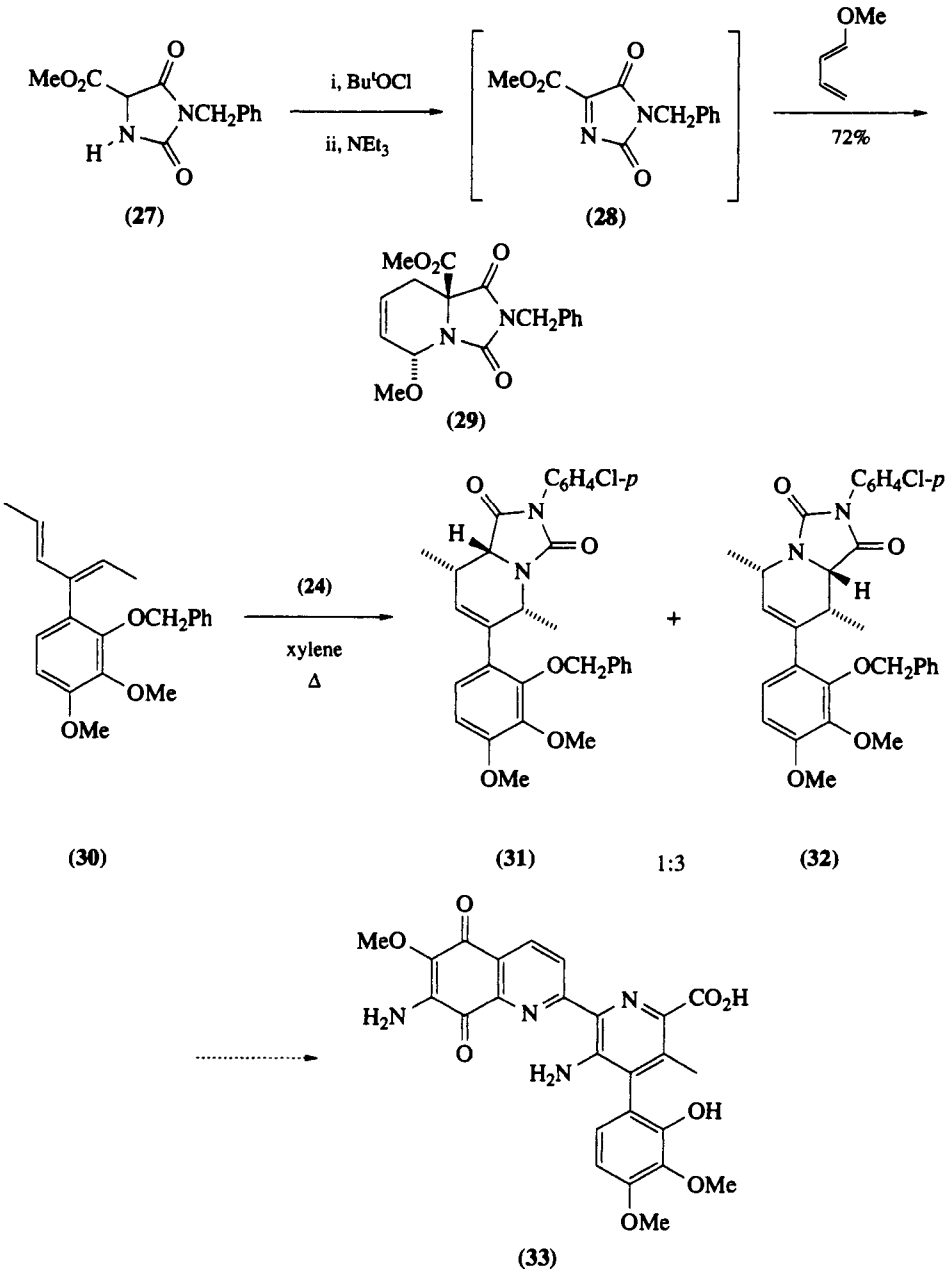
A number of diverse structural types of cyclic imino dienophiles have been used in cycloadditions. For instance, dehydrohydantoins are useful partners in hetero Diels–Alder reactions. Two methods have been developed for *in situ* generation of these species. In one approach, methoxyhydantoins such as (**24**) (equation 8) are heated or are treated with acid to promote elimination of methanol, affording dienophile (**25**).[22,23] This intermediate can be trapped regio- and stereo-selectively with 1,3-dienes. For example, with 1,3-cyclohexadiene only *endo* adduct (**26**) is formed. There is no ambiguity in this case concerning the dienophile configuration, and thus product (**26**) clearly derives from an *endo* transition state.



(8)

Another method for producing dehydrohydantoins involves *N*-chlorination of a compound such as (**27**) followed by dehydrohalogenation to give (**28**) which reacts with 1-methoxybutadiene forming adduct (**29**) (equation 9).[24] As can be seen, this cycloaddition is both regio- and stereo-selective.

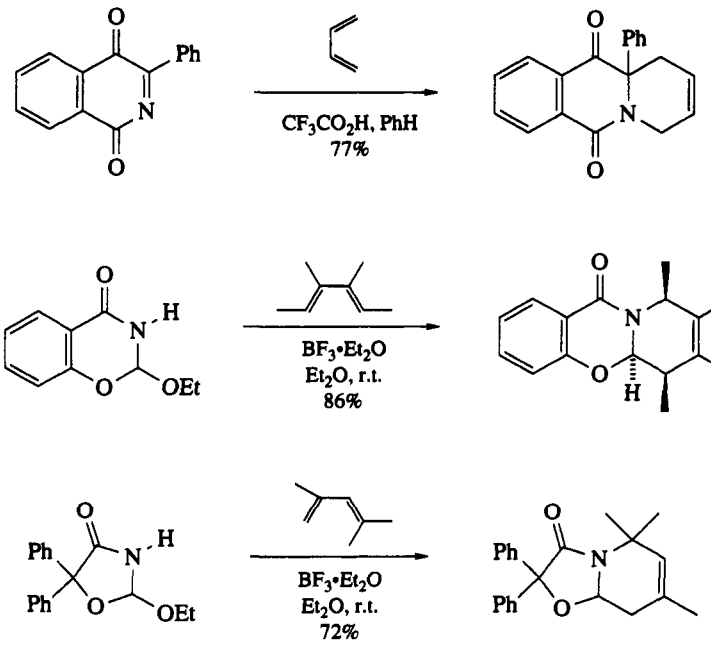
The Diels–Alder cycloaddition of a dehydrohydantoin has been utilized as a key step in a total synthesis of the antitumor antibiotic streptonigrin (**33**) (equation 10).[23b] Addition of diene (**30**) to hydantoin (**24**) afforded a 1:3 mixture of the tetrahydropyridines (**31**) and (**32**). The desired regioisomer (**32**) was converted in several steps to the natural product.



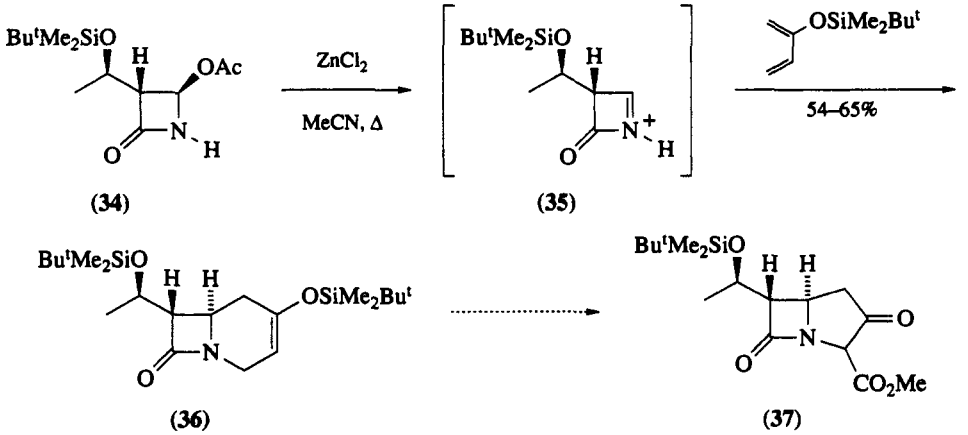
There are some scattered reports of other cyclic *N*-acyl imines which have been used as dienophiles.[25-27] In particular, the group of Ben-Ishai has described the cycloadditions shown in Scheme 6, along with several other systems.[25] These dienophiles have not been used in synthesis to any significant extent.

Recently, a few examples of imino Diels–Alder reactions using azetinones as dienophiles have been described in work aimed at synthesis of carbapenems.[28] In one sequence of reactions, acetate (**34**) was treated with a Lewis acid in the presence of a siloxy diene to afford adduct (**36**) (equation 11).[28b] This transformation presumably involves imine (**35**) which reacts both regio- and stereo-selectively with the diene. Adduct (**36**) was converted in a few steps to carbapenem (**37**).

Edwards and coworkers have investigated the cycloaddition chemistry of cyclic immonium ion (**39**) produced from ethoxy lactam (**38**) (Scheme 7).[29] It was found that under a variety of acidic reaction conditions (**38**) usually produced complex mixtures of Diels–Alder adducts along with 'one bond' solvolysis products. Some representative examples are shown in Scheme 7. It was concluded that these results are more consistent with a stepwise ionic mechanism than a concerted one.



Scheme 6



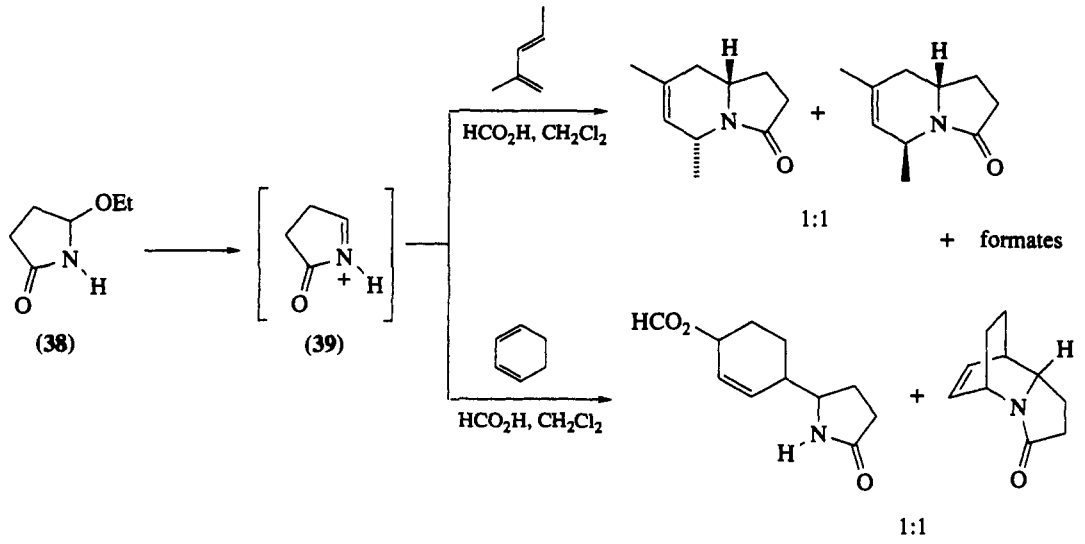
(11)

4.2.2.3 *C*-Acyl Imines

Simple *C*-acyl imines have been used rarely in Diels–Alder reactions, and little is presently known about the structural features necessary to make these species useful dienophiles.[30–34]

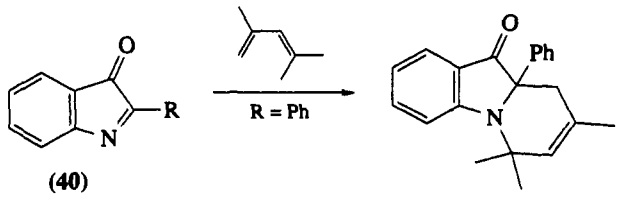
Indolones such as (**40**) have been exploited on a few occasions as heterodienophiles (equation 12).[30] Cycloaddition of (**40**; R = Ph) with several dienes was regioselective (*cf.* equation 12). The reactions with (*E*,*Z*)- and (*E*,*E*)-2,4-hexadiene were *syn* stereoselective with respect to the diene but *exo*/*endo* selectivity was not determined.[30b] With the related dienophile (**40**; R = CO_2Et), regioselectivity deteriorated in the cycloadditions.

Acyclic *C*-acyl imines have recently been studied as dienophiles.[32–34] For example, Prato and coworkers examined the reaction of imines (**41**) (equation 13) with several cyclic and acyclic 1,3-dienes.[33] Under neutral conditions, (**41**) is unreactive as a dienophile. However, under Lewis acid catalysis these imines react to afford mixtures of adducts. With 1,3-cyclohexadiene, bicyclic adducts (**42**) and (**43**) are produced along with (**44**) in which the imine has acted as an azadiene.[35] The ratios of these sorts of products are dependent upon the particular imine and diene used. The formation of adducts of type (**43**) proved to be both regio- and stereo-selective. Product formation in these cases can be rationalized both by concerted and by stepwise ionic mechanisms.[33]



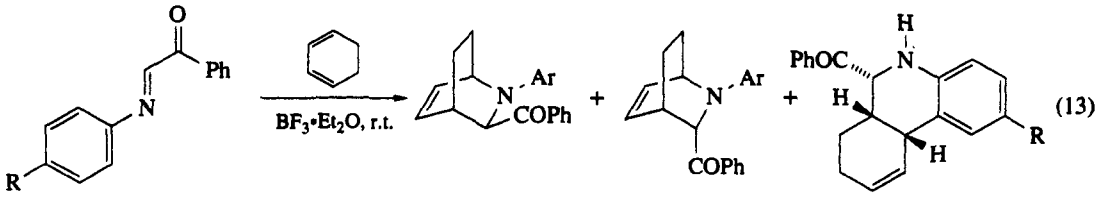
(38) (39)

Scheme 7



(12)

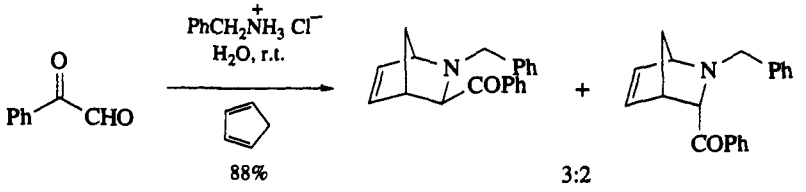
(40)



(13)

(41) R = NO_2, Cl, Me, OMe (42) (43) (44)

In another recent study, Grieco *et al.* have found that *C*-acyl immonium ions formed *in situ* under aqueous conditions undergo [4 + 2] cycloadditions as shown in equation (14).[34] This group has utilized similar methodology for other immonium Diels–Alder reactions (see Sections 4.2.2.4 and 4.2.2.8).

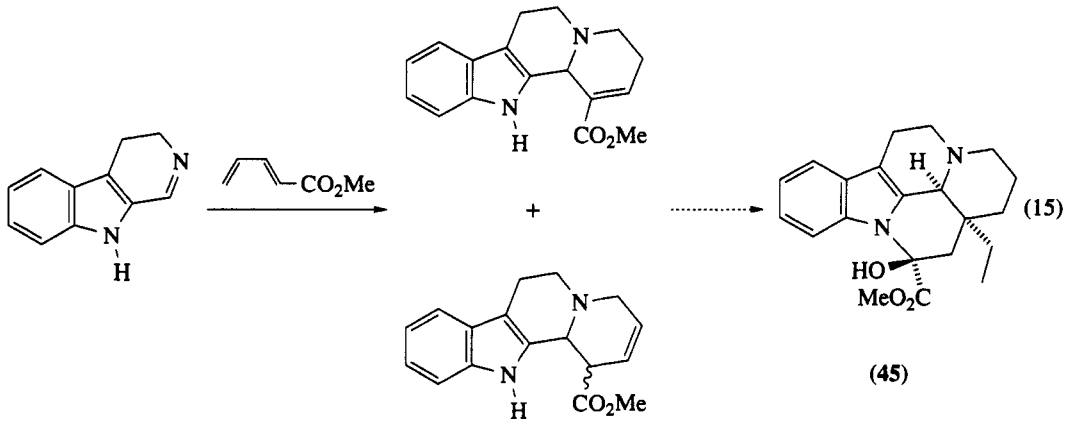


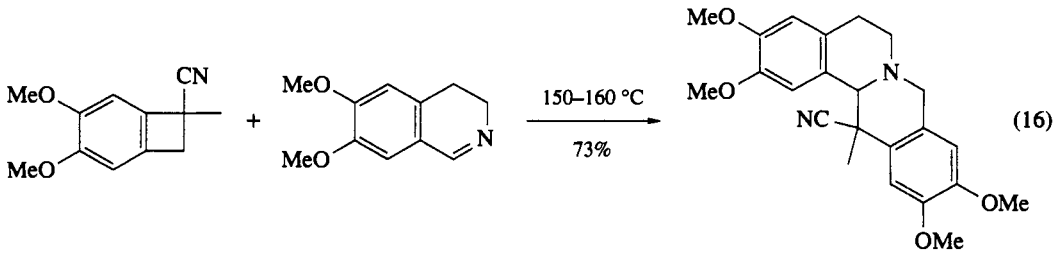
(14)

4.2.2.4 Alkyl and Aryl Imines and Immonium Salts

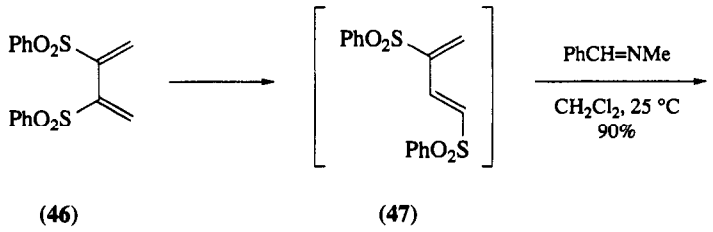
Simple, neutral electron-rich imines are generally not useful dienophiles unless appropriately reactive dienes are used. Thus it is possible to effect cycloadditions of neutral imines with some electron-deficient dienes.[36,37] In a series of papers, Langlois and coworkers[37] have described Diels–Alder reactions of cyclic imines and methyl 2,4-pentadienoate to afford adducts used in alkaloid synthesis. For example, the cycloaddition shown in equation (15) was used in a total synthesis of the indole alkaloid vincamine (**45**).

Neutral imines also add to *o*-quinodimethanes.[38] Kametani's group has reported several cycloadditions of the type shown in equation (16).

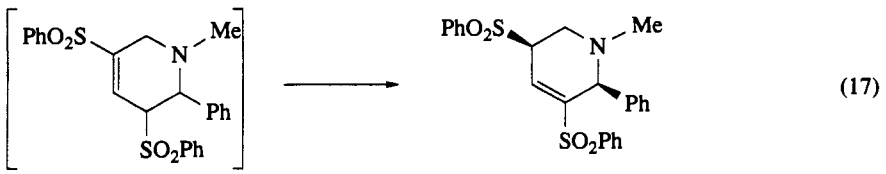




Another type of reactive electron-deficient diene which combines with neutral imines is disulfone (**46**) (equation 17).[39] Interestingly, this diene rearranges under the reaction conditions to isomer (**47**) which undergoes regioselective [4 + 2] cycloadditions with neutral imines to give initial adducts such as (**48**). However, this product suffers a subsequent 1,3-hydrogen shift to provide isolable adduct (**49**). Independent synthesis and cycloaddition of (**47**) provided good evidence for the overall reaction pathway shown.



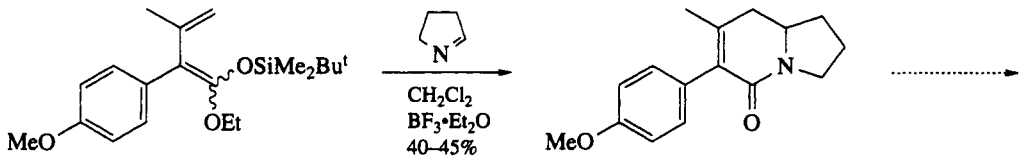
(**46**) (**47**)



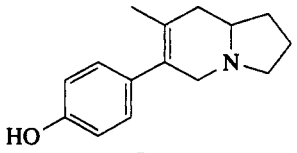
(**48**) (**49**)

Immonium salts constitute a class of generally reactive hetero dienophiles.[1,40] During the past several years a number of examples have been described of [4 + 2] cycloadditions of imines with oxygenated dienes under Lewis acid catalysis.[41,42] These reactions probably involve intermediate immonium salts which react regio- and often stereo-selectively with these electron-rich 1,3-dienes. Danishefsky and co-workers have provided several instances of this type of process.[41a,b,f] Equation (18) shows an approach to

the indolizidine alkaloid ipalbidine (**52**) which utilized a regioselective [4 + 2] cycloaddition of diene (**50**) with 1-pyrroline to afford lactam (**51**).[41f]

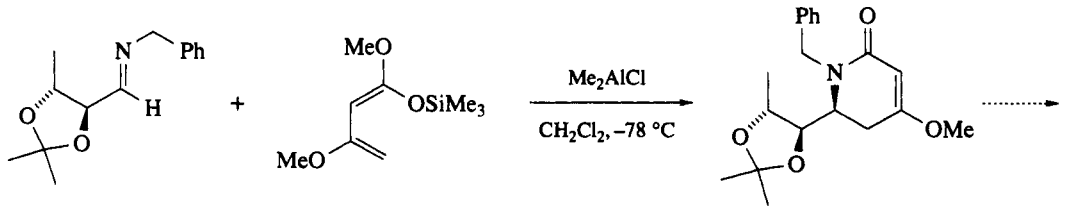


(**50**) (**51**)

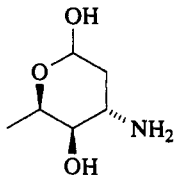


(**52**) (18)

Another example of this process is delineated in equation (19).[41i] In this case, chiral imine (**53**) was found to react under Lewis acid catalysis with diene (**54**) to provide adduct (**55**) stereoselectively *via* a Cram 'chelation controlled' process. This cycloadduct was transformed in a few steps to amino sugar (**56**).



(**53**) (**54**) (**55**)



(**56**) (19)

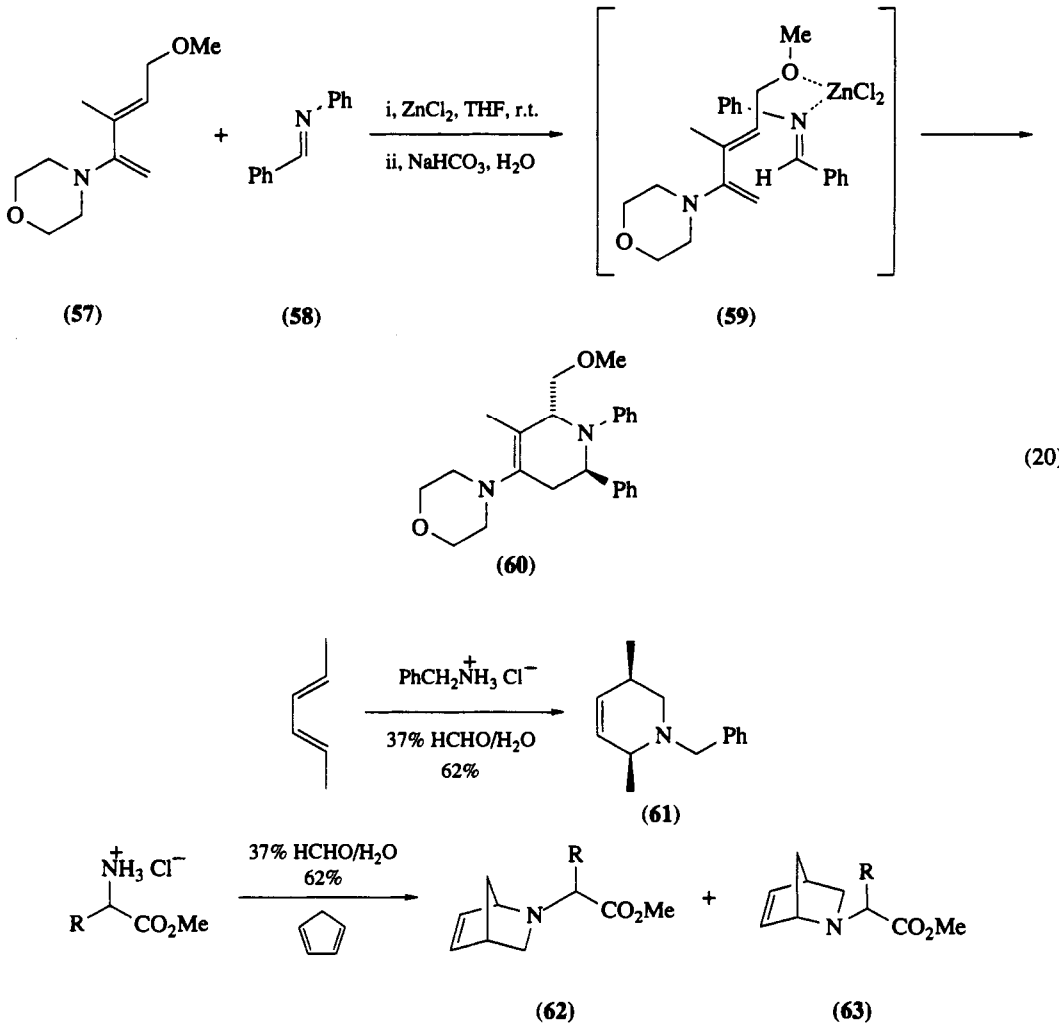
In related work, Barluenga *et al.* have reported that electron-rich dienamine (**57**) reacts with imine (**58**) in the presence of zinc chloride to afford adduct (**60**) regio- and stereo-selectively (equation 20).[42] It was suggested that the stereochemical outcome is due to involvement of a chelated intermediate (**59**).

An important advance in immonium Diels–Alder methodology has been reported by Grieco and co-workers[34,43] (*cf.* Sections 4.2.2.3 and 4.2.2.8). The procedure consists of treating a 1,3-diene with an amine hydrochloride and an aldehyde under aqueous conditions to produce a Diels–Alder adduct, presumably *via* an *in situ* produced immonium salt. Conversion of (*E,E*)-hexadiene to adduct (**61**) (Scheme 8) exemplifies the method. Waldman[43c] has recently applied the Grieco approach to various α-amino acid methyl ester derivatives. It was found that condensation of the immonium intermediates with various cyclic and acyclic 1,3-dienes gave mixtures of diastereomers (*cf.* **62** and **63**) ranging from 93:7 to 63:37 depending upon the particular substrates utilized.

4.2.2.5 Cycloadditions with Heterocyclic Azadienes

A limited number of examples of this class of reactions exist. One heteroaromatic compound which has been used as an azadiene in inverse electron demand reactions with electron-rich imines is tetrazine

(64).[44,45] Scheme 9 outlines two cycloadditions of this substance. As can be seen, the intermediate adduct cannot be isolated but, rather, triazines are produced.

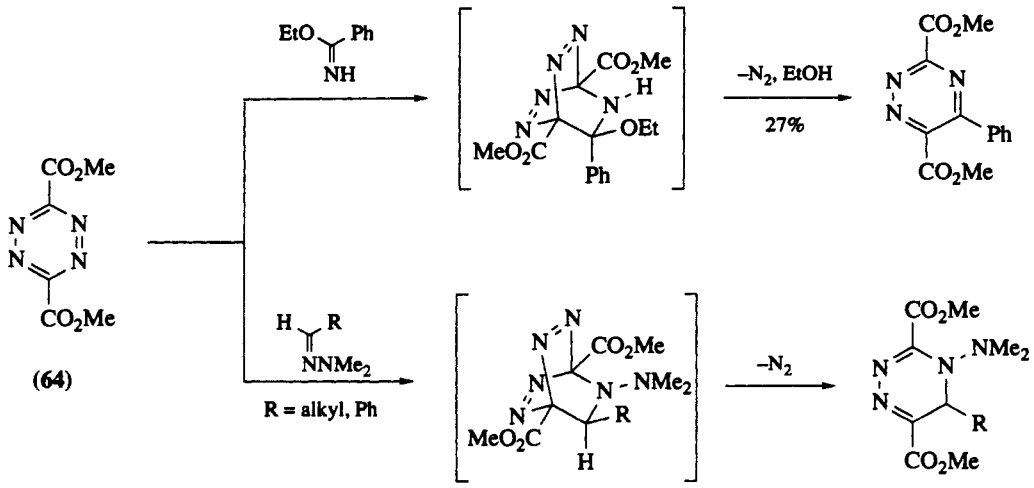


Scheme 8

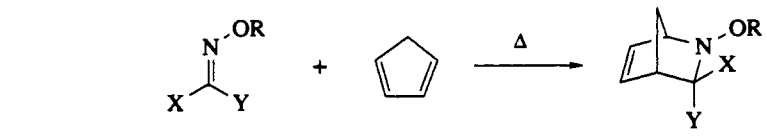
4.2.2.6 Oximino Dienophiles

Oximes bearing electron-withdrawing substituents on both carbon and oxygen have been used upon occasion as imino dienophiles. Fleury and coworkers, in an extensive study, investigated cycloadditions of oxime derivatives (**65**) with cyclopentadiene to afford adducts (**66**) (equation 21). It was found that groups X and Y on the dienophile impart reactivity in the order CN >> CO_2R > $CONH_2$. The oxygen substituent R has a reactivity sequence Ts > Ms > COAr. Carbonyl substituents as X or Y have a preference over cyano for being *endo* in the cycloaddition but a complication is that *exo*/*endo* equilibration often occurs in the products. The cycloaddition is not totally general, and is only successful with relatively reactive 1,3-dienes. Butadiene and 1,4-diphenylbutadiene, for instance, do not react with (**65**). The process does show good regioselectivity with unsymmetrical dienes (*vide infra*) in the few cases reported.

The cycloaddition does provide a useful route to certain pyridine derivatives.[46,47] For example, oxygenated dienes (**67**) add to oximino dienophile (**68**) to afford adducts (**69**)[47b] in a totally regioselective manner (equation 22). Treatment of this adduct with base provides the pyridine amide (**70**).



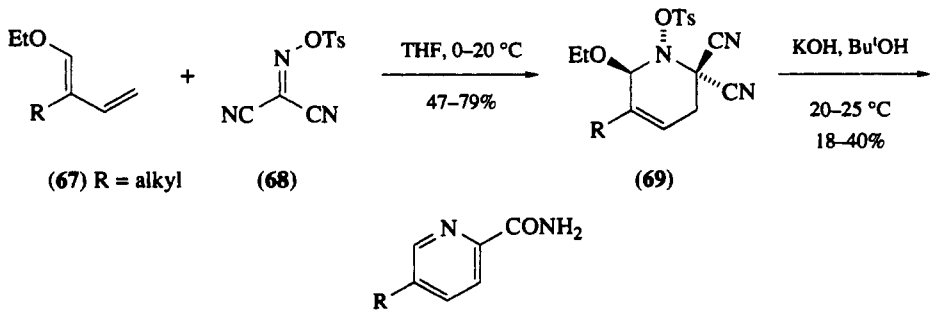
Scheme 9



(21)

(65)
X, Y = CN, CO_2Et, $CONH_2$
R = Ts, Ms, COAr

(66)



(22)

(67) R = alkyl (68) (69)

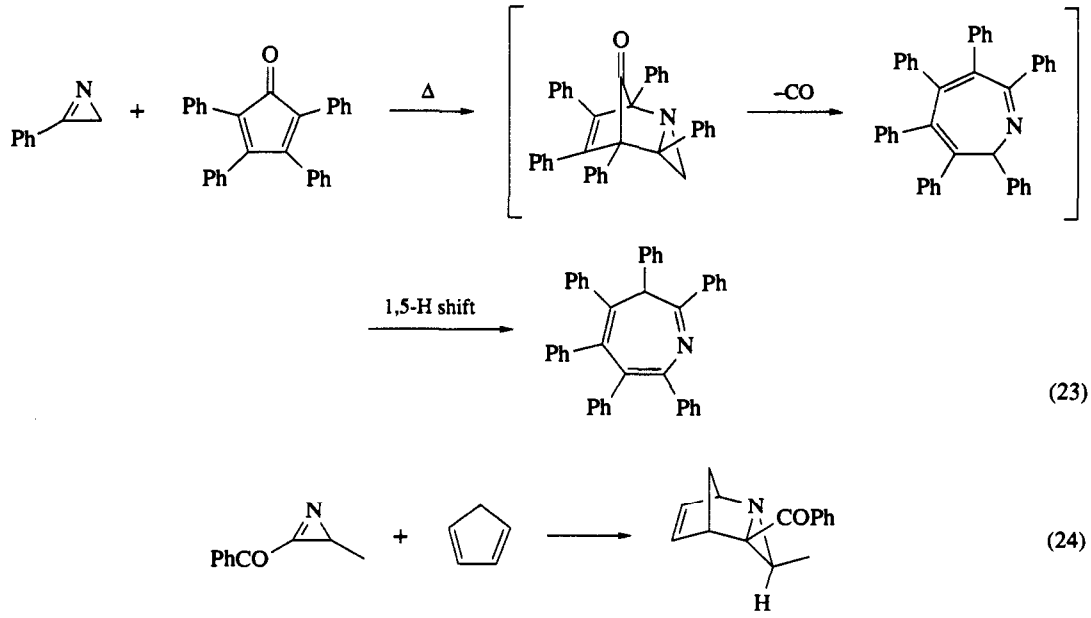
(70)

4.2.2.7 Azirines

Several reports of the participation of azirines as hetero dienophiles have appeared, and this subject has been reviewed.[1,48] Simple alkyl and aryl azirines react with cyclopentadienones to afford azepines as the ultimate products (equation 23). This type of azirine does not react with cyclopentadiene, but the benzoyl azirine shown in equation (24) does to afford an isolable Diels–Alder adduct.[49] Azirines have also been shown to react stereoselectively in [4 + 2] fashion with tetrazines such as (**64**) and isobenzofuran.

4.2.2.8 Intramolecular Cycloadditions

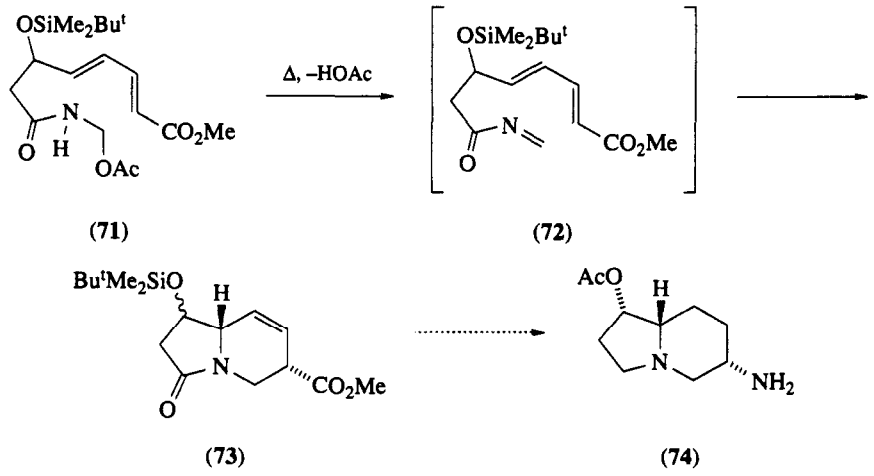
Over the past ten years, intramolecular imino Diels–Alder reactions have become a useful tool for alkaloid synthesis. This subject has been thoroughly reviewed[1b,c,50] and the discussion below is intended to exemplify various important aspects of the methodology.[51]



(23)

(24)

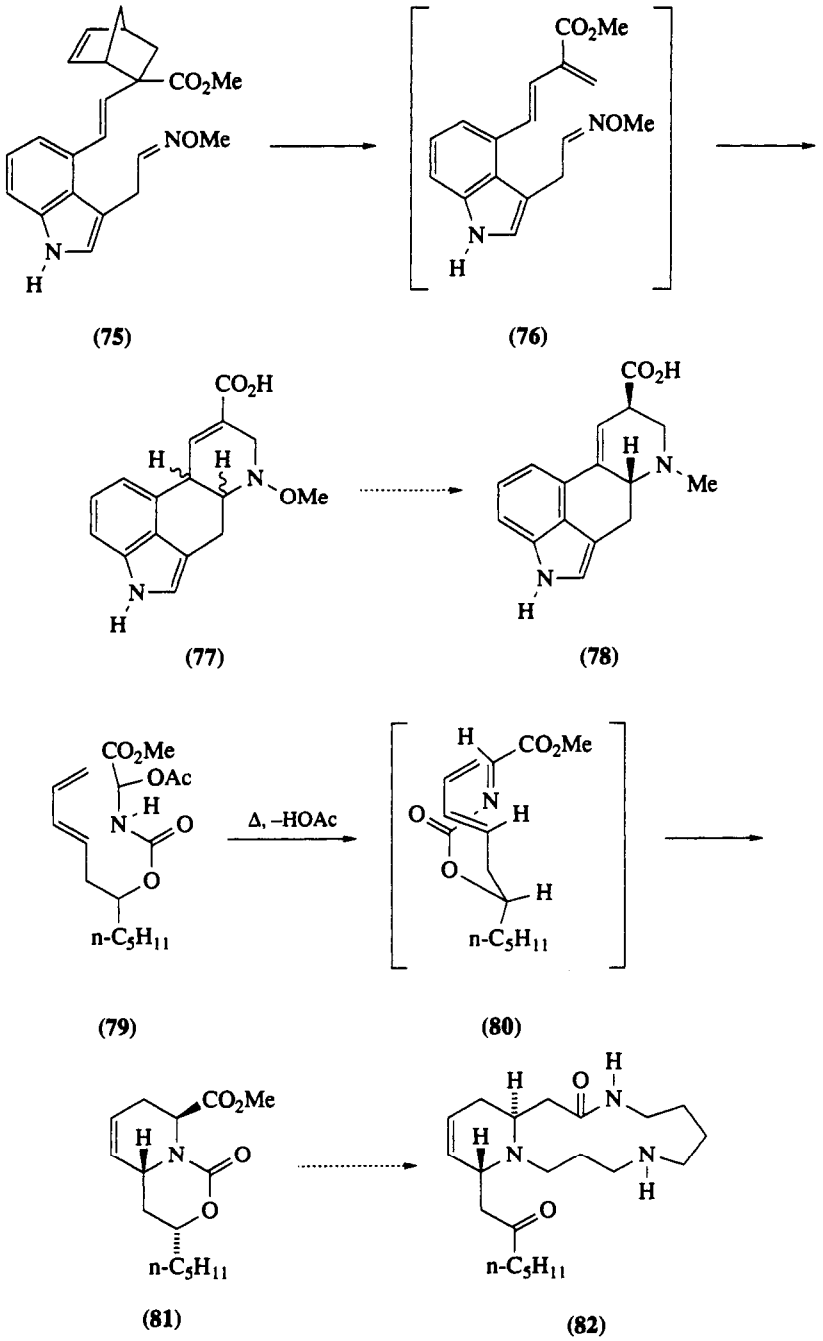
The Weinreb group has used an intramolecular imino Diels–Alder cycloaddition as the key step in a total synthesis of the fungal neurotoxin slaframine (**74**) (equation 25).[52] Thus, thermolysis of acetate (**71**) produced an intermediate *N*-acyl imine (**72**) which underwent [4 + 2] cycloaddition to afford bicyclic lactam (**73**) as a 1.8:1 mixture of epimers. Both compounds were converted to the natural product in a few steps.



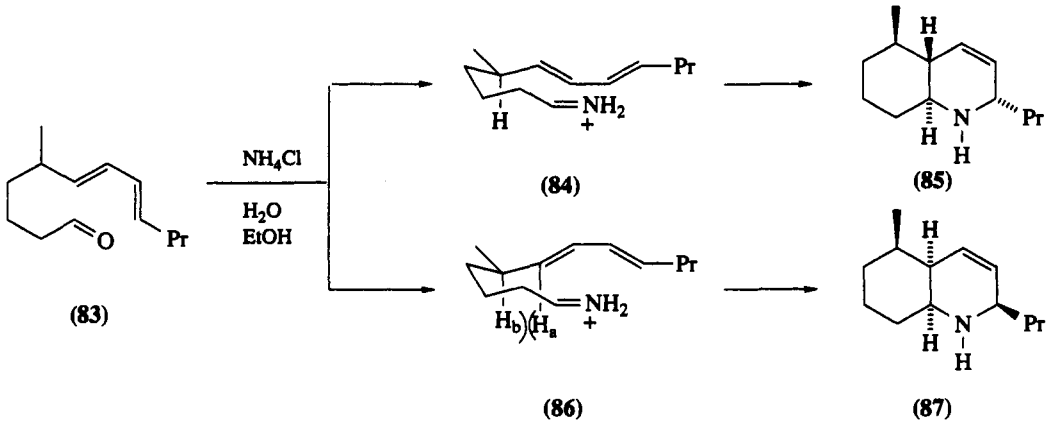
(25)

A clever approach to lysergic acid (**78**) has been described by Oppolzer and coworkers (equation 26).[53] Their approach involved an initial retro Diels–Alder reaction of (**75**) to give diene (**76**). This compound then underwent intramolecular cycloaddition with the oxime ether to afford adduct (**77**) as a 3:2 mixture of diastereomers (67% yield). This mixture could be converted to lysergic acid by a short sequence of reactions.

In a study directed towards total synthesis of the spermidine-derived alkaloid anhydrocannabisativine (**82**), Weinreb and coworkers investigated the intramolecular cyclizations of azafumarates.[54] It was found that, upon heating, acetate (**79**) provided Diels–Alder adduct (**81**) as a single stereoisomer (equation 27). The suggestion was made that (**79**) loses acetic acid to produce azafumarate (**80**), which cyclizes *via* the conformation shown. This conformation is favored over other possibilities since it has the *N*-carbonyl group *endo* to the diene and the connecting chain is chair-like with the large alkyl group quasi-equatorial.[54]



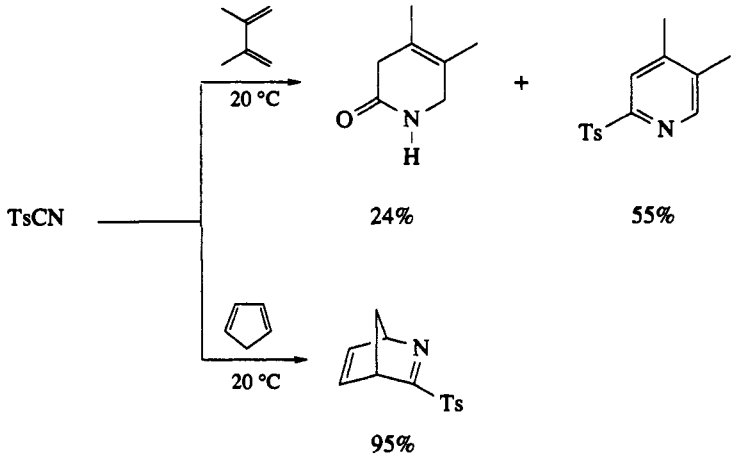
Grieco has used his aqueous immonium Diels–Alder procedure to effect a number of intramolecular reactions.[51b–d] In one case, diene aldehyde (**83**) was treated with ammonium chloride to afford a 2.2:1 mixture of isomeric Diels–Alder adducts (**87**) and (**85**) (Scheme 10). Since intermediate immonium ions (**84**)/(**86**) cannot participate in secondary orbital effects as is the case with *N*-acyl imines (*cf.* **80**),[55] these results are probably due to steric factors. It was suggested that adduct (**85**) derives from conformation (**84**) and adduct (**87**) comes from (**86**). Conformer (**84**) is favored since there is a severe eclipsing of H_a/H_b in (**86**). A more detailed account of the stereochemical aspects of intramolecular Diels–Alder reactions can be found in Chapter 4.4.



Scheme 10

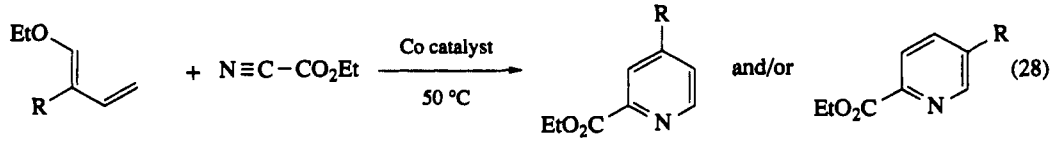
4.2.3 NITRILES

There is only sparse literature on [4 + 2] cycloadditions of nitriles with 1,3-dienes. In general, simple alkyl and aryl nitriles will only react at high temperatures and under these conditions the product dihydropyridines usually disproportionate.[1d] However, certain types of electron-deficient nitriles appear to be reactive dienophiles under milder conditions. For example, arylsulfonyl cyanides cycloadd to 1,3-dienes to afford adducts as shown in Scheme 11.[56,57] This methodology has not been widely explored and little is known about the regiochemistry of the process.



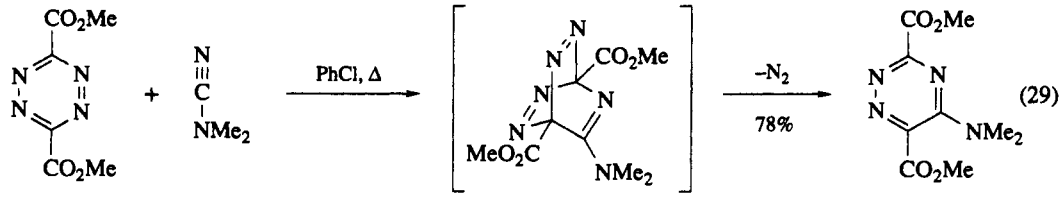
Scheme 11

More recently, Potthoff and Breitmaier found that alkoxy dienes (**83**) react with cyanoformate (**84**) under mild conditions if a cobalt catalyst is used (equation 28).[58] The products of the reaction are pyridines (**85**) and/or (**86**) depending upon the 2-alkyl substituent in the diene. Thus, if R = methyl, only isomer (**85**) is formed. When R = ethyl, a mixture of pyridines is produced, whereas when R is large only (**86**) is detected. The origin of these results is not clear.

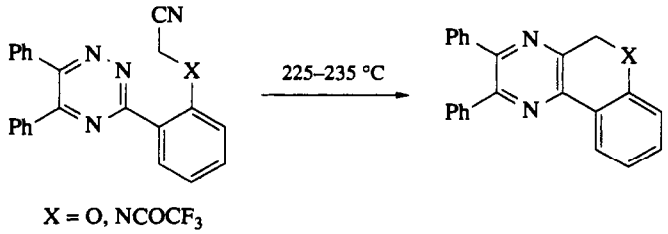


(**83**) R = alkyl (**84**) (**85**) (**86**)

Inverse demand Diels–Alder cycloadditions of electron-rich nitriles with electron-deficient heteroaromatic dienes are also known. Typical examples of inter-[59] and intra-molecular[60] instances of this process are shown in equations (29) and (30), respectively.



(29)



(30)

X = O, $NCOCF_3$

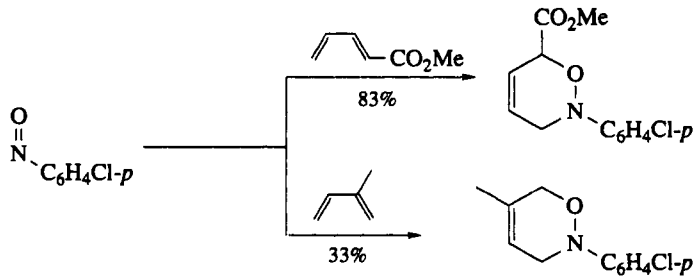
4.2.4 NITROSO COMPOUNDS

A wide range of *C*-nitroso compounds have proven to be useful dienophiles in [4 + 2] cycloadditions.[1,61] On the other hand, *N*-nitroso compounds and nitrosyl chloride do not act as dienophiles. In general, this class of cycloadditions proceeds with excellent regioselectivity.

A unified picture of the mechanism of this cycloaddition for various structural types of nitroso dienophiles is not available. Depending upon the electronic and steric nature of the particular nitroso compound, the reaction apparently may vary from a concerted pericyclic process to one involving discrete dipolar intermediates.[61–63] The net result of this mechanistic diversity is a few 'anomalous' regiochemical results in the cycloaddition.

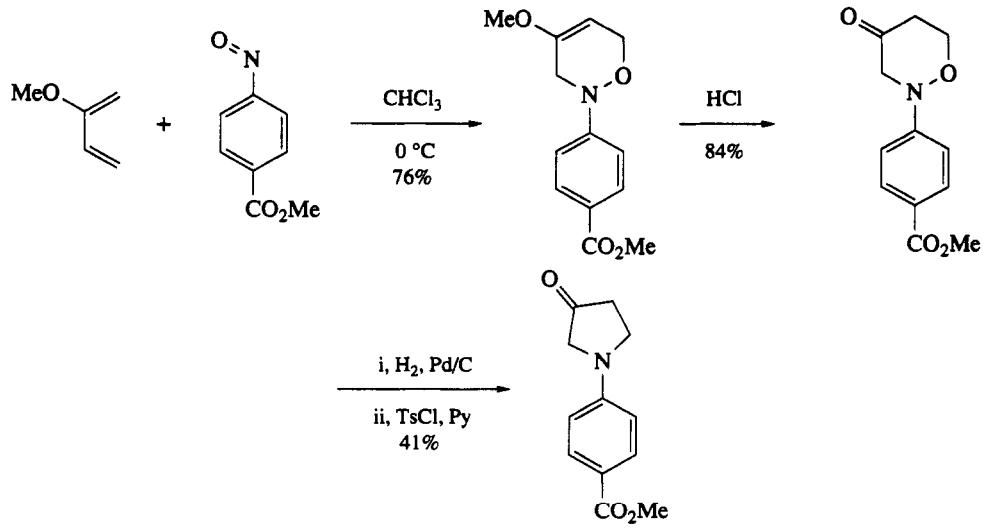
4.2.4.1 Aryl Nitroso Compounds

Aryl nitroso compounds, which are readily available synthetic intermediates, react regioselectively with most 1,3-dienes.[1,61,64] Scheme 12 shows two examples of cycloadditions with unsymmetrical dienes, affording single isomeric 3,6-dihydro-1,2-oxazines in each case.[61] Kresze and coworkers have examined the cycloaddition of aromatic nitroso compounds in some detail and have rationalized the orientational results of this process. It appears that, depending upon the specific nitroso compound used, the reaction transition state varies from nonpolar to dipolar.[64]



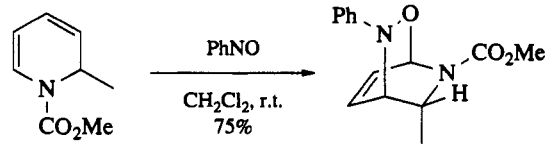
Scheme 12

The dihydrooxazines which are produced from aryl nitroso compounds have not found wide use in synthesis.[65] One application to the syntheses of an *N*-aryl-3-pyrrolidone is shown in equation (31).[66] The initial Diels–Alder reaction in this sequence was totally regioselective.



(31)

A number of cases of additions of aryl nitroso compounds to 1,2-dihydropyridine derivatives have been effected.[67] For instance, compound (**87**) reacts with nitrosobenzene regioselectively and *anti* to the C-2 methyl group to afford adduct (**88**) (equation 32).



(87) (88)

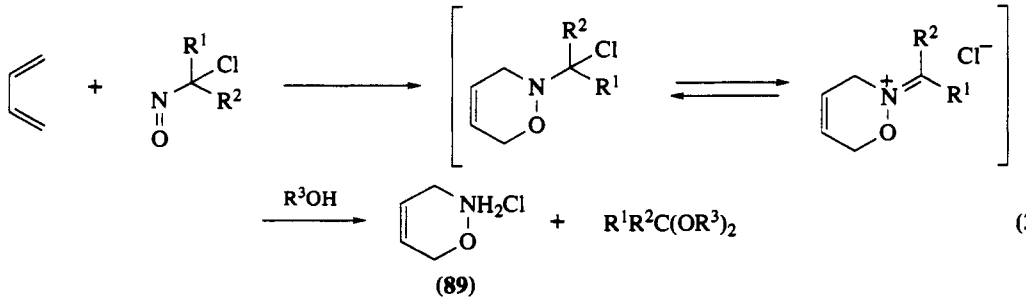
(32)

4.2.4.2 α-Chloro Nitroso Compounds

Readily available α-chloro nitroso compounds have been used on a number of occasions as heterodienophiles since the first report appeared in 1947.[68] The initial adduct of this reaction is unstable and if alcohol solvent is used a dihydrooxazine hydrochloride (**89**) is produced (equation 33). The cycloadditions proceed under very mild conditions with most 1,3-dienes and, as outlined in Scheme 13, the regioselectivity is excellent.[61,69]

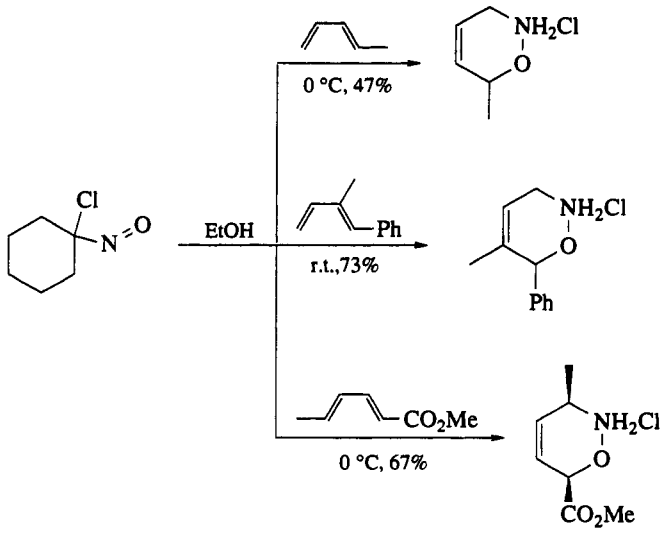
Kresze and coworkers have used nitroso Diels–Alder reactions in synthesis of a variety of inosamines and related compounds.[70] One example of this work is the synthesis of conduramine-F1 (**92**) as shown in equation (34). In this case, diene (**91**) reacted with α-chloro nitroso cyclohexane to afford adduct (**91**) as the only product. Just why this stereoisomer was formed is not obvious. Compound (**91**) could be converted to the conduramine in a few steps.

In a series of interesting papers, Kresze has explored chiral nitroso Diels–Alder reactions.[71] Several different chiral α-chloro nitroso substrates have been examined and mannose derivative (**93**) proved to be one of the best auxiliaries. This dienophile is very reactive with both cyclic and acyclic dienes, affor-

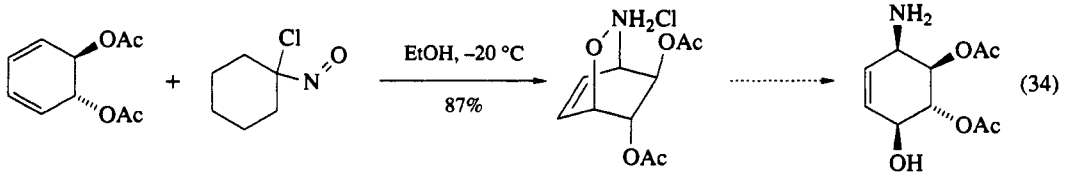


(89)

(33)



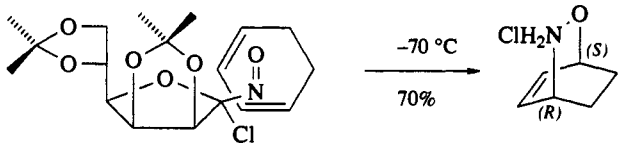
Scheme 13



(34)

(90) (91) (92)

ding adducts with high enantiomeric excesses. For example, dienophile (**93**) reacts with 1,3-cyclohexadiene as depicted in equation (35) to afford (**94**) with >96% *ee*.

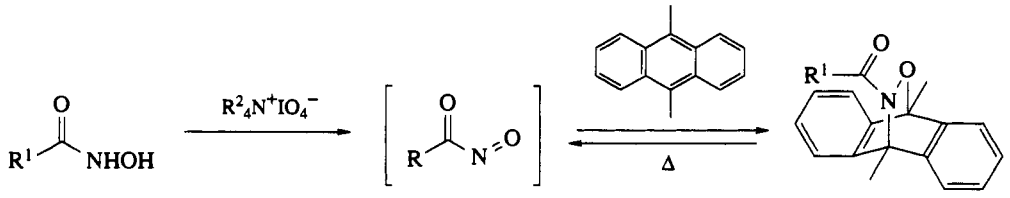


(35)

(93) (94)

4.2.4.3 Acyl Nitroso Compounds

The use of acyl nitroso compounds as dienophiles was first described by Kirby.[72] The primary method for generating these highly reactive, unstable species is by periodate oxidation of hydroxamic acids.[73] The acyl nitroso compounds can be trapped in a Diels–Alder reaction with 9,10-dimethylanthracene to give adduct (**95**) (equation 36) which can act as an alternative source of the dienophile, since retro [4 + 2] cycloaddition occurs under mild thermal conditions.

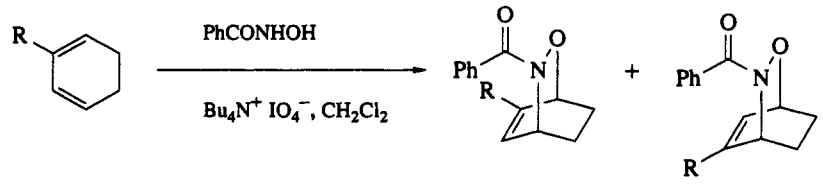


(36)

(95)

A few examples of cycloadditions of acyl nitroso compounds with unsymmetrical dienes have been described[74] and it generally appears that the process shows good regioselectivity. Boger *et al.* found that

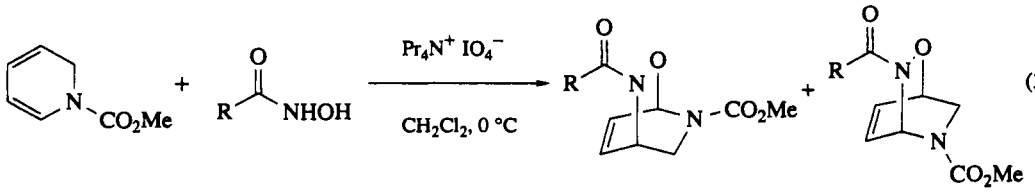
dienes (**96a**) and (**96b**) cycloadd to afford regioisomeric adducts (**97a/98a**) and (**97b/98b**), respectively in 3:1 ratios (equation 37).[62] It was suggested that the results with (**96a**) are consistent with a HOMO-diene/LUMO-dienophile cycloaddition, whereas in the case of (**96b**) this same situation or an inverse electron demand (LUMO-diene/HOMO-dienophile) process may apply.



(37)

(**96**) a: R = $CH_2OSiMe_2Bu^t$ b: R = CO_2Me (**97**) 3:1 (**98**)

Studies on the addition of acyl nitroso compounds to 1,2-dihydropyridine derivatives have been described,[75] and some of the results are shown in equation (38). It was found that the nitroso dienophiles produced from hydroxamic acids (**100**) reacted with dihydropyridine (**99**) at different rates and afforded the ratios of regioisomeric products indicated. Both the relative reaction rates and orientation are in accord with a HOMO-diene/LUMO-dienophile controlled process.

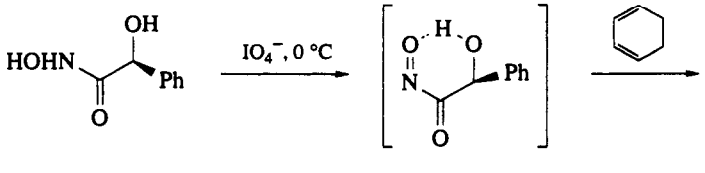


(38)

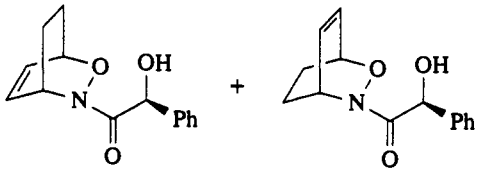
(**99**) (**100**)

R =		
	PhCO	0:100
	$PhCH_2CO$	0:100
	MeOCO	50:50
	$PhCH_2OCO$	50:50
	Me_2NCO	75:25

Brief reports of cycloadditions with chiral acyl nitroso dienophiles have recently appeared.[75,76] In one study, acyl nitroso compound (**101**) derived from the corresponding hydroxamic acid was added to cyclohexadiene to afford a 3.5:1 mixture of diastereomeric adducts (**102**) and (**103**).[76] It was proposed that dienophile (**101**) reacts in the cyclic chelated form shown, since the related methyl ether which cannot internally hydrogen bond shows much lower diastereoselectivity.[75,76]



(**101**)

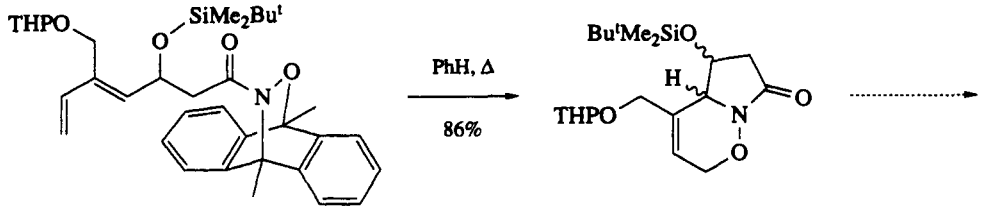


(39)

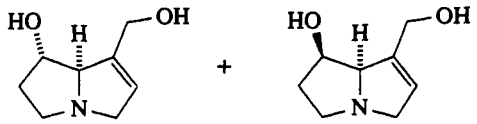
(**102**) 3.5:1 (**103**)

Intramolecular acyl nitroso Diels–Alder reactions have been utilized as key steps in some elegant alkaloid total syntheses. Keck has prepared compound (**104**) (equation 40) which upon thermolysis gave an intermediate acyl nitroso species leading to adduct (**105**) as a mixture of epimers.[77] This mixture was

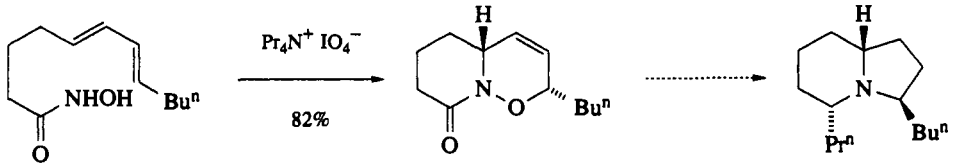
converted to the pyrrolizidine alkaloids heliotridine (**106**) and retronecine (**107**). Kibayashi and coworkers have used the intramolecular cycloaddition shown in equation (41) to synthesize the neurotoxic alkaloid gephyrotoxin 223AB (**108**).[78]



(**104**) (**105**)



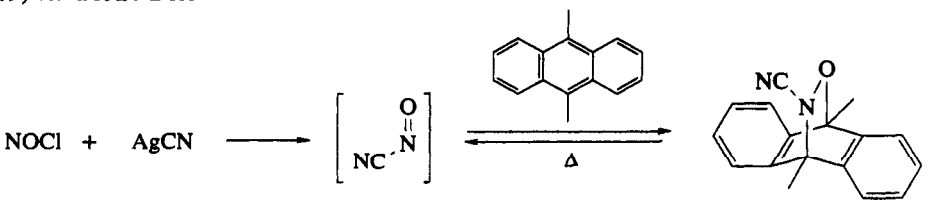
(**106**) (**107**) (40)



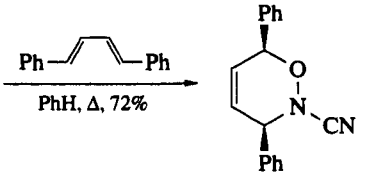
(**108**) (41)

4.2.4.4 Cyano and Sulfonyl Nitroso Compounds

Nitrosyl cyanide (**109**) has been briefly examined as a dienophile by Kirby *et al.*[79] This intermediate can be generated from nitrosyl chloride and silver cyanide (equation 42) and trapped with 9,10-dimethylanthracene to yield adduct (**110**). As with acyl nitroso compounds, this adduct can be used as a stable source of (**109**) *via* a retro Diels–Alder reaction.

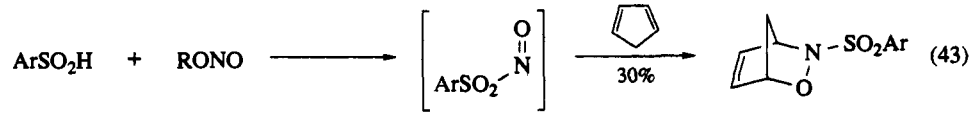


(**109**) (**110**)



(42)

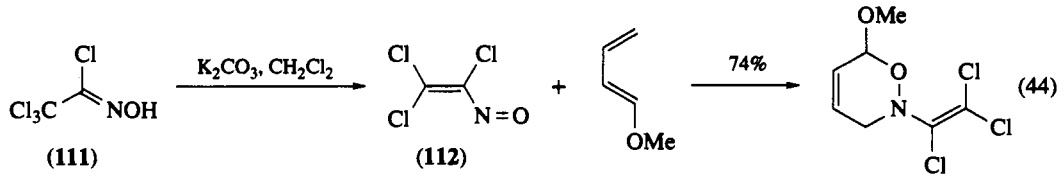
Sulfonyl nitroso compounds have been used only rarely as dienophiles.[80] One source of these species is from arylsulfinic acids and alkyl nitrites (equation 43). These compounds probably warrant further investigation.



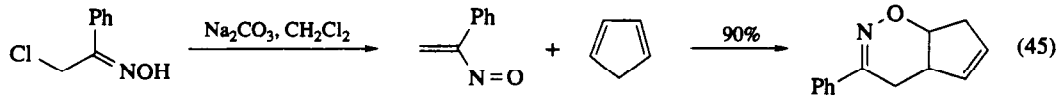
(43)

4.2.4.5 Vinyl Nitroso Compounds

Vinyl nitroso compounds have proven to be rather interesting species since they can act as either 2π or 4π components in Diels–Alder cycloadditions.[81] The particular reaction which occurs is dependent upon the structure of the vinyl nitroso compound and the diene which are used. For example, vinyl nitroso compound (**112**), prepared from oxime (**111**), reacts as a dienophile (equation 44). On the other hand, nitroso compound (**113**) (equation 45) reacts with cyclopentadiene to give oxazine (**114**). Not enough data are presently available to interpret these results satisfactorily.



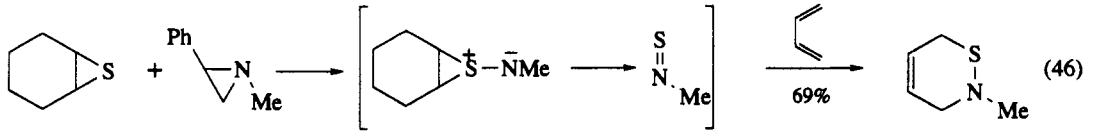
(111) (112) (44)



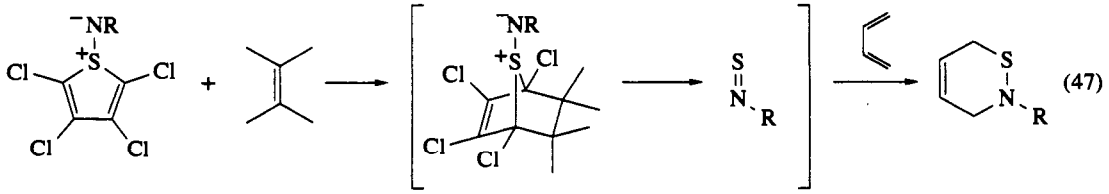
(113) (114) (45)

4.2.5 THIONITROSO COMPOUNDS

Thionitroso compounds are reactive, unstable species which have been used upon occasion as dienophiles.[1,82] The scant activity in this area is probably due to a lack of general methods for preparing these compounds. Recent examples of some cycloadditions of thionitroso dienophiles are shown in equations (46),[83] (47)[84] and (48).[85]

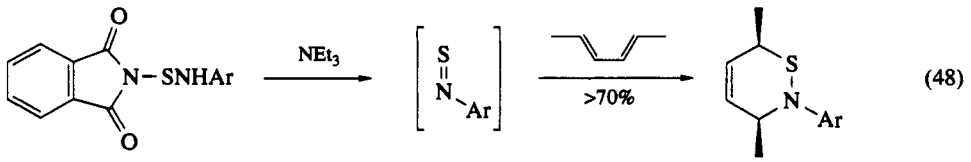


(46)



(47)

R = CO_2Ph, Ts



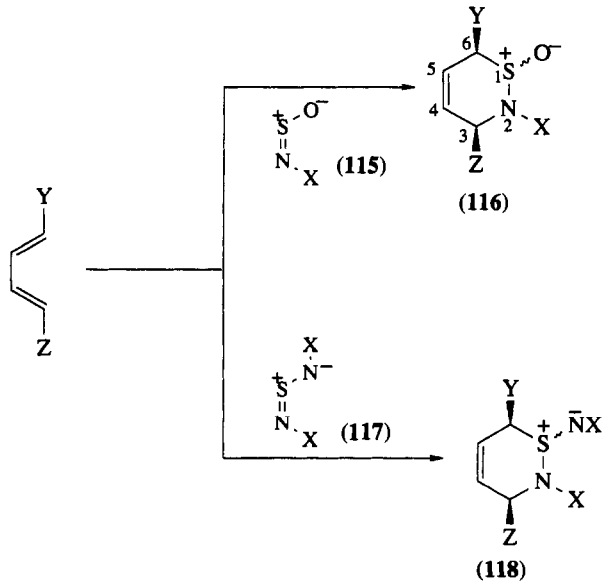
(48)

Ar = *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4

4.2.6 *N*-SULFINYL DIENOPHILES

Two general classes of *N*-sulfinyl compounds have been employed as dienophiles. The most widely utilized type are *N*-sulfinyl species (**115**), formally monoimines of sulfur dioxide, which produce 3,6-dihydrothiazine 1-oxides (**116**) (Scheme 14) upon cycloaddition.[1,86–88] The analogous bis-imines of sulfur dioxide (**117**) have also been used upon occasion as dienophiles to yield the 3,6-dihydrothiazine 1-imines (**118**). Both processes show excellent regioselectivity and are *syn* stereoselective with respect to the

diene. In both cycloaddition products (**116**) and (**118**) sulfur is chiral, but the factors controlling stereochemistry at this center are not understood (*vide infra*).

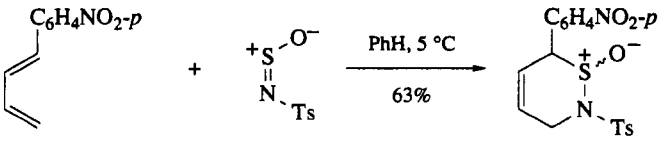


X = Ar, COR, CO_2R, SO_2R, $\overset{+}{S}Me_2$, CN, $(RO)_2PO$, NMe_2

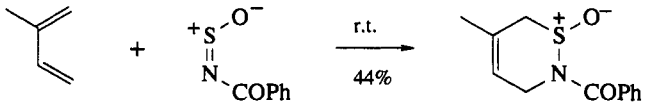
Scheme 14

4.2.6.1 Monoimines

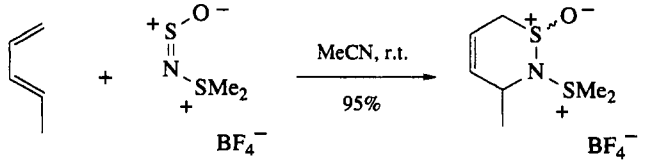
N-Sulfinyl compounds (**115**) are very reactive as dienophiles provided they bear an electron-withdrawing substituent. Several of the structural types of *N*-sulfinyl dienophiles which have been used are indicated in Scheme 14. In general, these cycloadditions proceed at room temperature or below, and are highly regioselective as shown in equations (49),[88] (50)[89] and (51).[90] *N*-Sulfinyl compounds which are substituted with an electron-donating group do not react under these conditions. However, a recent study by Bell and Weinreb has shown that *N*-alkyl sulfinyl compounds undergo [4 + 2] cycloaddition provided a Lewis acid catalyst or high pressure is utilized.[91] Some results of this work are compiled in Scheme 15. As can be seen, with (*E,E*)-2,4-hexadiene the reactions are *syn* selective with regard to the 4π component, but sulfur stereochemistry varies depending upon conditions. The best yields were obtained at 12 kbar pressure in most of the systems investigated.



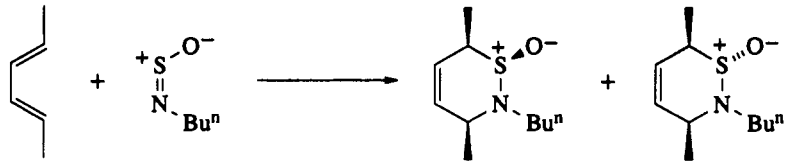
(49)



(50)



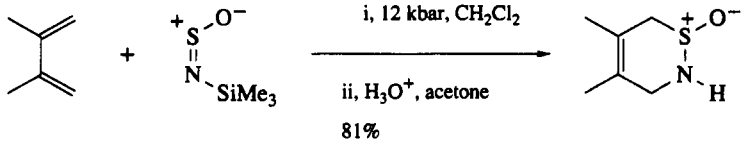
(51)



Conditions	Isomer ratio	Isolated yield
$TiCl_4$, CH_2Cl_2, –78 °C (1.0 equiv.)	100:0	27%
$SnCl_4$, CH_2Cl_2, –78 °C (0.5 equiv.)	40:60	47%
BF_3•Et_2O, CH_2Cl_2, –78 °C (1.0 equiv.)	100:0	54%
12 kbar, Et_2O, r.t.	11:89	56%
12 kbar, hexane, r.t.	12:88	66%
12 kbar, CH_2Cl_2, r.t.	18:82	80%

Scheme 15

The high pressure reaction also works well with *N*-silyl dienophile (**119**).[92] This process allows easy access to 3,6-dihydrothiazine 1-oxides which are unsubstituted on nitrogen.

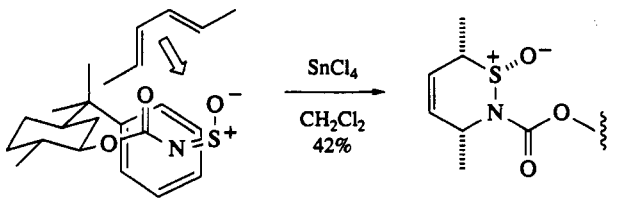


(**119**)

Two studies on the mechanism of this type of [4 + 2] cycloaddition which have led to very different interpretations have appeared.[93,94] Mock and Nugent suggested that the Diels–Alder reactions of *N*-sulfinyl-*p*-toluenesulfonamide are stepwise, ionic processes.[93] On the other hand, Hanson and Stockburn prefer a concerted, pericyclic mechanism in accord with frontier molecular orbital theory.[94] Both proposals satisfactorily rationalize the observed regioselectivity of these reactions.

As noted above, the stereochemical outcome at sulfur in these cycloadditions is not yet understood. Relatively few systems, particularly among the older examples, have been well characterized with respect to sulfur stereochemistry and thus existing data are sparse. Moreover, although *N*-sulfinyl compounds prefer to exist as the (*Z*)-isomers, it is not clear if they always undergo cycloaddition in this geometrical form. It is also known that the Diels–Alder reactions of *N*-sulfinyl compounds are sometimes reversible, which complicates the issue.[95]

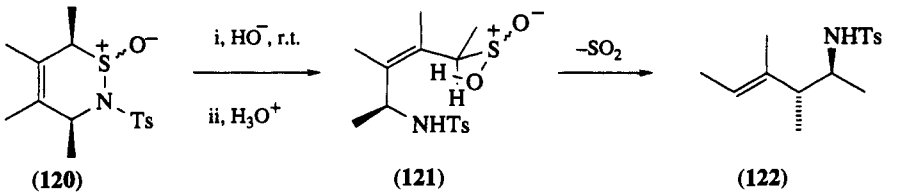
Two groups have recently examined enantioselective *N*-sulfinyl dienophile Diels–Alder reactions.[96,97] In one case, Whitesell *et al.* found that a phenylmenthol derived *N*-sulfinyl carbamate adds to (*E,E*)-2,4-hexadiene under Lewis acid catalysis to afford a single diastereomer (equation 52).[96] If the Lewis acid was omitted, a complex mixture of cycloaddition products was obtained. Attack of the diene on the *N*-sulfinyl dienophile as shown in the equation would rationalize the observed results. The site of Lewis acid complexation, however, is unknown.



(52)

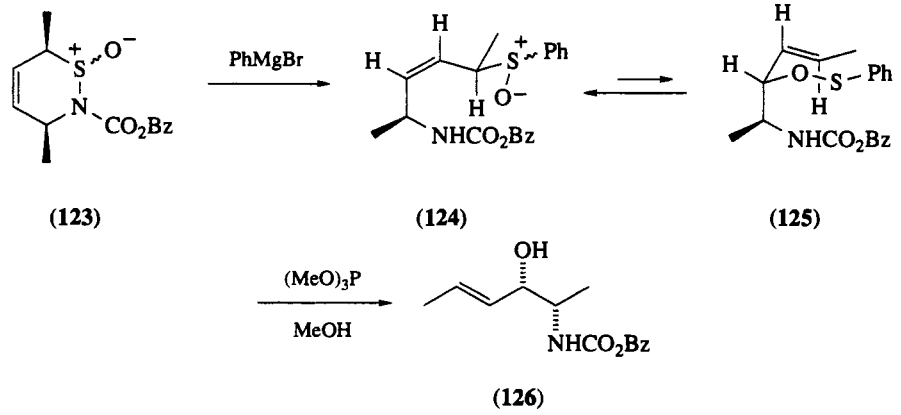
Until recently, dihydrothiazine oxides had not found much use in synthesis. Recently, Weinreb and coworkers have exploited some of the known reactions of these adducts, along with some new transformations, in stereoselective preparation of some complex nitrogen-containing molecules.[87] One useful transformation of these adducts is the hydrolysis/retro-ene elimination of sulfur dioxide shown in equation (53).[98] Thus dihydrothiazine oxide (**120**), prepared from (*E,E*)-tetramethylbutadiene, underwent hydrolysis to allylic sulfinic acid (**121**) which suffered a retro-ene reaction *via* the chair-like conformation

shown to give exclusively homallylic sulfonamide (**122**). The diastereotopic face of the alkenic double bond in (**121**) to which the proton is transferred is controlled by the pseudo-equatorial methyl substituent adjacent to the sulfur. The isomer of (**120**) derived from (*E,Z*)-tetramethylbutadiene affords the epimer of sulfonamide (**122**) stereoselectively.



(120) (121) (122) (53)

Another useful reaction of these Diels–Alder adducts is shown in equation (54).[99] Dihydrothiazine oxide (**123**) from (*E,E*)-2,4-hexadiene can be opened with a Grignard reagent to allylic sulfoxide (**124**) which undergoes a stereoselective 2,3-sigmatropic rearrangement *via* the envelope-like transition state conformation shown, having a quasi-equatorial methyl group to afford sulfenate ester (**125**). Desulfurization of (**125**) provides (*E*)-*threo*-amino alcohol derivative (**126**) in excellent overall yield. If (*E,Z*)-2,4-hexadiene is used, the (*E*)-*erythro* epimer of (**126**) is formed cleanly.



(123) (124) (125)

(126) (54)

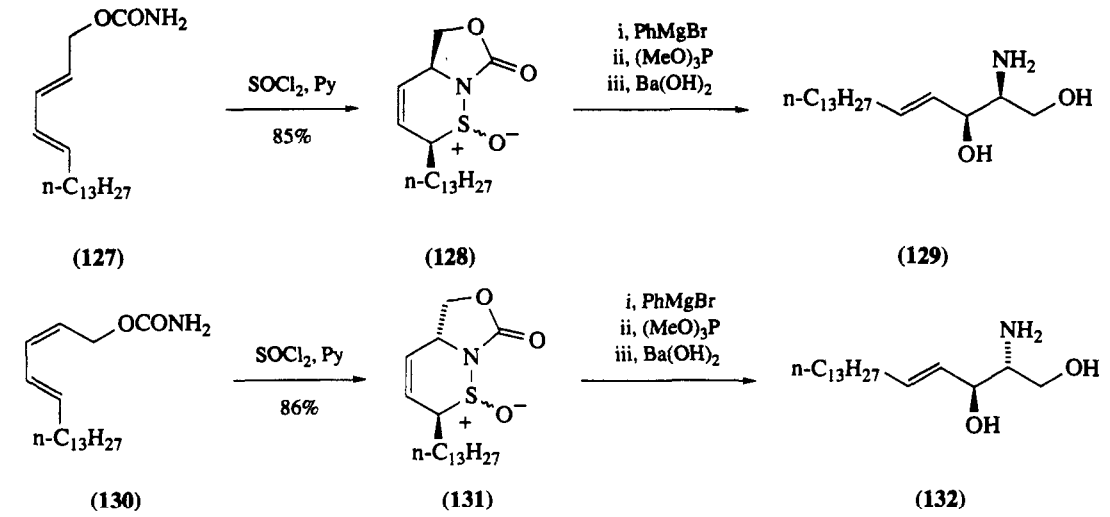
4.2.6.2 Intramolecular Cycloadditions

The Weinreb group has reported the only examples of intramolecular [4 + 2] cycloadditions of *N*-sulfinyl compounds.[87,99,100] For example, diene carbamate (**127**) could be converted to an *N*-sulfinyl compound which cyclized intramolecularly to dihydrothiazine oxide (**128**) (Scheme 16). Using the chemistry outlined in equation (54), (**128**) was transformed stereoselectively to *threo*-sphingosine (**129**). Similarly, (*E,Z*)-diene carbamate (**130**) was transformed *via* adduct (**131**) to *erythro*-sphingosine (**132**).

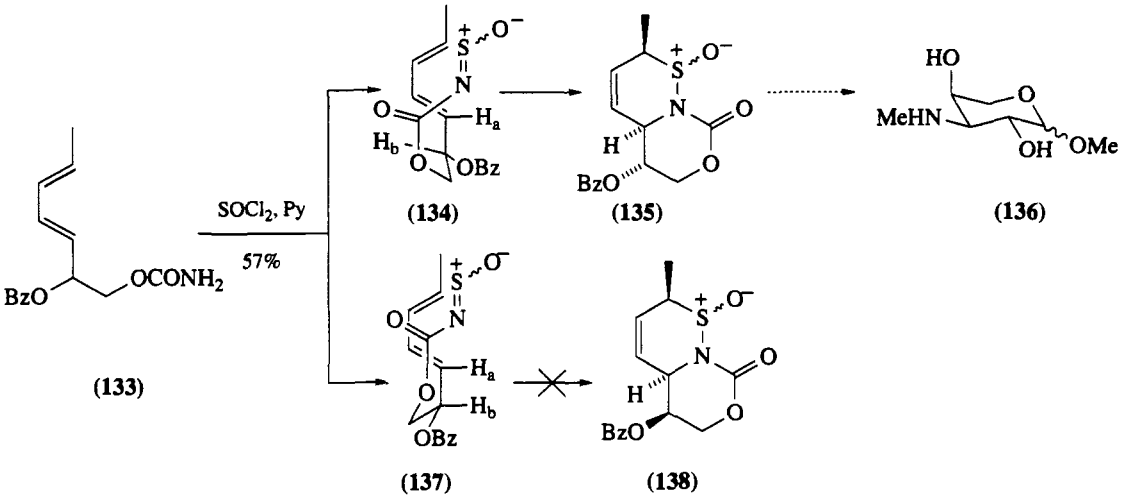
One other example of an intramolecular *N*-sulfinyl carbamate cycloaddition is depicted in Scheme 17. In this case, diene carbamate (**133**) was converted to a sulfinyl compound which cyclized to give exclusively adduct (**135**).[100] It was suggested that the cycloaddition occurs *via* an *endo* boat-like *N*-sulfinyl carbamate conformation (**134**). The alternate *endo* chair-like conformation (**137**) leading to isomeric adduct (**138**) is destabilized relative to (**134**) due to an eclipsing interaction between H_a and H_b. Adduct (**135**) was converted to amino sugar (**136**) in a few steps.

4.2.6.3 Bis-imines

Bis-imines (**117**) have been used far less than the monoimines as dienophiles. However, there are enough examples of these cycloadditions to indicate clearly that they are regioselective and, provided at least one electron-withdrawing group is present on nitrogen, that they proceed under mild reaction conditions.[1] As with the monoimines, little is known with regard to the establishment of sulfur stereochemistry in the dihydrothiazine imines (**118**). Equations (55),[101] (56)[102] and (57)[103] demonstrate both the regioselectivity of the process and some of the structural types of bis-imino compounds which have been



Scheme 16



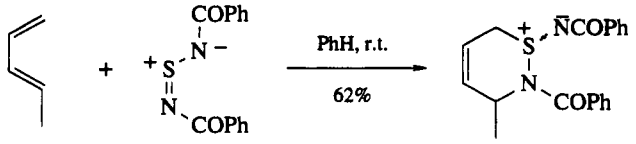
Scheme 17

used. It should be noted that unsymmetrical *N*-sulfinyl compound (**139**) reacts regioselectively at the N=S double bond bearing the least electron-withdrawing substituent. This is apparently a general phenomenon which has not been satisfactorily rationalized.

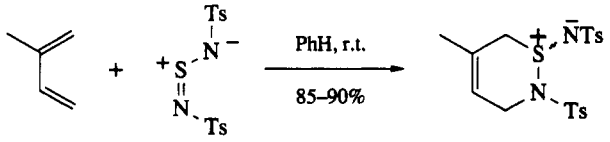
Weinreb and coworkers have examined some reactions of dihydrothiazine imines and have developed a new approach to vicinal diamines using these intermediates.[87,104] Their method is outlined in Scheme 18. Cycloaddition of (*E,E*)-2,4-hexadiene with the tosyl bis-imine gives a 1.1:1 mixture of epimeric dihydrothiazine imines (**140**) and (**144**). Subsequent transformations of these adducts took two different courses. In one, adduct (**140**) could be opened to allylic sulfilimine (**141**) which underwent a stereoselective 2,3-sigmatropic rearrangement to sulfenamide (**142**) (*cf.* equation 54). Desulfurization of (**142**) yielded (*E*)-*threo* vicinal sulfonamide (**143**). Adduct (**144**), which presumably exists in conformation (**145**), suffers a unique stereoselective transannular 2,3-sigmatropic rearrangement to thiadiazolidine (**146**) which can also be converted to bis-sulfonamide (**143**).

4.2.7 AZO DIENOPHILES

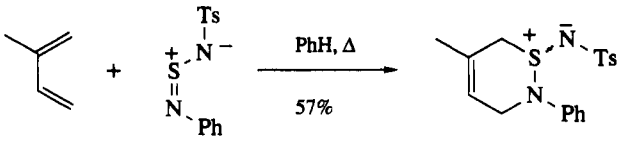
The reaction of diethyl azodicarboxylate with cyclopentadiene reported by Diels in 1925 is of historical significance since it is one of the first examples of a Diels–Alder [4 + 2] cycloaddition (equation 58).[1,105,106] These cycloadditions usually proceed under mild conditions and are *syn* selective with



(55)

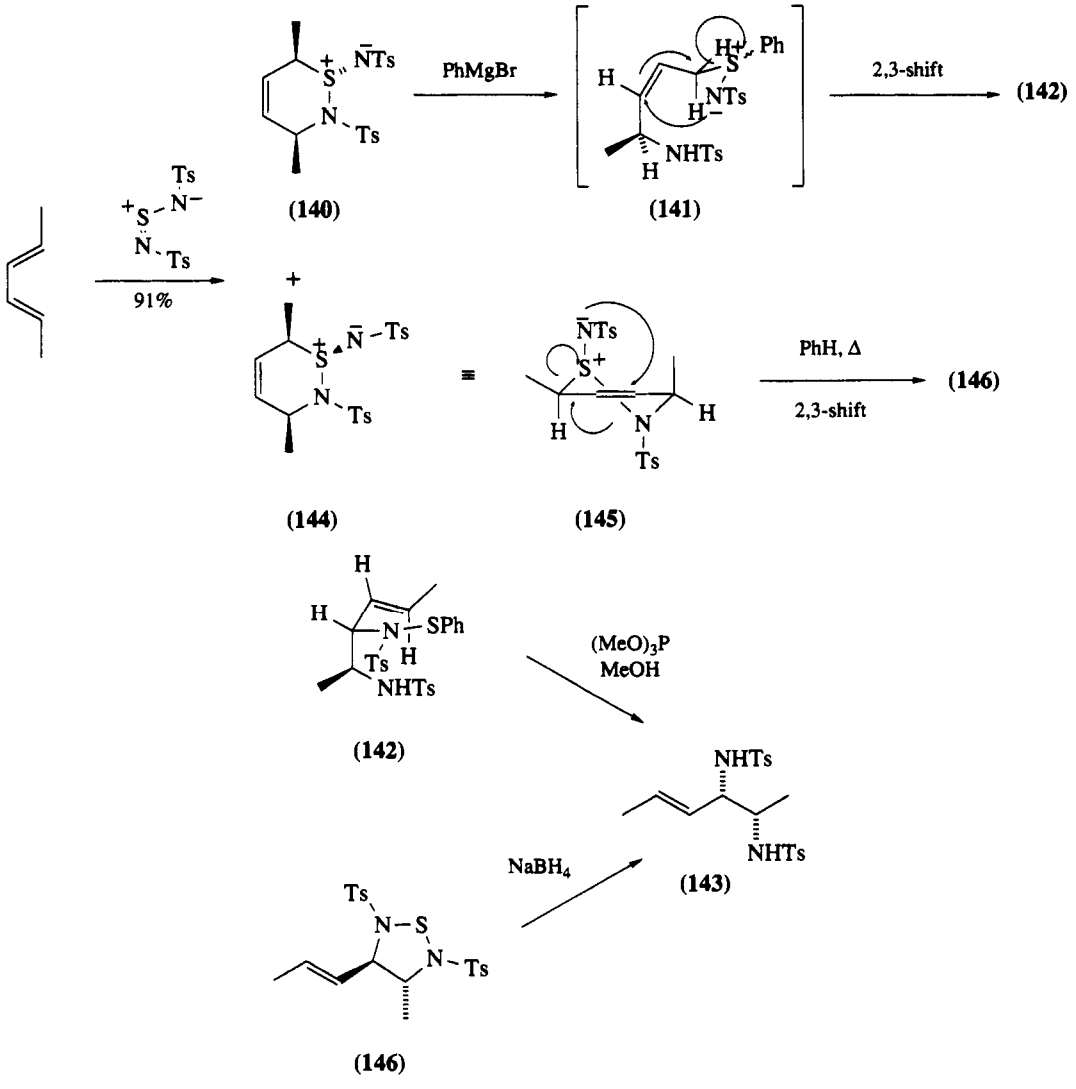


(56)



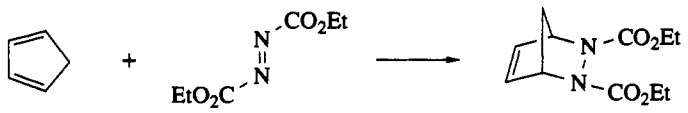
(57)

(139)



Scheme 18

respect to the diene. Cycloadditions of azo dienophiles are among the most widely utilized hetero Diels–Alder reactions and examples of these cycloadditions abound in the literature.

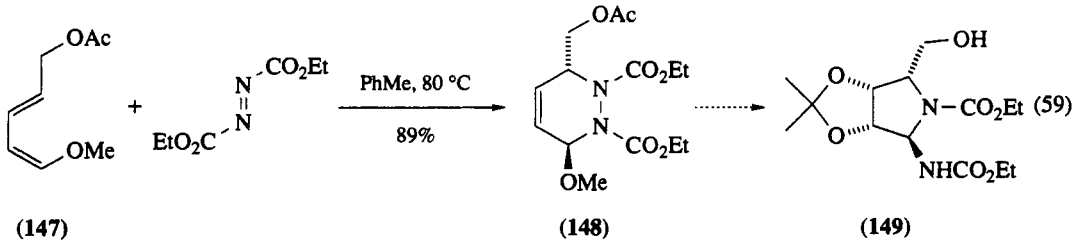


(58)

The mechanism of this type of reaction has received some attention.[105,107] It has been suggested that these reactions are pericyclic processes, and since N=N dienophiles have lower lying LUMOs than C=C compounds, they are more reactive. Cyclic N=N species have an even lower LUMO energy.[105] However, a recent investigation of the cycloadditions of 4-phenyl-1,2,4-triazoline-3,5-dione (*vide infra*) indicates that in at least some cases the Diels–Alder reactions involve discrete intermediates.[107] It would appear that a range of mechanisms may be available to azo dienophiles.

4.2.7.1 Acyclic Azo Systems

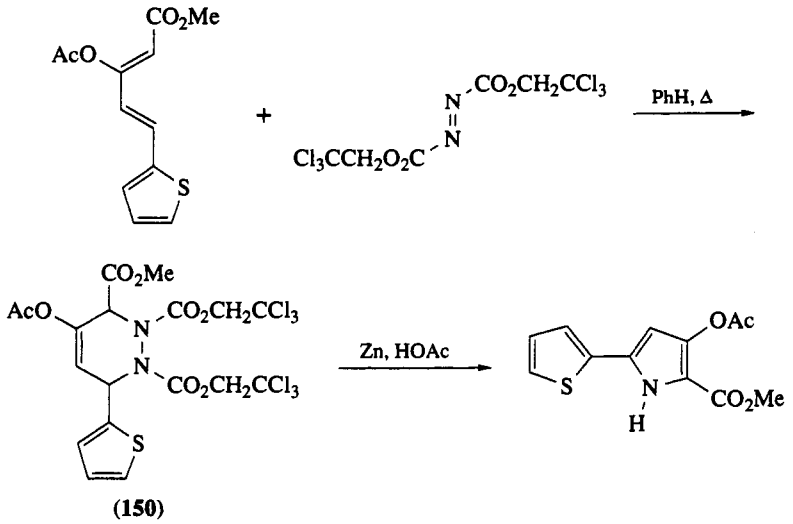
Azodicarboxylates and related compounds have been widely used as dienophiles over the last six decades.[108] A thorough description of these reactions is beyond the scope of this review. In a recent representative example of such a cycloaddition, Schmidt and coworkers found that diene (**147**) adds to diethyl azodicarboxylate to yield (**148**).[109] This product was used in synthesis of aminoxylose derivative (**149**) (equation 59).



(59)

(147) (148) (149)

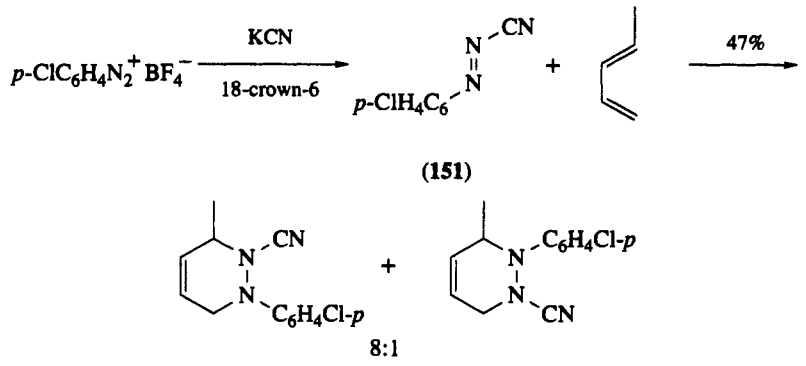
Another example of a cycloaddition of this type is shown in equation (60), in which Kresze *et al.* used adduct (**150**) to prepare a highly substituted pyrrole.[110]



(60)

(150)

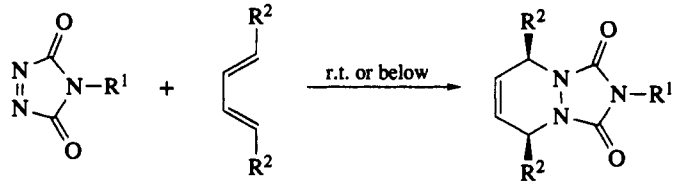
A structural variation of azodicarboxylate is arenediazocyanide (**151**) prepared from the corresponding diazonium salt (equation 61).[111] Dienophiles of this class add regioselectively to 1,3-dienes in a Diels–Alder sense. This selectivity is consistent with both stepwise polar and concerted pericyclic mechanisms.



(61)

4.2.7.2 Cyclic Azo Systems

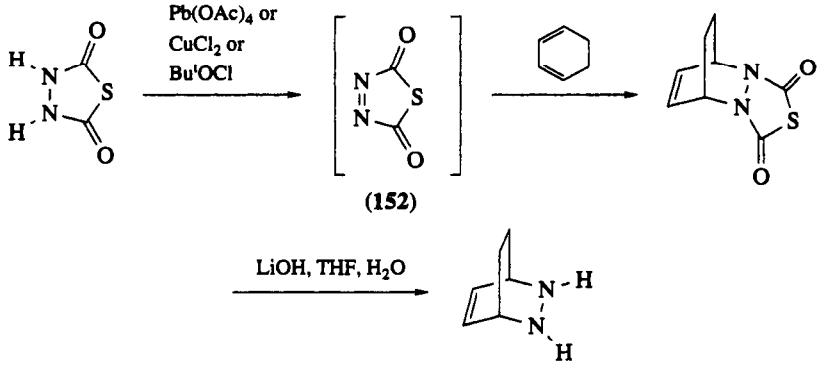
Since their introduction by Cookson *et al.* in 1962,[112] 4-substituted 1,2,4-triazoline-3,5-diones have been used extensively as dienophiles (equation 62).[1,105] These dienophiles are highly reactive towards most 1,3-dienes and undergo cycloadditions under very mild conditions. In general, these Diels–Alder reactions are *syn* selective with respect to the diene, although with some (*Z*)-dienes this selectivity is lost. As noted above, it has been found that these cycloadditions are stepwise reactions in (*Z*)-dienes which cannot achieve an *s-cis* conformation.[107] However, it is not clear if all cycloadditions of triazolinediones with 1,3-dienes proceed this way.



R = alkyl, aryl

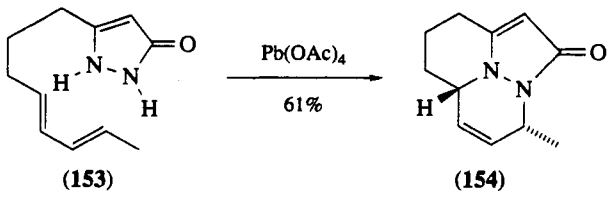
(62)

The triazolinedione adducts in equation (**62**) are often difficult to hydrolyze to the parent cyclic hydrazine derivatives and therefore a modified dienophile (**152**) was developed independently by Corey[113a] and by Beak[113b] (equation 63). The adducts of this compound are readily converted to the hydrazine by mild basic hydrolysis.

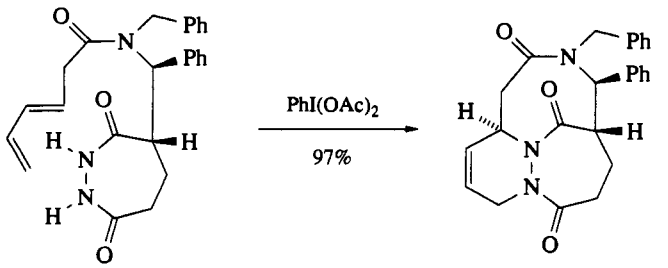


(63)

Two interesting examples of intramolecular Diels–Alder reactions of azo dienophiles have recently been published. In the first, Kyler and coworkers oxidized systems such as (**153**) to an intermediate azo compound which underwent cycloaddition to afford adduct (**154**) (equation 64).[114] In another case, Kahn *et al.* found that diacylhydrazide (**155**) could be oxidized to yield Diels–Alder adduct (**156**) (equation 65).[115]



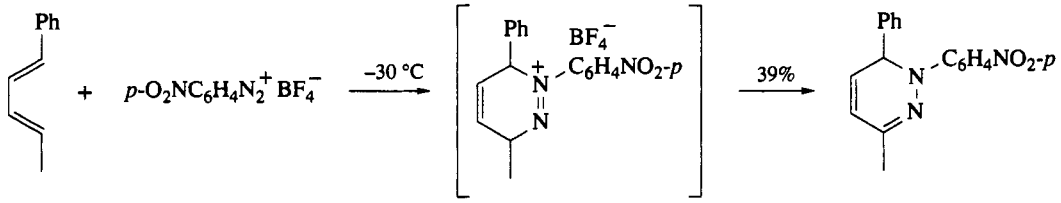
(153) (154) (64)



(155) (156) (65)

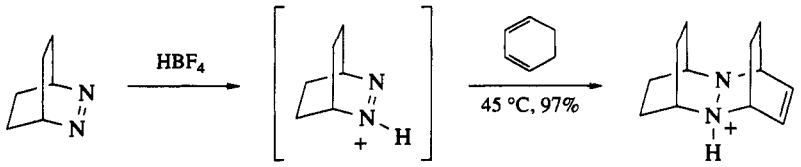
4.2.7.3 Charged Dienophiles

Diazonium salts have been briefly investigated as hetero dienophiles.[116] It appears that electron-rich dienes and electron-deficient diazonium compounds are the best partners in this cycloaddition. The reactions are usually regioselective (equation 66). It has been proposed that these cycloadditions are one-step pericyclic processes.[116b]



(66)

Nelsen *et al.* have discovered that simple alkyl diazo compounds, which are normally not dienophiles, will react in a Diels–Alder fashion if protonated (equation 67).[117] It was suggested that protonation facilitates the reaction thermodynamically, since hydrazines are much stronger bases than azo compounds.



(67)

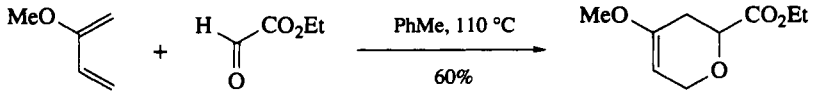
4.2.8 CARBONYL DIENOPHILES

Diels–Alder cycloadditions of carbonyl compounds with aldehydes and ketones provide a powerful method for synthesis of 5,6-dihydropyrans, which are useful synthons for a variety of purposes.[1,118] This methodology was slow to develop since early work indicated that simple carbonyl compounds react poorly with most alkyl and aryl substituted 1,3-dienes. However, with the understanding that [4 + 2] cycloadditions are facilitated by Lewis acid catalysts and high pressure, along with the recent availability of highly reactive oxygenated dienes, this chemistry has been increasingly exploited in total synthesis.

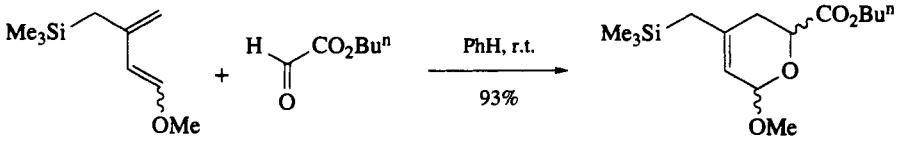
Cycloadditions with these heterodienophiles are usually regioselective and are in accord with FMO theory. The reactions are *syn* selective with the diene component. Other stereochemical features of the process are outlined in some of the examples described below, as well as in previous reviews.[1,118] It should also be mentioned that only aldehydes and some ketones act as dienophiles. Except for rare exceptions, other types of carbonyl compounds apparently do not participate in Diels–Alder cycloadditions.

4.2.8.1 Electron-deficient Aldehydes

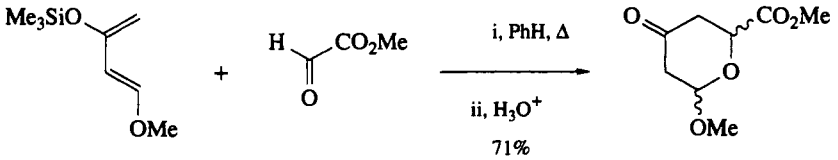
Aldehydes bearing electron-withdrawing substituents are reactive as heterodienophiles under mild conditions with a range of 1,3-dienes. In particular, glyoxylate derivatives have been widely used in these cycloadditions. Some examples of Diels–Alder reactions of this type are shown in equations (68),[119] (69)[120] and (70).[121] As can be seen, these reactions occur at relatively low temperatures and are regioselective.[122]



(68)

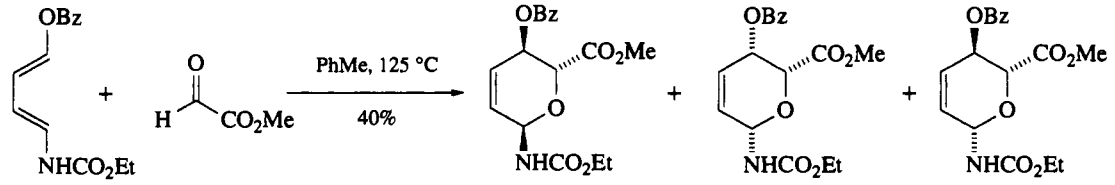


(69)

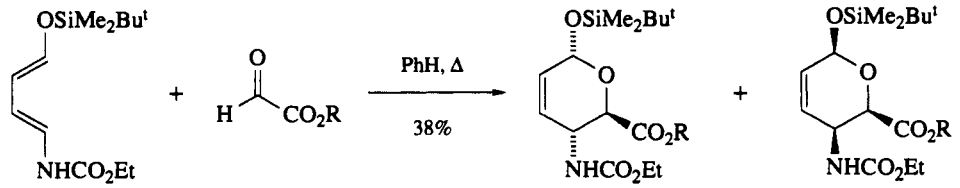


(70)

Some very interesting stereo- and regio-chemical features of the cycloaddition can be seen in the work of Schmidt and Wagner outlined in Scheme 19.[123] They found that the unsymmetrically 1,4-substituted diene (**157**) reacts with methyl glyoxylate regioselectively to afford adducts (**158**), (**159**) and (**160**).[123a] Compounds (**158**) and (**159**) result from *exo* and *endo* transition states, respectively, and (**160**) presumably arises from (**158**) *via* isomerization at the anomeric center. When siloxy diene (**161**) was used in a cycloaddition with glyoxylate (**162**), *exo* and *endo* adducts (**163**) and (**164**), respectively, were produced.[123b] However, the regiochemistry here is completely reversed relative to diene (**157**). It was proposed that these results occur since the magnitude of the C-1 and C-4 HOMO coefficients of benzoyl-substituted diene (**157**) are reversed in the siloxy diene (**161**).[123b]



(**157**) (**158**) 2:1 (**159**) 1:2 (**160**)

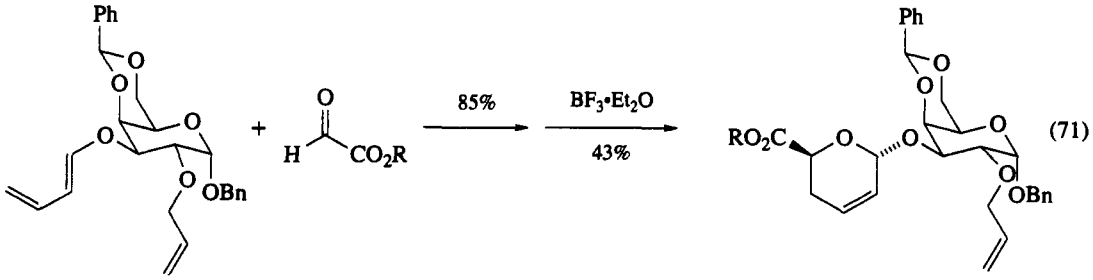


(**161**) (**162**) (**163**) 1:1 (**164**)

R = $CH_2C_6H_4NO_2$-*p*

Scheme 19

Several reports of Diels–Alder cycloadditions of chiral glyoxylate esters have been published.[124–126] In general, reactions with menthyl esters of glyoxylate do not show very high selectivities either thermally or under high pressure.[124,125] Better results have been obtained by David and coworkers using (*E*)-1-oxygenated butadienes attached to chiral sugars.[126] In a nice application of this methodology to the synthesis of a blood group antigenic determinant, the principle of double diastereoselection was used.[127] Thus chiral diene (**165**) was combined with L-menthyl glyoxylate to afford a mixture of epimeric pyrans, which was equilibrated at the anomeric center to yield (**166**) (equation 71).

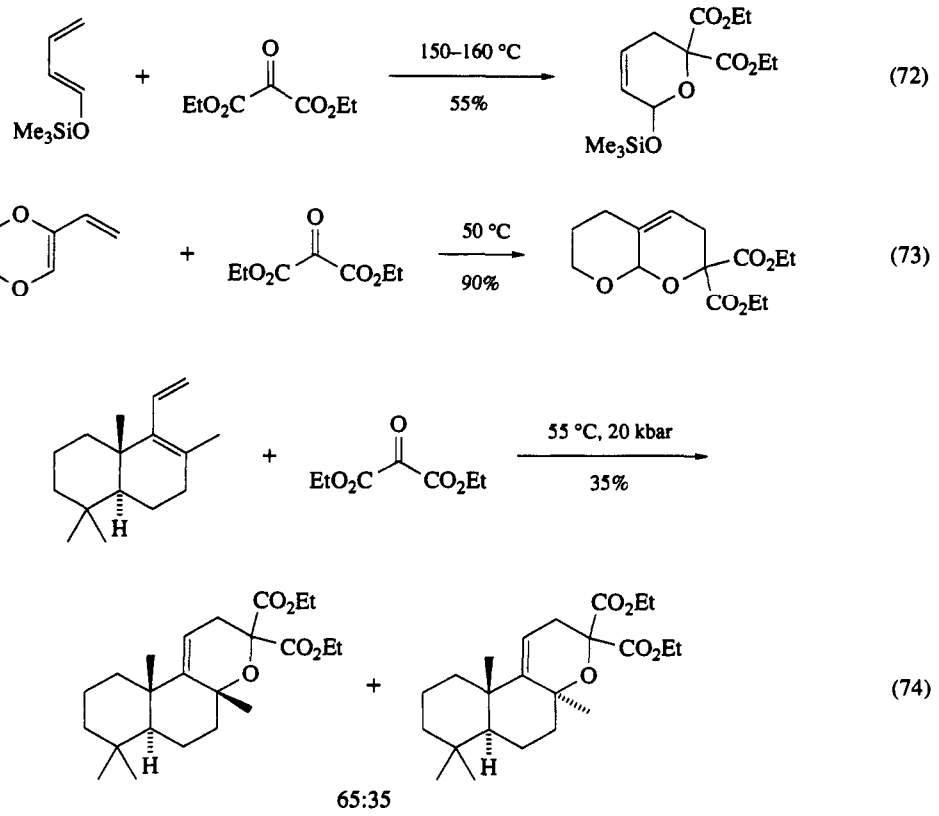


(**165**) R = L-menthyl (**166**)

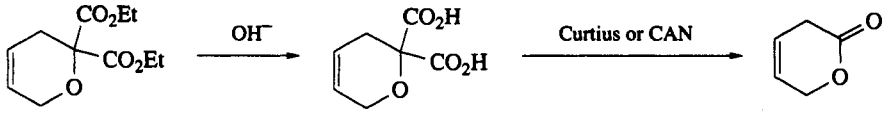
It should also be noted that it has recently been found that chiral Lewis acid catalysts promote glyoxylate Diels–Alder reactions, but enantiomeric excesses are usually low.[128,129]

4.2.8.2 Electron-deficient Ketones

The large majority of cycloadditions of keto dienophiles have involved mesoxylate. Some typical examples of this process are shown in equations (72),[130] (73)[131] and (74).[132] The cycloaddition appears to be regioselective in most cases.[133]

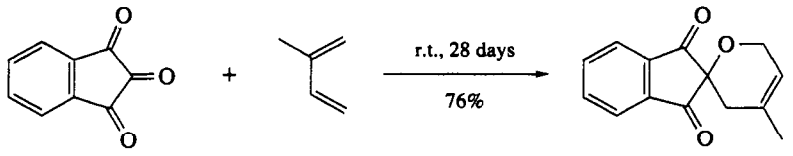


One very useful transformation of these adducts is given in equation (75). Hydrolysis of the diester to the diacid, followed by bis-decarboxylation either by a double Curtius rearrangement[134] or oxidatively with ceric ammonium nitrate,[133a] yields an unsaturated lactone. This overall sequence is equivalent to effecting a Diels–Alder reaction with carbon dioxide, which is unreactive as a dienophile.

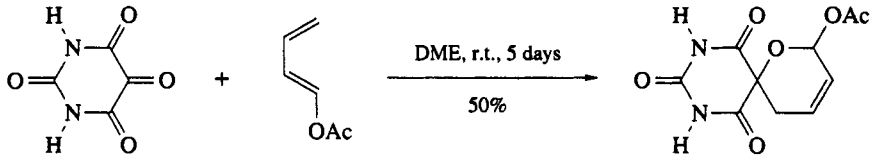


(75)

A few examples of cycloadditions with other electron-deficient ketones have appeared.[130b,135,136a] Two such systems are shown in equations (76)[135a] and (77).[135b] However, this chemistry has not been widely applied to date.



(76)



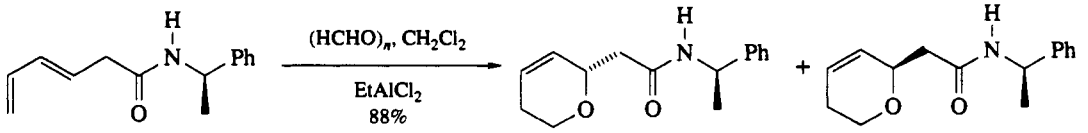
(77)

4.2.8.3 Aliphatic and Aromatic Aldehydes

Until recently, relatively little work had been reported on Diels–Alder reactions of simple aromatic and aliphatic aldehydes with 1,3-dienes.[1] It was initially thought that these reactions did not work well. However, a better understanding of the factors governing the cycloaddition has led to important methodological advances. This section and the following one briefly outline work in this area.

Few examples of [4 + 2] cycloadditions of aromatic aldehydes with simple alkyl-, halo- and alkoxy-substituted 1,3-dienes exist. Ansell and Charalambides found that benzaldehydes substituted with electron-withdrawing groups such as nitro and cyano undergo thermal cycloaddition.[136b] Other benzaldehydes were found to cycloadd only in the presence of *p*-toluenesulfonic acid.

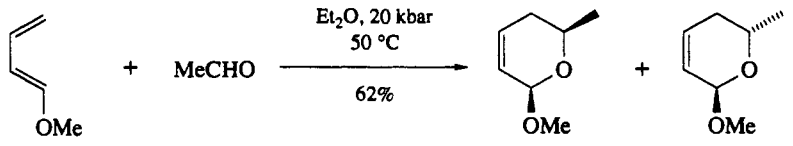
Formaldehyde reacts thermally with 1-alkoxybutadienes, but not with most simple alkyl-substituted dienes.[137a] However, in the presence of a Lewis acid this type of cycloaddition is synthetically useful.[137b,c] A recent example of this reaction is shown in equation (78).[138b]



1:1

(78)

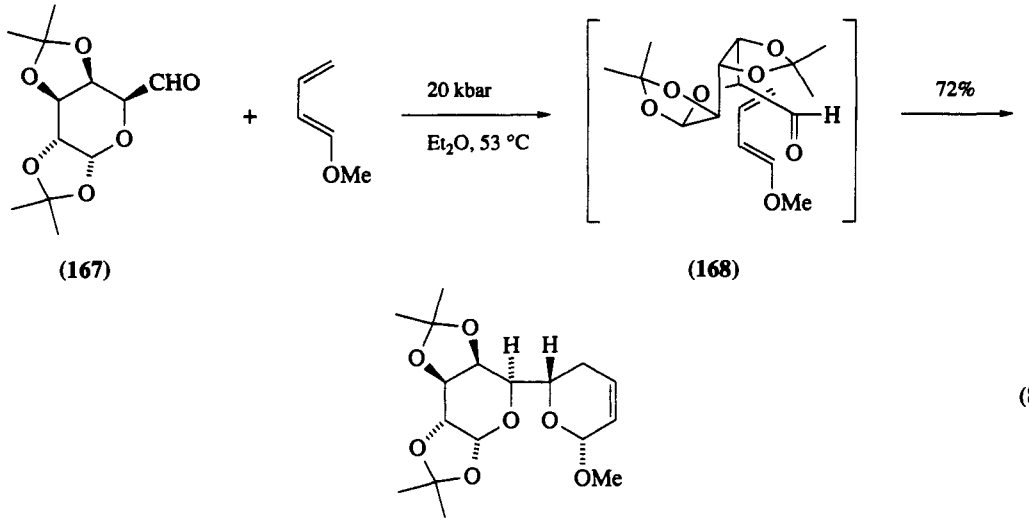
In an extensive study, Jurczak and coworkers have looked at the high pressure induced cycloaddition of (*E*)-1-methoxybutadiene with various aliphatic aldehydes.[138,139] An example is shown in equation (79).[139a] If a lanthanide catalyst is used the pressure can be reduced from 20 to 10 kbar, but yields appear to be somewhat lower.[139f]



70:30

(79)

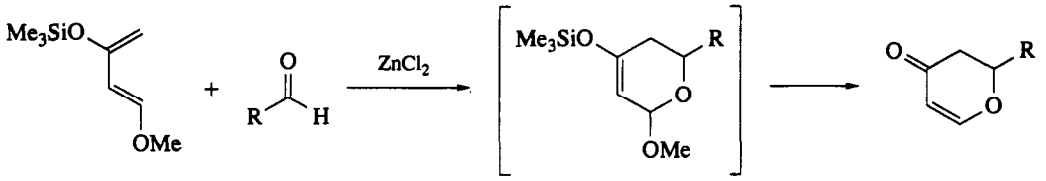
These workers have also examined asymmetric induction in the process in some detail. For instance, cycloaddition of sugar aldehyde (**167**) occurred to afford only adduct (**169**) at high pressure (equation 80). It was suggested that the Diels–Alder reaction proceeds *via* diene attack on the aldehyde conformation shown in (**168**) from the least congested face.[139i] Other chiral aldehydes have been investigated by this group, as has the effect of lanthanide catalysts upon the extent of asymmetric induction. Summaries of this work have recently been published.[138]



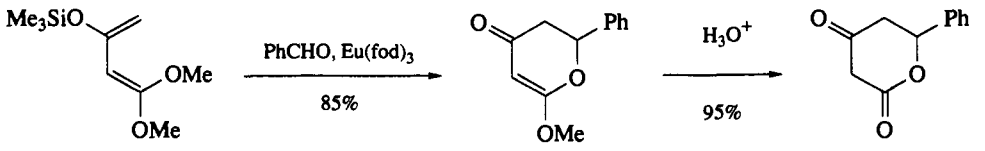
(**167**) (**168**) (**169**) (80)

4.2.8.4 Cycloadditions with Highly Oxygenated Dienes

An important discovery in the area of carbonyl cycloadditions is that highly oxygenated 1,3-dienes are excellent 4π components.[1,140] These reactions occur at low temperatures with a wide range of aldehydes provided Lewis acid catalysts are used.[121b,141,142] This general type of reaction is shown by the example in equation (81). It was also found by Danishefsky and coworkers that lanthanide shift reagents are effective catalysts for the cycloaddition.[143] An example of one of these cycloadditions is outlined in equation (82).[121d]



R = H, aryl, alkyl, alkenyl, *etc.* (81)

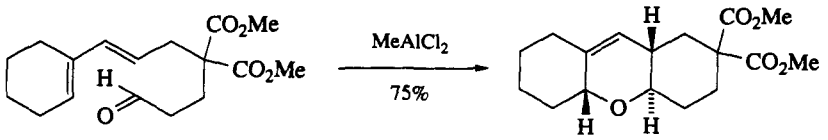


(82)

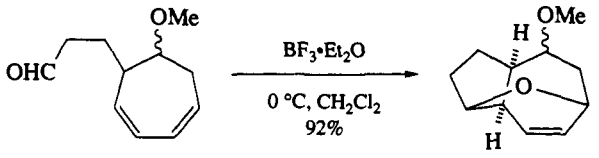
The Danishefsky group has investigated the mechanism of this process in some detail.[144] It has also been found that the cycloadditions show excellent diastereofacial selectivity with many chiral aldehydes.[144,145] Moreover, chiral catalysts have proven effective in controlling the enantioselectivity of the cycloaddition.[146–148] These features of the reaction, along with applications to natural product total syntheses, are discussed in detail in Volume 2, Chapter 2.5.

4.2.8.5 Intramolecular Reactions

Surprisingly few examples of intramolecular carbonyl Diels–Alder reactions exist. Two recent cases are shown in equations (83)[149] and (84).[150,151]

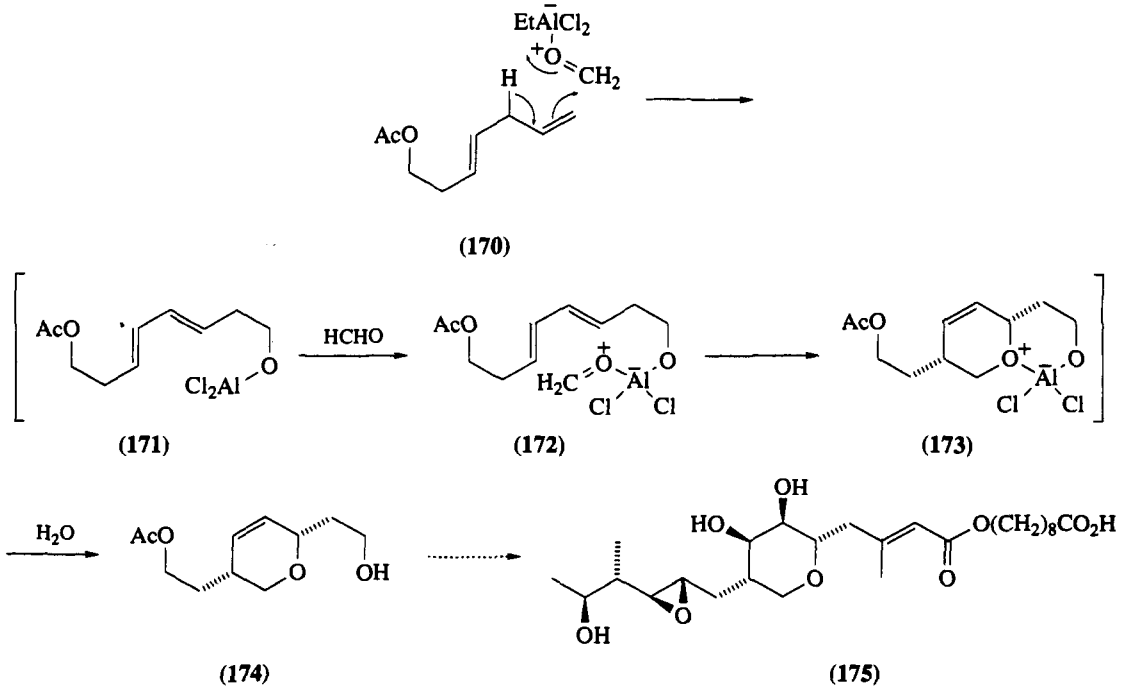


(83)



(84)

In a clever piece of work, Snider *et al.* have used a 'quasi' intramolecular carbonyl Diels–Alder cycloaddition to produce a key intermediate for syntheses of pseudomonic acid A (**175**) (Scheme 20).[137c] Thus a Lewis acid catalyzed ene reaction of alkene (**170**) and formaldehyde afforded (**171**), which complexed with additional formaldehyde to give (**172**). Intramolecular [4 + 2] cycloaddition of (**172**) gave adduct (**173**) which produced dihydropyran (**174**) upon hydrolysis.



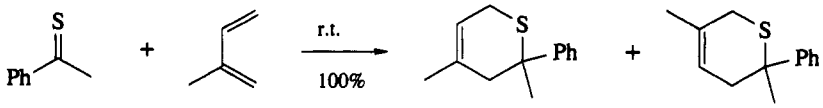
Scheme 20

4.2.9 THIOCARBONYL DIENOPHILES

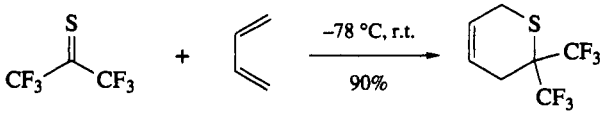
Thiocarbonyl compounds of all kinds are excellent heterodienophiles.[1,152] There has not been much systematic study of this class of reaction but it seems that such cycloadditions are generally regioselective. One difference between carbonyl and thiocarbonyl Diels–Alder reactions is that the dihydrothiopyran adducts from the latter dienophiles often undergo cycloreversion. The slow development of this field is perhaps mainly due more to lack of methods for generating certain thiocarbonyl compounds than with difficulties in effecting cycloadditions.

4.2.9.1 Thioketones

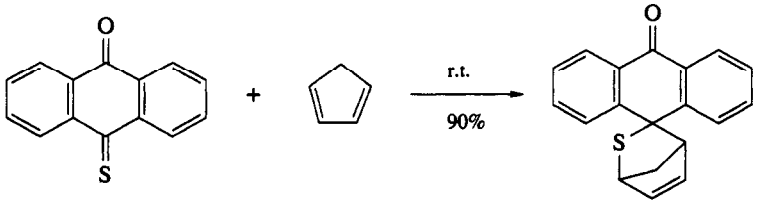
Thioketones are generally readily available and undergo [4 + 2] cycloadditions under mild thermal conditions. Representative examples of this process are shown in equations (85),[153] (86)[154] and (87).[155]



(85)

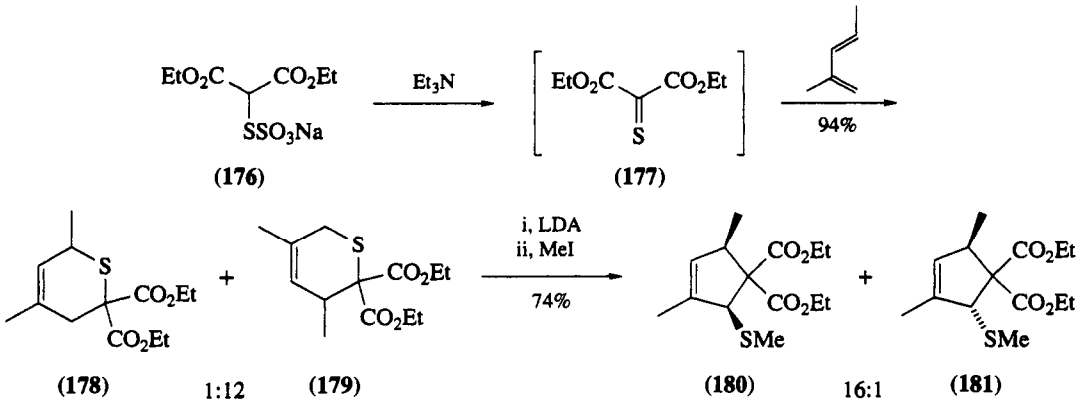


(86)



(87)

Larsen has recently described an interesting synthetic use for the cycloadducts of thiooxomalonate (Scheme 21).[156] Bunte salt (176) can be converted *in situ* to thiooxomalonate (**177**)[157] which undergoes regioselective [4 + 2] cycloaddition with 1,3-dienes at 25–70 °C to afford adducts. Thus with 1,3-dimethylbutadiene a 1:12 mixture of (**178**) and (**179**) are formed in excellent yield. It was found that treatment of major isomer (**179**) with base, followed by methyl iodide, yielded a 16:1 mixture of epimeric thiomethylcyclopentenes (**180**) and (**181**). Some mechanistic possibilities for formation of these products have been offered.[156]

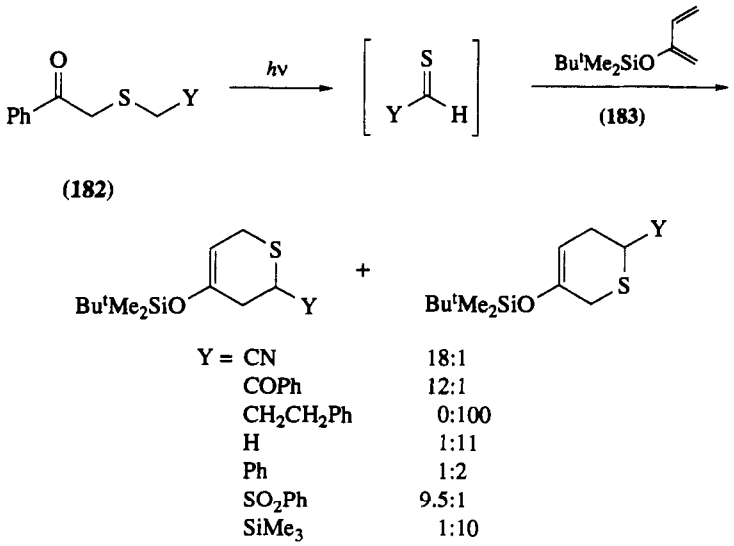


Scheme 21

4.2.9.2 Thioaldehydes

Until recently, few reliable methods were available for preparation of thioaldehydes, which are usually very unstable, and little had been done with these species as dienophiles. However, this problem has now been remedied and there has been considerable interest in using thioaldehydes in [4 + 2] cycloadditions.[1]

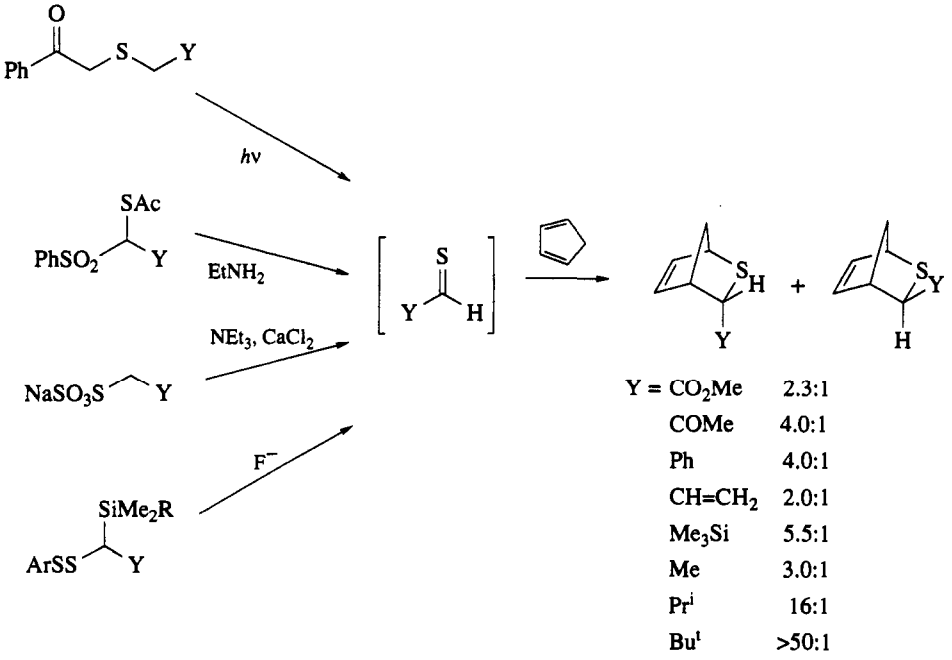
Vedejs and coworkers have developed a general procedure for generation and trapping of transient thioaldehydes with 1,3-dienes.[158] They found that photolysis of phenacyl sulfides (**182**) produced thioaldehydes which gave [4 + 2] cycloadducts in good yields (Scheme 22). Some regiochemical results using siloxybutadiene (**183**) and variously substituted thioaldehydes are shown in Scheme 22.[158a,b,g] This regioselectivity is in accord with molecular orbital calculations.[158b]



Y =	CN	18:1
	COPh	12:1
	CH_2CH_2Ph	0:100
	H	1:11
	Ph	1:2
	SO_2Ph	9.5:1
	$SiMe_3$	1:10

Scheme 22

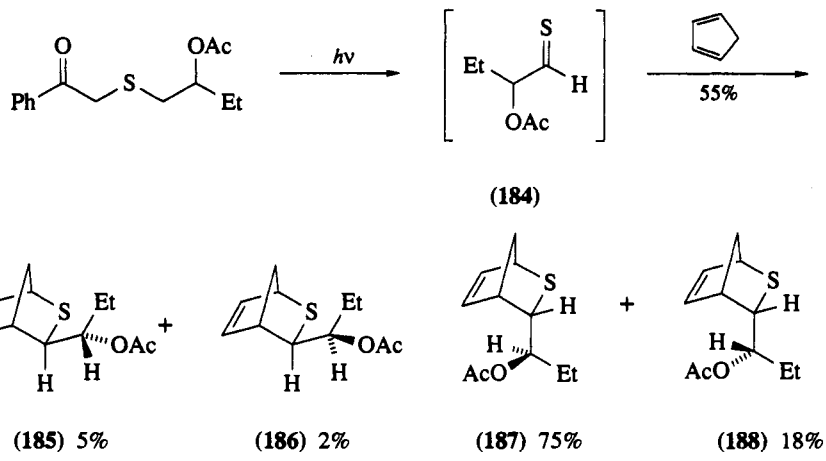
Several groups have examined the *exo*/*endo* stereoselectivity of thioaldehyde cycloadditions.[158f,159,160] Scheme 23 outlines some of the methods used for *in situ* generation of thioaldehydes and selected stereochemical results with cyclopentadiene. As can be seen, these reactions generally give a predominance of *endo* products kinetically. Vedejs has rationalized this outcome as arising from steric factors.[158f]



Y =	CO_2Me	2.3:1
	COMe	4.0:1
	Ph	4.0:1
	$CH{=}CH_2$	2.0:1
	Me_3Si	5.5:1
	Me	3.0:1
	Pr^i	16:1
	Bu^t	>50:1

Scheme 23

Another stereochemical aspect of these Diels–Alder reactions which has been studied by the Vedejs group is the facial selectivity in cycloadditions of chiral thioaldehydes.[158f] For instance, thioaldehyde (**184**), generated by the photochemical method, added to cyclopentadiene to give *exo* adducts (**185**) and (**186**) along with *endo* isomers (**187**) and (**188**) (Scheme 24). As was the case for achiral thioaldehydes, the *endo* adducts predominated (~9:1). The facial selectivity obtained can be rationalized *via* a Felkin–Anh or Cornforth model for asymmetric induction.[158f]

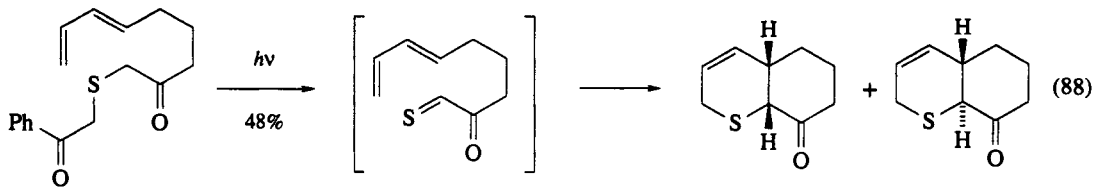


(184)

(185) 5% (186) 2% (187) 75% (188) 18%

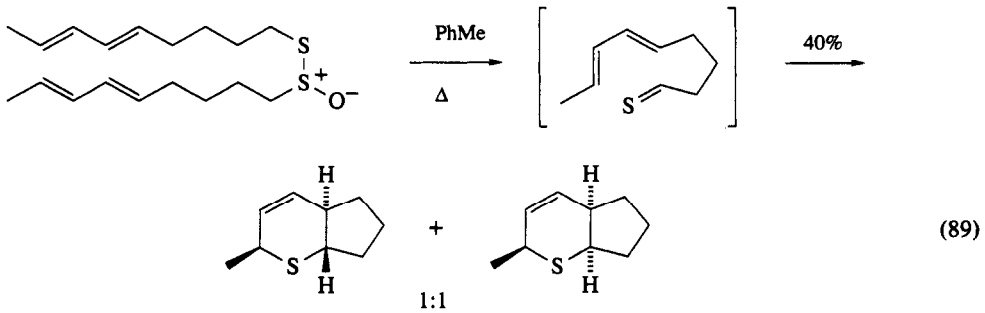
Scheme 24

Only a few intramolecular thioaldehyde [4 + 2] cycloadditions have been executed to date. Vedejs *et al.* have looked at systems such as that shown in equation (88).[158d] Their photochemical method is useful in effecting intramolecular reactions but stereoselectivity in the process was only moderate. Baldwin and Lopez have described the single intramolecular cycloaddition shown in equation (89) which involves a new thermal method for generating thioaldehydes from alkyl thiosulfinates.[161,162]



(88)

3.5:1

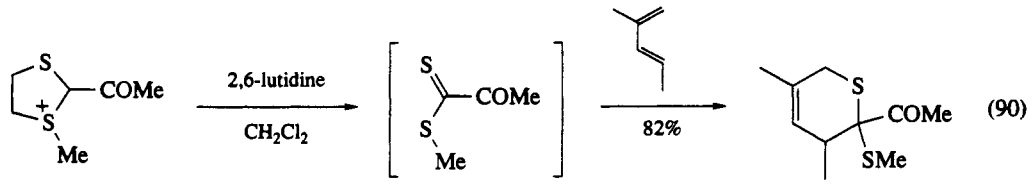


(89)

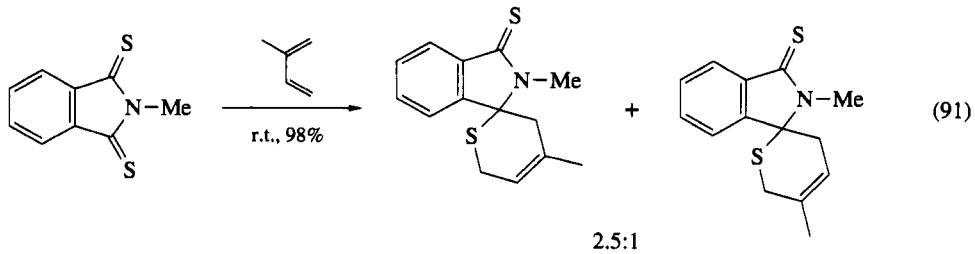
1:1

4.2.9.3 Thioesters, Dithioesters and Related Compounds

A number of thiocarbonyl compounds in the carboxylic acid oxidation state have been utilized in Diels–Alder reactions, but no systematic study in this area has been done. Some of the various structural types of thiocarbonyls which are reactive dienophiles are indicated in equations (90),[163] (91)[164] and (92).[165] Reactions of this class show good to moderate regioselectivity, but relatively little is known with regard to stereoselectivity. Additional examples can be found in earlier reviews.[1]



(90)



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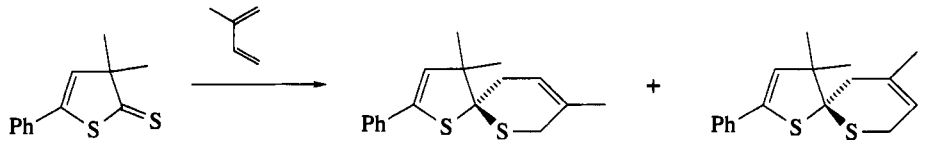
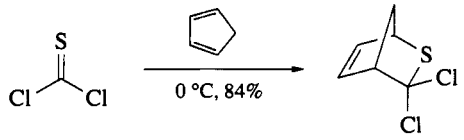


(92)

PhMe, Δ, 73% 1:1
$BF_3 \cdot Et_2O$, 60% 3:1

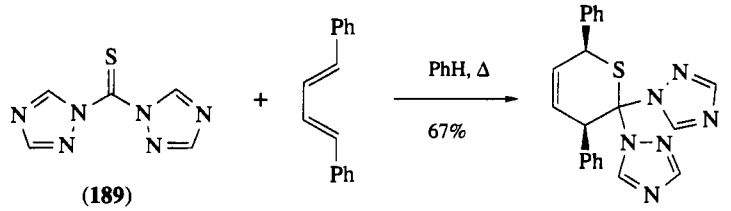
4.2.9.4 Thiophosgene and Related Compounds

Although carbon disulfide is not reactive as a heterodienophile, thiophosgene and its derivatives do participate in Diels–Alder reactions.[154,166] One example is shown in equation (93).

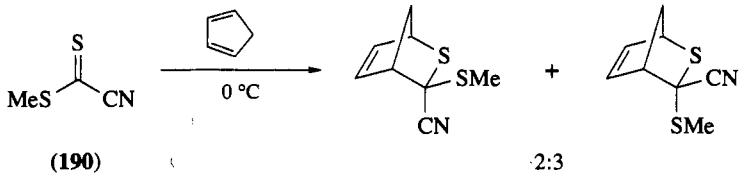


(93)

A few examples of cycloadditions with the thiophosgene equivalent (**189**) have been reported (equation 94).[167] In addition, methyl cyanodithioformate (**190**) has also been utilized several times as a heterodienophile (equation 95).[168]



(94)

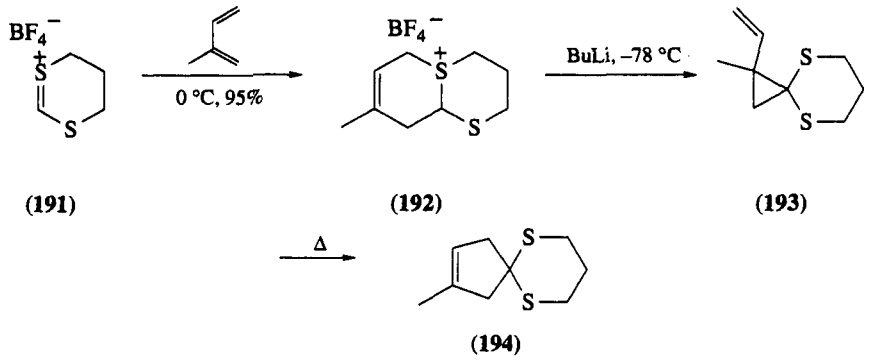


(95)

4.2.9.5 Thienium Salts and Related Cations

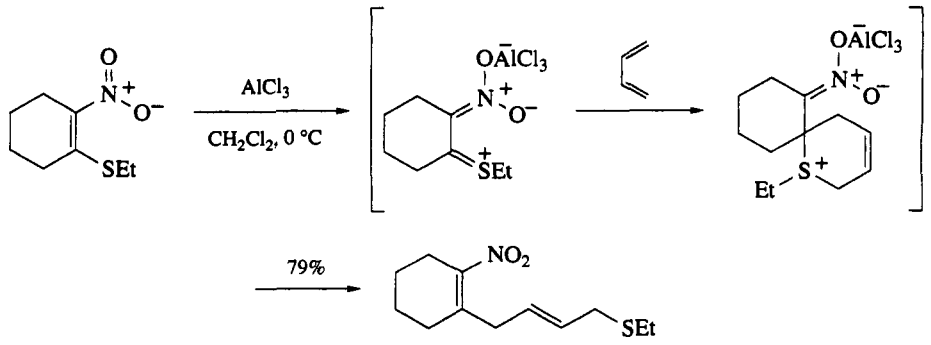
There are several scattered instances of [4 + 2] cycloadditions with charged thienium dienophiles.[169–171] The first reported example of this type of Diels–Alder reaction was by Corey and Walinsky, who used dithienium compound (**191**) in cycloadditions.[169] For instance, (**191**) reacts at low temperature with isoprene regioselectively to afford adduct (**192**) (equation 96). This compound can be converted to cyclo-

propane (**193**) and thermally rearranged to cyclopentanone derivative (**194**). The overall process is equivalent to addition of carbon monoxide to a 1,3-diene.



(**191**) (**192**) (**193**) (**194**) (96)

Another interesting use of a thienium dienophile is outlined in equation (97).[171] The initial Diels–Alder adduct was not isolated in these systems but was inferred based upon the nitro sulfide actually produced.

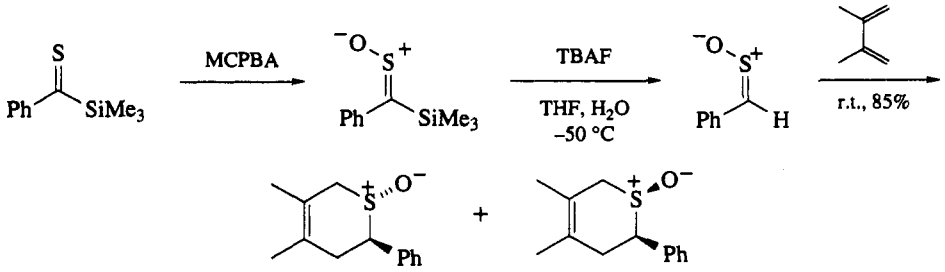


(97)

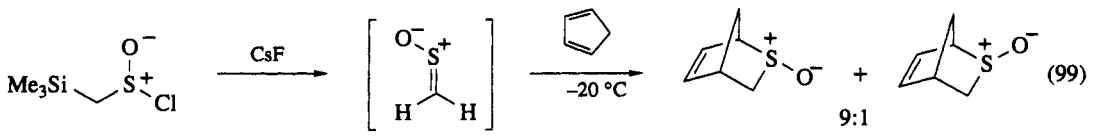
4.2.9.6 Sulfines and Sulfenes

Sulfines, which are thiocarbonyl *S*-oxides, have been used many times as heterodienophiles.[1,172] As with thioaldehydes, the development of this field has been limited more by the availability of these often unstable species rather than by problems with the Diels–Alder chemistry. It should be noted that sulfines can exist as configurationally stable (*E*)- or (*Z*)-isomers and this stereochemistry can play a role in the outcome of the cycloaddition reactions.

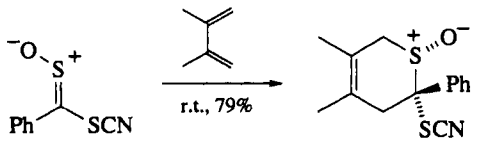
Two recent examples of cycloadditions with simple sulfines are shown in equations (98)[173] and (99).[174] Surprisingly, the first case is nonstereospecific, a feature unique to this particular reaction. The example shown in equation (100), which involves retention of dienophile configuration, is more typical.[175]



(98)

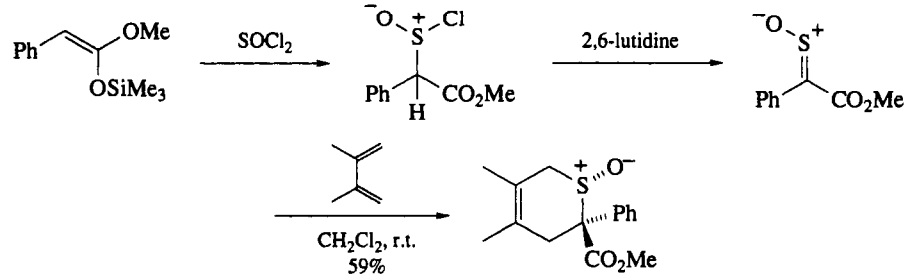


(99)

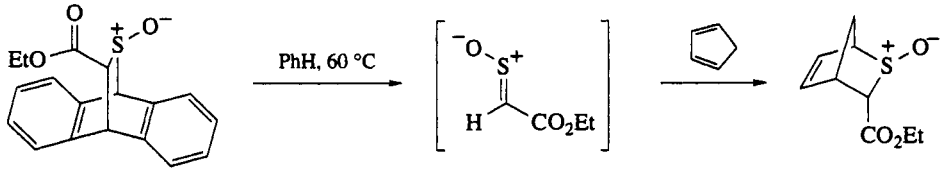


(100)

α-Oxosulfines have been the object of some research during recent years and these compounds have proven to be excellent dienophiles.[176] Two cases are shown in equations (101)[176d] and (102).[176f] It should be noted that sulfine geometry is retained in these cycloadditions. The former example shows a preference for an *endo* methoxycarbonyl group.

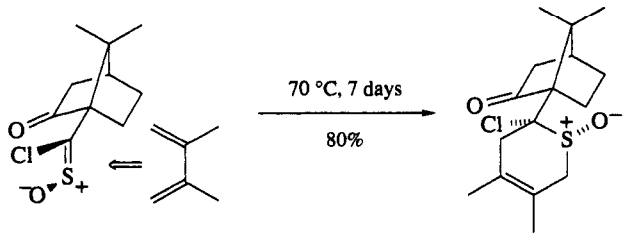


(101)



(102)

Zwanenburg and coworkers have examined the diastereoselectivity of chiral sulfine systems in Diels–Alder reactions.[177] In one case, α-chlorosulfine (**195**) derived from camphor reacts with 2,3-dimethylbutadiene *via* attack on the sulfine conformer indicated in equation (103) to afford adduct (**196**) as a single diastereomer.

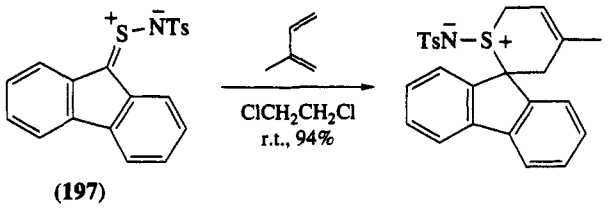


(103)

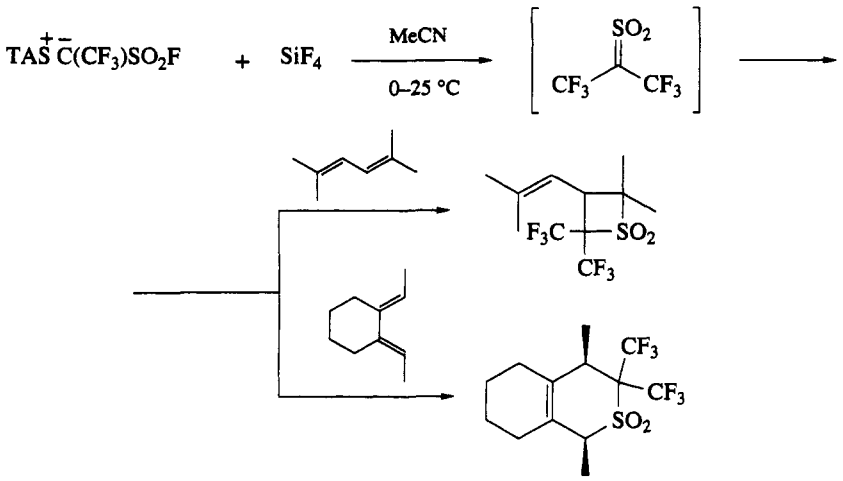
(**195**) (**196**)

One example exists of a thione imine (*i.e.* the nitrogen analog of a sulfine) acting as a dienophile.[178] Saito and Motoki have found that (**197**) reacts regioselectively with 1,3-dienes in a Diels–Alder sense (equation 104). This potentially useful reaction seems worthy of further exploration, provided general methods for generation of these imines can be developed.

Sulfenes have received little attention to date as dienophiles.[174,179] These reactive species undergo [4 + 2] cycloadditions with certain dienes upon occasion, but [2 + 2] cycloadditions and electrophilic reactions are also common (*cf.* Scheme 25).[179b] In addition, the mode of reaction of a sulfene may depend upon its method of formation.[174]



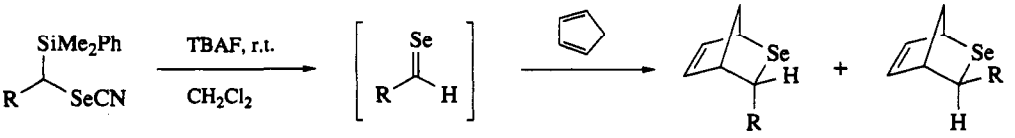
(197) (104)



Scheme 25

4.2.10 SELENOCARBONYL DIENOPHILES

Essentially all of the work on [4 + 2] cycloadditions of selenocarbonyl compounds has been reported within the past five years.[180–185] Krafft and coworkers have developed a novel method for producing seleno-aldehydes and -ketones, and have investigated in some detail the Diels–Alder chemistry of these species.[180] Alkyl- and aryl-substituted selenocarbonyl compounds could be formed from silyl selenocyanates (**198**) (equation 105). As is the case with thioaldehydes,[158] selenoaldehydes react with cyclopentadiene to afford predominantly *endo* cycloadducts. This stereochemical preference has also been observed by Segi *et al.*[185a] using a different method for generating selenoaldehydes.

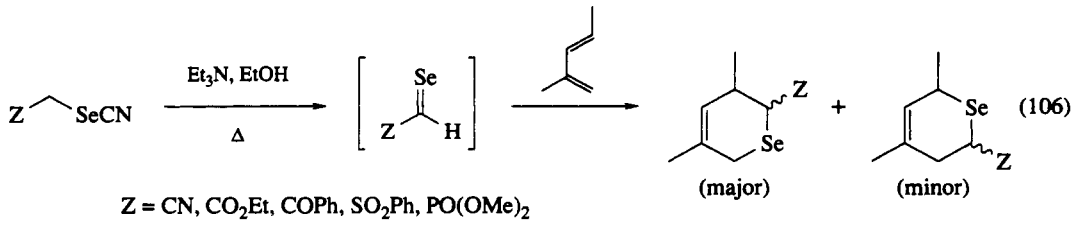


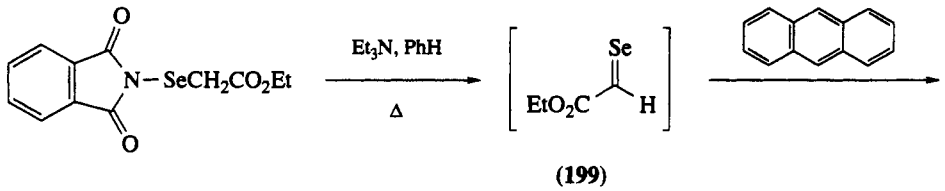
(**198**) R = alkyl, aryl 2.3–9.0:1 (105)

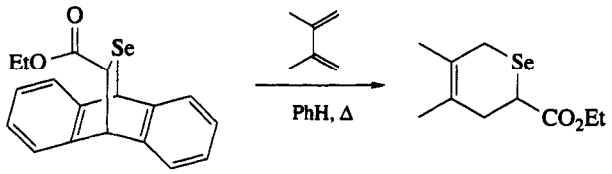
Alkyl-substituted selenoaldehydes only cycloadd to certain reactive dienes such as cyclopentadiene or 1,3-diphenylisobenzofuran. On the other hand, selenoaldehydes bearing electron-withdrawing groups react with a wide range of electron-rich dienes. One method of formation of this type of dienophile and some regiochemical results with an unsymmetrical 1,3-diene are shown in equation (106). The orientation observed here is in accord with a dienophile-LUMO/diene-HOMO controlled process.[180d]

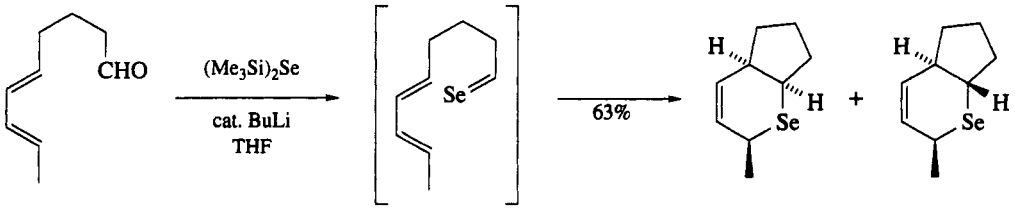
Another selenoaldehyde preparation has been developed by Kirby and Trethewey (equation 107).[184] Dienophile (**199**) can be trapped directly by 1,3-dienes or by anthracene to give adduct (**200**). Retro Diels–Alder reaction of (**200**) in the presence of another diene affords a new cycloadduct.

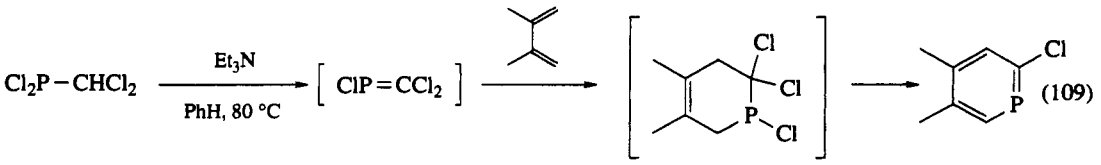
Segi and coworkers have invented a direct method for converting aldehydes to selenoaldehydes.[185] This procedure can be used to effect intermolecular reactions as well as intramolecular selenoaldehyde Diels–Alder reactions as outlined in equation (108).

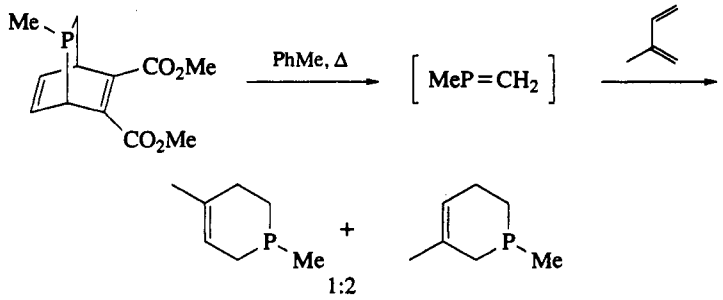

Et3N, EtOH
Δ
Z
SeCN
Se
H
Z
Z
Se
Se
Z
(major)
(minor)
(106)
Z = CN, CO2Et, COPh, SO2Ph, PO(OMe)2

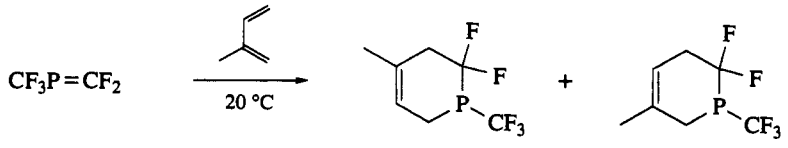

O
N–SeCH2CO2Et
O
Et3N, PhH
Δ
Se
EtO2C
H
(199)

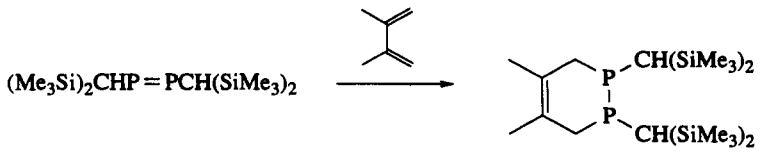

O
EtO
Se
PhH, Δ
Se
CO2Et
(107)
(200)


CHO
(Me3Si)2Se
cat. BuLi
THF
Se
63%
H
Se
H
+
H
Se
H
65:35
(108)


Cl2P–CHCl2
Et3N
PhH, 80 °C
ClP=CCl2
Cl
Cl
P
Cl
Cl
P
(109)


Me
P
CO2Me
CO2Me
PhMe, Δ
MeP=CH2
P
Me
+
P
Me
1:2
(110)


CF3P=CF2
20 °C
F
F
P
CF3
+
F
F
P
CF3
68:32
(111)



(112)

4.2.11 PHOSPHORUS-CONTAINING DIENOPHILES

Multiply bonded phosphorus compounds are often reactive as heterodienophiles. However, this is a diffuse area of research and little systematic study of these Diels–Alder reactions has been done. A complete listing of the various types of phosphorus dienophiles is beyond the scope of this review. Some of this material is available in previous summaries.[1] Selected representative examples of recent activity in this area is given in equations (109),[186] (110),[187] (111)[188] and (112).[189]

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4.3
Heterodiene Additions

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4.3.1 INTRODUCTION

In 1906, Wieland described the formation of 1:1 dimerization products of selected conjugated dienes under thermolysis conditions in the first report of a [4 + 2] cycloaddition reaction.[1] Albrecht's concurrent investigation of the reaction of cyclopentadiene with *p*-benzoquinone resulted in the observed formation of a 1:1 as well as a 2:1 diene:quinone adduct,[2] the structures of which were determined by Diels and Alder.[3] As a consequence of subsequent comprehensive studies,[7,9] Diels and Alder defined the fundamental structural,[3,4] regiochemical (*ortho/para* effect),[5] and stereochemical (*endo* addition, *cis* principle)[5,6,9] features of this reaction that now bears their names.[7–9] In the intervening time, the Diels–Alder reaction has been the continued subject of extensive preparative,[10–45] mechanistic,[44–49] and theoretical studies[50–54] that have led to the detailed understanding of the factors governing the rate, regioselectivity, and diastereoselectivity of the pericyclic [4 + 2] cycloaddition reaction. Perhaps more than any single re-

action in organic chemistry, the Diels–Alder reaction has served to demand mechanistic studies and theoretical models of sufficient accuracy to accommodate the experimental observations; the widespread use of the Diels–Alder reaction in organic synthesis has continued to demonstrate the elegance and efficiency with which it may be employed in the stereocontrolled preparation of substituted six-membered carbocyclic and heterocyclic systems.

The Diels–Alder reaction may be subclassified into three types of [4 + 2] cycloaddition reactions: (1) the normal Diels–Alder reaction appropriately referred to as a $HOMO_{diene}$-controlled [4 + 2] cycloaddition reaction; (2) the neutral Diels–Alder reaction; and (3) the inverse electron demand or $LUMO_{diene}$-controlled Diels–Alder reaction (Figure 1). Historically, it has been the normal or $HOMO_{diene}$-controlled Diels–Alder reaction comprised of the [4 + 2] cycloaddition reaction of an electron-rich diene and an electron-deficient dienophile that has serviced the preparative needs of organic chemistry and has occupied the central focus of mechanistic and theoretical studies. Pertinent to the topic of this chapter and the inherent electron-deficient nature of all fundamental heterodienes (Table 1), the $LUMO_{diene}$-controlled Diels–Alder reaction possesses a characteristic rate acceleration and high levels of predictable regio- and diastereo-control comparable with those observed in the $HOMO_{diene}$-controlled Diels–Alder reaction.

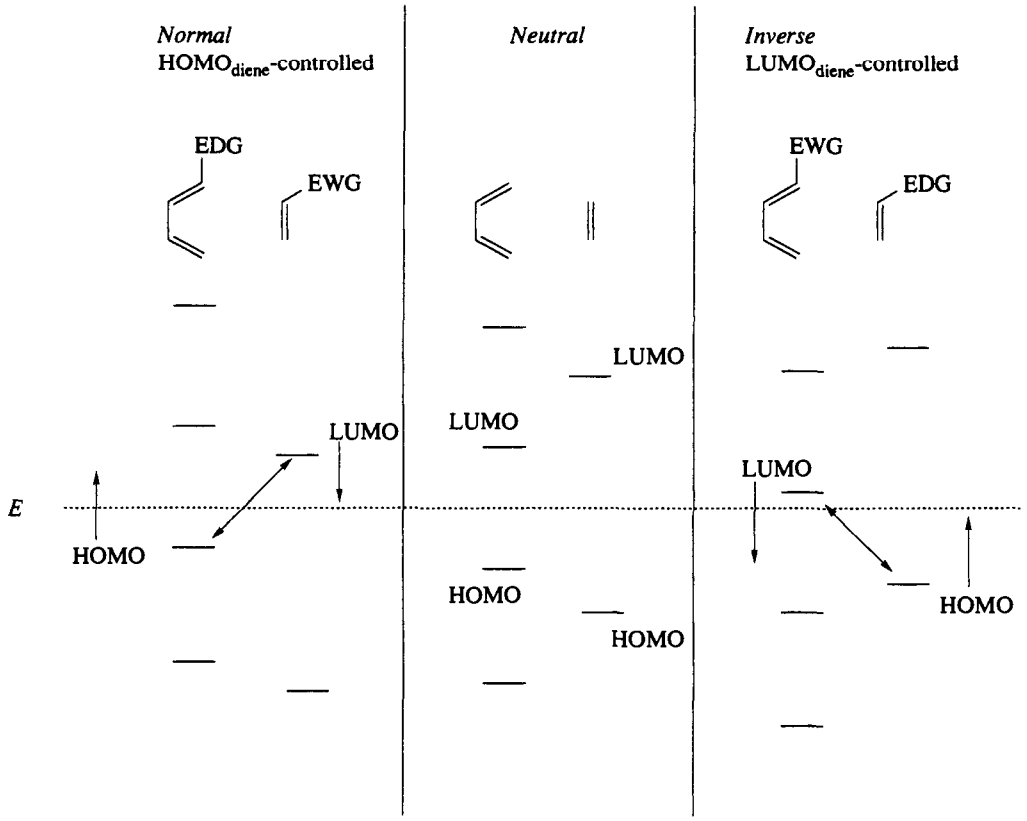


Figure 1

Table 1 Experimental Ionization Potentials (IP), Theoretical Highest Occupied π Orbital (HOMO), Experimental Electron Affinities (EA), and Theoretical Lowest Unoccupied π Orbital (LUMO) of Fundamental Heterodienes[a]

Diene	*IP*[b]	*HOMO (3-21G)*[c]	*−EA*[d]	*LUMO (3-21G)*[c]
$H_2C{=}CH{-}CH{=}CH_2$	−9.2	−8.9	0.6 eV	3.4
$H_2C{=}CH{-}CH{=}O$	−10.8	−10.8	<0.0	2.6
$H_2C{=}CH{-}CH{=}OH^+$	—	−23.7[e]	—	−6.5[e]
$H_2C{=}CH{-}CH{=}NH$	—	−9.9	—	2.9
$H_2C{=}CH{-}CH{=}S$	—	−9.4	—	0.7
$H_2C{=}CH{-}N{=}CH_2$	—	−9.2	—	2.9
$H_2C{=}CH{-}N{=}O$	—	−11.0	—	1.6
$O{=}CH{-}CH{=}O$	−13.9	−14.1	—	1.5

[a]All values in eV. [b]Taken from ref. 55. [c]Taken from ref. 56. [d]Taken from ref. 57. [e]Protonated acrolein; taken from ref. 58; CINDO/2 values are reported.

Although the early examples of the 4π participation of heterodienes in [4 + 2] cycloaddition reactions describe their reactions with electron-deficient alkenes, *e.g.* the thermal dimerization of α,β-unsaturated carbonyl compounds,[55] the introduction of one or more heteroatoms into the 1,3-butadiene framework does convey electrophilic character to the heterodiene. Consequently, such systems may be expected to participate preferentially in $LUMO_{diene}$-controlled Diels–Alder reactions with electron-rich, strained, or simple alkene and alkyne dienophiles. The complementary substitution of the heterodiene with one or more electron-withdrawing substituents further lowers the heterodiene E_{LUMO}, accelerates the rate of heterodiene participation in the $LUMO_{diene}$-controlled Diels–Alder reaction, and enhances the observed regioselectivity of the [4 + 2] cycloaddition reaction.[15]

The noncomplementary substitution of the heterodiene with electron-withdrawing substituents significantly lowers the heterodiene E_{LUMO}, accelerates its rate of reaction in a $LUMO_{diene}$-controlled Diels–Alder reaction, and in selected instances enhances the *endo* selectivity of heterodiene Diels–Alder reaction.[15,60,61]

The complementary substitution of the heterodiene with one or more strongly electron-donating substituents raises the heterodiene E_{HOMO} and in selected instances has proven sufficient to promote its 4π participation in $HOMO_{diene}$-controlled Diels–Alder reactions.[15] The combined use of a nucleophilic heterodiene and reactive, electrophilic alkenes, *e.g.* ketenes, permits the observation of Diels–Alder products often formed in competition with [2 + 2] cycloaddition products and represents examples of stepwise [4 + 2] cycloaddition reactions proceeding with zwitterionic intermediate generation.

The entropic assistance provided in the intramolecular Diels–Alder reaction often is sufficient to promote heterodiene 4π participation in poorly matched [4 + 2] cycloaddition reactions, including those with unactivated and electron-deficient dienophiles.[15,30–34]

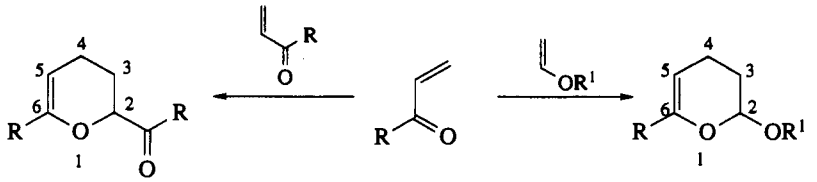
The use of a range of modified reaction conditions including the use of protic acids or conventional and nonconventional Lewis acid catalysts,[62] pressure-promoted reaction conditions,[63,64] cation-radical catalysts,[65] and dry-state adsorption reaction conditions[66] has been employed to accelerate the 4π participation of sensitive heterodienes in thermally slow or problematic Diels–Alder reactions. The former two techniques have proven useful for promoting the typically poor reactions of simple, unactivated 1-oxa-1,3-butadienes or acyclic azadienes.

4.3.2 OXABUTADIENES

4.3.2.1 1-Oxa-1,3-butadienes

Since the disclosures that the thermal dimerizations of acrolein and methyl vinyl ketone provide the 3,4-dihydro-2*H*-pyrans (**1, 2**)[59] derived from 4π and 2π participation of the α,β-unsaturated carbonyl compound in a Diels–Alder reaction, an extensive series of related observations have been detailed. This work has been the subject of several comprehensive reviews[15,24,27,44] including the Desimoni and Tacconi extensive tabular compilation of work through 1974. Consequently, the prior reviews should be consulted for thorough treatments of the mechanism, scope, and applications of the [4 + 2] cycloaddition reactions of α,β-unsaturated carbonyl compounds. The [4 + 2] cycloaddition reactions of 1-oxa-1,3-butadienes with their 4π participation in the Diels–Alder reaction exhibit predictable regioselectivity with the preferential or exclusive formation of 2-substituted 3,4-dihydro-2*H*-pyrans (equation 1). The exceptions to the predicted regioselectivity that have been observed involve the poorly matched [4 + 2] cycloaddition reaction of an electron-deficient 1-oxa-1,3-butadiene with an electron-deficient dienophile, *e.g.* methyl crotonate or methacrolein.[24,68,69] Rigorous or simplified theoretical treatments of the [4 + 2] cycloaddition reaction of 1-oxa-1,3-butadienes predict the preferential formation of 2-substituted 3,4-dihydro-2*H*-pyrans and accommodate the preferred *endo* approach of the reactants in which the carbon–carbon bond formation is more advanced than carbon–oxygen bond formation, *i.e.* a concerted but nonsynchronous [4 + 2] cycloaddition reaction.[67]

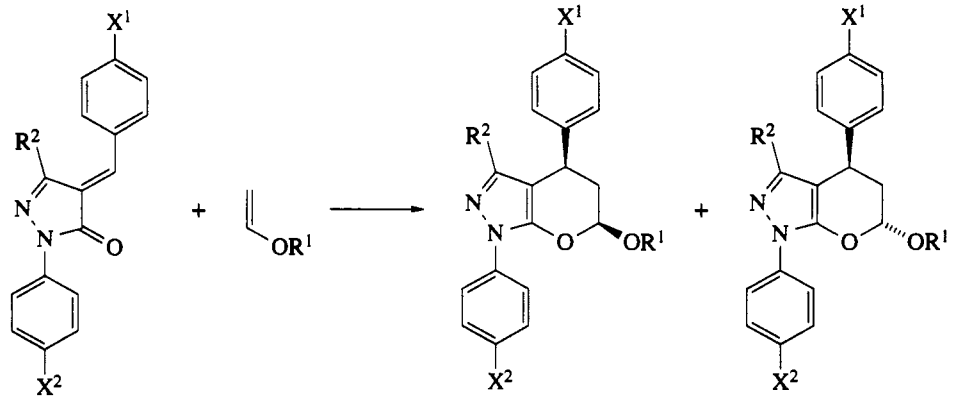
Simple α,β-unsaturated aldehydes, ketones, and esters (R = CO_2Me >> H > alkyl, aryl >> OR; equation 1)[15,60] preferentially participate in $LUMO_{diene}$-controlled Diels–Alder reactions with electron-rich, strained, and selected simple alkene and alkyne dienophiles,[15,24] although the thermal reaction conditions required are relatively harsh (150–250 °C) and the reactions are characterized by the competitive dimerization and polymerization of the 1-oxa-1,3-butadiene. Typical dienophiles have included enol ethers, thioenol ethers, alkynyl ethers, ketene acetals, enamines, ynamines, ketene aminals, and selected simple alkenes; representative examples are detailed in Table 2.[15,24] The most extensively studied reaction in the series is the [4 + 2] cycloaddition reaction of α,β-unsaturated ketones with enol ethers and Desimoni,



(1)

(1) R = H
(2) R = Me

Tacconi and coworkers have conducted the most thorough studies to date.[70] Characteristic of the [4 + 2] cycloadditions of enol ethers with α,β-unsaturated carbonyl compounds, the Diels–Alder reactions of 4-arylidene-5-pyrazolones proceed with the maintenance of dienophile alkene geometry preferentially through an *endo* cycloaddition transition state (equation 2). Good correlations of the $LUMO_{pyrazolone}$ with kinetic cycloaddition rates were observed, thereby confirming the 1-oxa-1,3-butadiene 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions under FMO control, although Sustmann's approximations of perturbation theory did not adequately accommodate the experimental observations. As can now be intuitively anticipated, pyrazolone C-3 substituents (R^2) have no effect on the rate of reaction; increasing the electron-withdrawing character of the substituent X^2 increased the rate of reaction and a good correlation between log *k* (reaction rate) and $\sigma(X^2)$ was observed; increasing the electron-withdrawing character of the substituent X^1 increased the reaction rate and a good correlation between log *k* and $\sigma^+(X^1)$ was observed; and increasing the electron-donating ability of R^1 increased the rate of [4 + 2] cycloaddition and a good correlation between log *k* and $\sigma^*(R^1)$ was observed.



(2)

4:1

A number of experimental techniques have been employed to compensate for the poor conversions and include the use of a substantial excess of diene, addition of a free radical inhibitor, Lewis acid catalysis,[15] and pressure-promoted reaction conditions.[63] The latter two techniques have been used to conduct successfully the [4 + 2] cycloaddition reactions under mild thermal conditions (25–100 °C) and it is surprising that these techniques have not been applied more extensively. Representative results are summarized in Table 3 and common problems accompanying the use of Lewis acid catalysts have been cycloadduct C-2 epimerization or decomposition, as well as the intervention of stepwise addition–cyclization reactions with the interception of zwitterionic intermediates. Lewis acid coordination of the α,β-unsaturated carbonyl nonbonding electrons will result in the lowering of the energies of its π-orbitals (*cf.* Table 1) and redistribution of its orbital electron densities. In instances where C-2 epimerization has been avoided, the Lewis acid-catalyzed [4 + 2] cycloaddition reaction of 1-oxa-1,3-butadienes with electron-rich dienophiles proceeds at a substantially faster rate than the uncatalyzed reaction (≤ 10^6 acceleration), with increased regio- and diastereo-selectivity that may be attributed to a decrease in the $LUMO_{diene}$–$HOMO_{dienophile}$ energy separation (*cf.* Table 1 and Table 5, rate), the increased polarization of the diene (Δ C-4/O-1 coefficient, regioselectivity), and the enhanced secondary orbital overlap achieved with cycloaddition through an *endo* transition state (increased C-2 coefficient, diastereoselectivity) (Figure 2).[58] Similarly, liquid high-pressure techniques have proven useful in increasing the rate and diastereoselectivity of the [4 + 2] cycloaddition reaction of simple or activated

Table 2 Representative [4 + 2] Cycloaddition Reactions of Simple 1-Oxa-1,3-butadienes

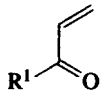
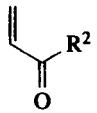
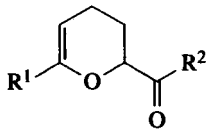
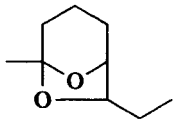
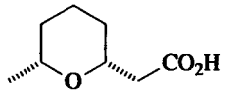
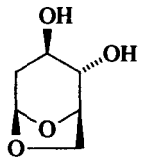
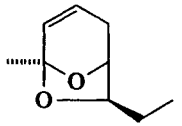
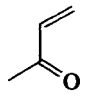
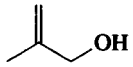
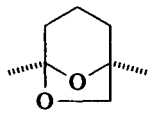
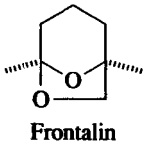
Reactants		*Conditions*	*Product*	*Yield (%)*	*Natural product*	*Ref.*
					 Brevicomin	
R^1 = Me	R^2 = H	—		—		74
R^1 = H	R^2 = H	—				75
R^1 = Me	R^1 = Me	—				69, 76
R^1 = Me	R^2 = Me	185 °C, 2 h				77
R^1 = H	R^2 = H	—				78
R^1 = Me	R^2 = Me	—				69, 79
R^1 = H	R^2 = H	—				75
					 Frontalin	
				6–7		80
				35–40		81

Table 2 *(continued)*

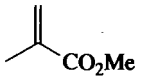
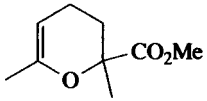
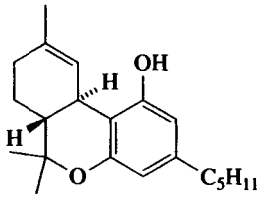
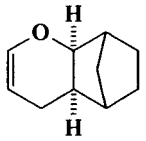
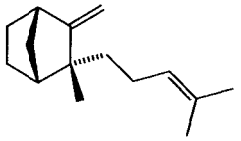
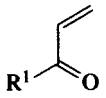
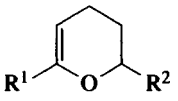
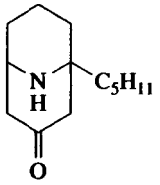
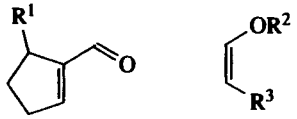
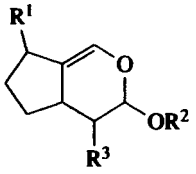
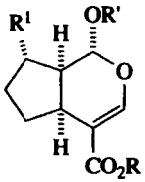
Reactants		*Conditions*	*Product*	*Yield (%)*	*Natural product*	*Ref.*
		PhH, 200 °C, 2 h				82
		190 °C		44	 β-Santalene	83
					 Adaline	
R^1 = Me	R^2 = SPh	160 °C, 1 h		73	Brevicomin	84
R^1 = H	R^2 = C_5H_{11}	190 °C, 25 h		50	Massoia lactone	85
R^1 = C_5H_{11}	R^2 = OMe	180 °C, 40 h		*ca.* 60	Adaline	86
R^1 = Me	R^2 = OPr^i	—			β-L-Boivinoside	87

Table 2 *(continued)*

Reactants	*Conditions*	*Product*	*Yield (%)*	*Natural product*	*Ref.*
					
$R^1 = H$, $R^2 = Et$, $R^3 = H$	185 °C		95	Iridoids	88
$R^1 = Me$, $R^2 = Pr^i$, $R^3 = Me$	130 °C, 48 h		42	Iridomymecin	89
$R^1 = Me$, $R^2 = Me$, $R^3 = CH_2OMe$	200 °C		47	(–)-Valerainine (–)-Tecostidine, (–)-actinidine	90

α,β-unsaturated carbonyl compounds (Table 3). The rate acceleration of the pressure-promoted intermolecular Diels–Alder reaction can be attributed to the substantial decrease in the volume of activation that accompanies the formation of the [4 + 2] cycloaddition transition state ($-\Delta V^{\ddagger} > 30$ cm3 mol^{-1}, all-carbon Diels–Alder reaction; $-\Delta V^{\ddagger} = 20$–$26$ cm^3 mol^{-1}, heterodiene Diels–Alder reaction, rate);[63,71,72] the increased diastereoselectivity may be attributed to the added difference in the activation volume for formation of the *endo versus exo* transition state ($-\Delta\Delta V^{\ddagger}$ *endo:exo* = 5.8 ± 0.5 cm^3 mol^{-1}, diastereoselectivity).[73] Recent observations have suggested that this increased *endo* diastereoselectivity is enhanced further with *cis*-1,2-disubstituted dienophiles and the accompanying additional difference in the volume of activation between the reaction paths leading to the *endo* and *exo* diastereomers due to the additional dienophile C-2 substituent.[61] This effect overrides the rate deceleration due to the presence of the added destabilizing steric interactions that accompany the *endo* cycloaddition.

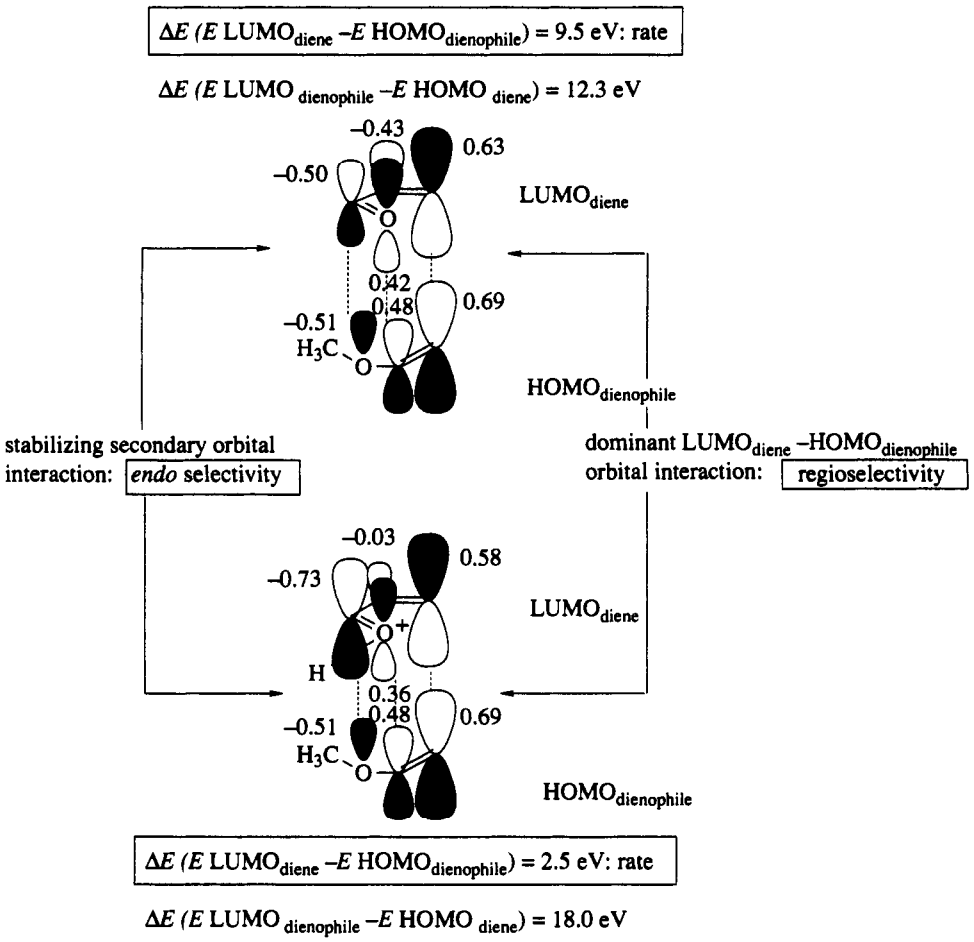


Figure 2 Thermal and (Lewis) acid catalyzed $LUMO_{diene}$-controlled [4+2] cycloaddition reaction of acrolein and methyl vinyl ether; AM1 results (Table 5)

4.3.2.2 Electron-deficient 1-Oxa-1,3-butadienes

The most successful approach to implementing the 4π participation of α,β-unsaturated carbonyl compounds in intermolecular Diels–Alder reactions has employed dienes substituted with a C-3 electron-withdrawing group. The additional C-3 electron-withdrawing substituent substantially lowers the 1-oxa-1,3-butadiene E_{LUMO}, thereby increasing the [4 + 2] cycloaddition reaction rate, increases the magnitude of the differences in the O-1/C-4 LUMO coefficients, thereby enhancing the regioselectivity of the cycloaddition reaction, and maintains a large C-2 LUMO coefficient, thus maintaining the diastereoselectivity (*endo* addition) of the cycloaddition reaction (Table 5). In addition, C-3 substitution of the heterodiene may increase the relative stability of the cisoid *versus* transoid diene conformation and in

Table 3 Representative Lewis Acid Catalyzed and Pressure-promoted [4 + 2] Cycloaddition Reactions of 1-Oxa-1,3-butadienes

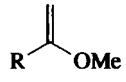
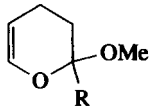
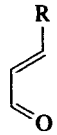
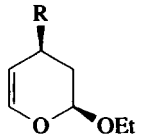
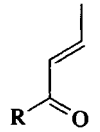
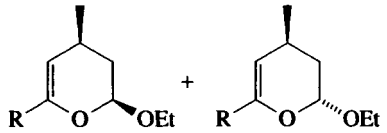
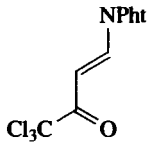
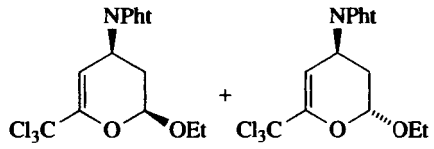
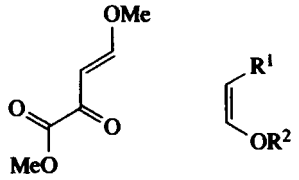
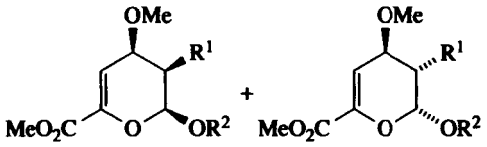
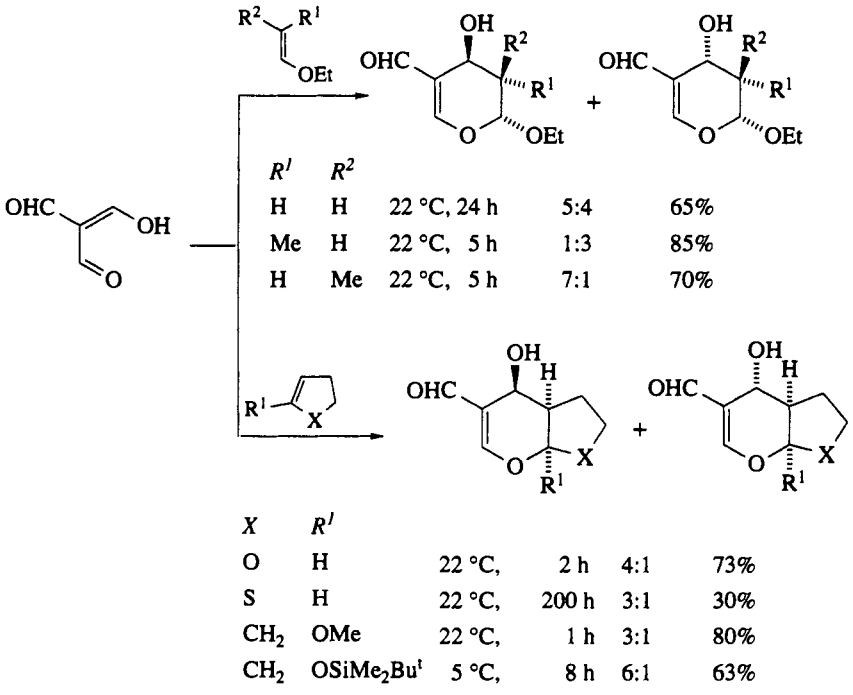
Reactants		*Conditions*	*Product(s)*	*Yield (%)*	*Product ratio*	*Ref.*
						91
	R = H	140 °C, 12 h		44		
	R = H	90 °C, 0.5 h, cat. $ZnCl_2$		55		
	R = Me	60 °C, 1.5 h, cat. $ZnCl_2$		61		
		$Yb(fod)_3$, 25 °C, neat		60–80	*endo* product only	92
						93
R = H		Et_2O, 75 °C, 15 kbar		89	100% endo	
R = Me		Et_2O, 110 °C, 15 kbar		68	10:1	
						72
		CH_2Cl_2, 90 °C, 1 atm			1.7:1	
		CH_2Cl_2, 60 °C, 1 atm			2.2:1	
		CH_2Cl_2, 60 °C, 6.5 kbar			6.1:1	
		CH_2Cl_2, 0 °C, 6.5 kbar			13.6:1	

Table 3 *(continued)*

Reactants	*Conditions*	*Product(s)*	*Yield (%)*	*Product ratio*	*Ref.*
					61
$R^1 = H, R^2 = Et$	110 °C, 1 atm		48	1.8:1	
	25 °C, 13 kbar		82	5.7:1	
	–78 °C, <5 min, cat. $EtAlCl_2$		75	0.8:1	
	25 °C, florisil (DSAC)		a	>45:1	94
$R^1 = H, R^2 = CH_2Ph$	25 °C, 13 kbar		69	6.5:1	
$R^1 = Me, R^2 = CH_2Ph$	80 °C, 1 atm		11	3.0:1	
	–78 °C, <5 min, cat. $EtAlCl_2$		50	6.0:1	
	25 °C, 9.5 kbar		56	19.0:1	
$R^1 = OAc, R^2 = CH_2Ph$	110 °C, 1 atm		0	—	
	25 °C, 13 kbar		50	>45:1	

[a] Yield not determined.

turn further increase the Diels–Alder reactivity of such dienes. These observations first pursued by Tietze[95–98] and Schmidt[110] and subsequently employed by a number of groups[15,99–101] have found considerable application (Scheme 1, Table 4). The [4 + 2] cycloaddition reaction of such dienes with electron-rich dienophiles proceeds under mild reaction conditions (0–100 °C) with: (1) exclusive regiocontrol; (2) excellent to modest diastereocontrol with preferential cycloaddition through an *endo* transition state in the absence of destabilizing steric interactions; (3) complete maintenance of the dienophile alkene geometry; and (4) little rate dependency on the solvent polarity.[102] The *endo* diastereoselectivity, the preservation of dienophile alkene geometry, and the increased reactivity of (*E*)-1-ethoxypropene *versus* (*Z*)-1-ethoxypropene [$k(E)/k(Z)$ = 35][100] toward 2-acetylcyclohex-2-enone (Table 4) have been interpreted to be consistent with and characteristic of a concerted $LUMO_{diene}$-controlled Diels–Alder reaction.



Scheme 1

Until recently, the reaction of α,β-unsaturated esters with electron-rich alkenes has been reported to provide cyclobutane [2 + 2] cycloaddition products. Amice and Conia first proposed the intermediacy of [4 + 2] cycloadducts in the reaction of ketene acetals with methyl acrylate,[103] and the first documented example of the 4π participation of an α,β-unsaturated ester in a Diels–Alder reaction appears to be the report of Snider and coworkers in their description of the reversible, intramolecular [4 + 2] cycloaddition reaction of 1-allylic-2,2-dimethyl ethylenetricarboxylates.[104] Subsequent efforts have demonstrated that substitution of an α,β-unsaturated ester with a C-3 electron-withdrawing substituent may permit their well-behaved 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions (equation 3).[15,105]

Similarly, the noncomplementary C-2[60,61,106,107] or C-4[15] addition of an electron-withdrawing substituent to the 1-oxa-1,3-butadiene serves to lower substantially the 1-oxa-1,3-butadiene E_{LUMO}, accelerates its 4π participation in a $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction, maintains the *endo*-derived diastereoselectivity through the maintenance (C-4) or enforcement (C-2) of a large LUMO C-2 coefficient, and does not alter the observed [4 + 2] cycloaddition regioselectivity, although such substitution may decrease the magnitude of the difference between the O-1/C-4 LUMO coefficients (Table 5).

Characteristic of such dienes, α-keto-β,γ-unsaturated esters such as (**3**; see also Table 3 and Table 5) exhibit good thermal reactivity toward simple vinyl ethers in [4 + 2] cycloaddition reactions that proceed with exclusive regiocontrol predominately through an *endo* transition state. The *endo* selectivity increases as the reaction temperature is decreased and both the reaction rate and the *endo* selectivity increase as the reaction pressure is increased (Figure 3, Table 3). The substantial increase in the diastereoselectivity of the pressure-promoted [4 + 2] cycloaddition reaction of (**3**) with a *cis* 1,2-disubstituted dienophile has been attributed to the additional differences in the volume of activation between the reaction paths leading to the *endo* and *exo* diastereomers due to the additional *cis* C-2 dienophile sub-

Table 4 Representative Diels–Alder Reactions of Electron Deficient 1-Oxa-1,3-butadienes

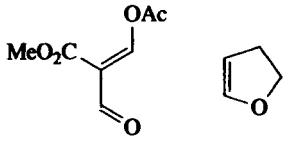
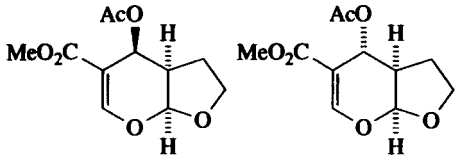
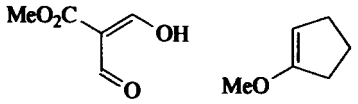
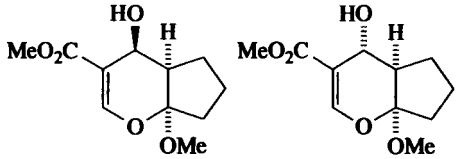
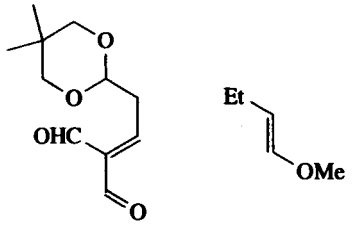
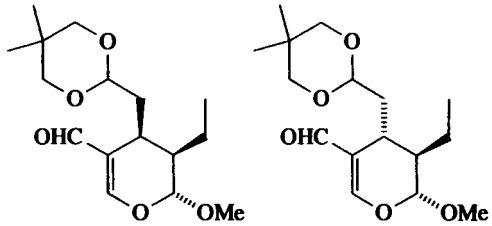
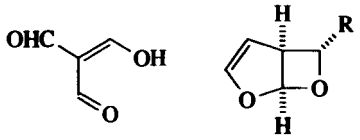
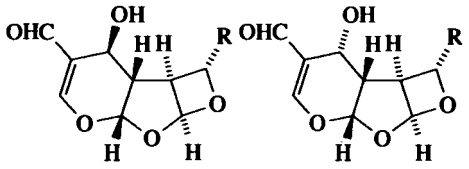
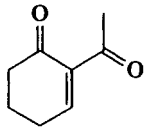
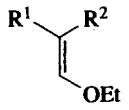
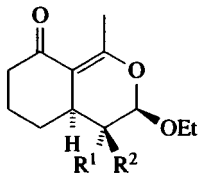
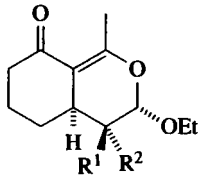
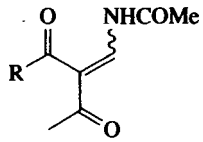
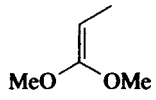
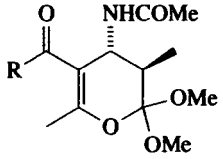
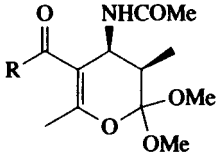
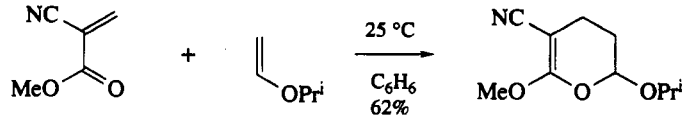
Reactants	*Conditions*	*Products*	*Yield (%)*	*Product ratio*	*Ref. (application)*
	25 °C, 4 h		85	1:2	97
	25 °C, 200 h		82	3:1	97
	25 °C, 2 h		62	3:1	98 Secoiridoids
	$CHCl_3$, 4 h, 67 °C		45	7:1	99

Table 4 *(continued)*

Reactants	*Conditions*	*Products*	*Yield (%)*	*Product ratio*	*Ref. (application)*
 		 			100
R^1 = H, R^2 = H	25 °C, 24 h		75	>20:1	
R^1 = H, R^2 = Me	25 °C, 28 d		30	3:1	
R^1 = Me, R^2 = H	25 °C, 48 h		70	7:1	
 		 			101 Carbapenems
R = OMe			90	1.2:1	
R = NHC_6H_4-4-Cl			90	20:1	



(3)

stituent, and this effect overrides the inherent rate deceleration imposed by destabilizing steric interactions that accompany the *endo* cycloaddition (Figure 3).[61]

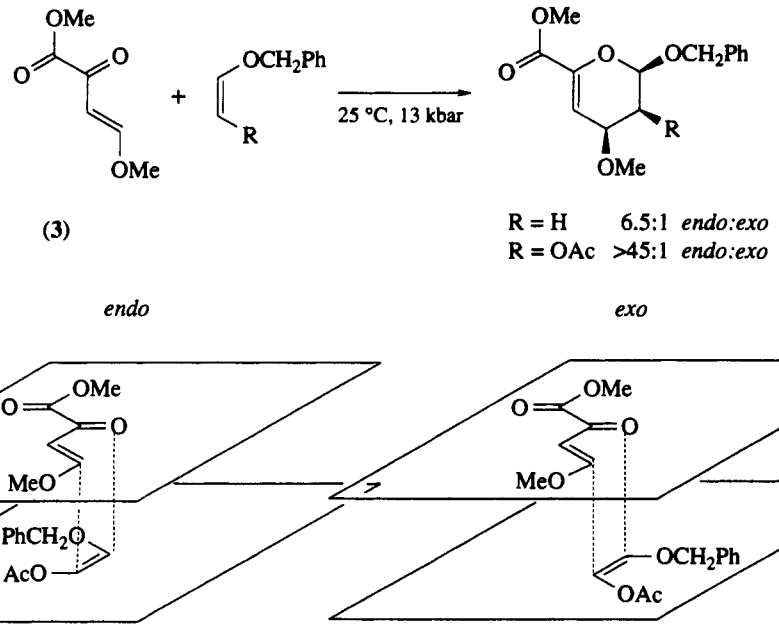


Figure 3

4.3.2.3 1-Oxa-1,3-butadienes Substituted with C-3, C-4 Electron-donating Substituents

The addition of a C-2 (equation 1; R = H > alkyl, aryl > OMe >> NR_2), C-3, or C-4 electron-donating substituent to a 1-oxa-1,3-butadiene electronically decreases its rate of 4π participation in a $LUMO_{diene}$-controlled Diels–Alder reaction (*cf.* Table 5). Nonetheless, a useful set of C-3 substituted 1-oxa-1,3-butadienes have proven to be effective dienes[107–113] and have been employed in the preparation of carbohydrates (Table 6).[114] The productive use of such dienes may be attributed to the relative increased stability of the cisoid *versus* transoid diene conformation that in turn may be responsible for the Diels–Alder reactivity of the dienes. Clear demonstrations of the anticipated [4 + 2] cycloaddition rate deceleration of 1-oxa-1,3-butadienes bearing a C-4 electron-donating substituent have been detailed (Table 6; entry 4).[114,115] In selected instances, the addition of a strong electron-donating substituent (OR, NR_2) to the C-4 position provides sufficient nucleophilic character to the 1-oxa-1,3-butadiene to permit the observation of [4 + 2] cycloaddition reactions with reactive, electrophilic alkenes including ketenes and sulfenes, often in competition with [2 + 2] cycloaddition reactions.[15]

4.3.2.4 Intramolecular 1-Oxabutadiene Diels–Alder Reactions

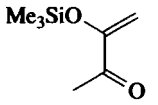
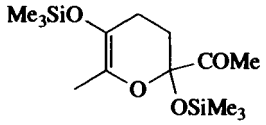
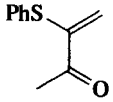
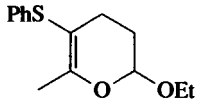
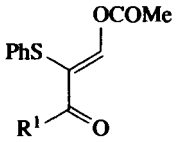
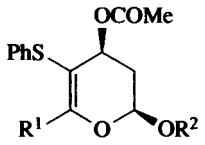
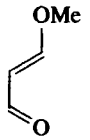
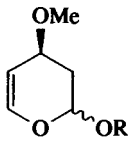
One of the most effective approaches to implementing the Diels–Alder 4π participation of 1-oxa-1,3-butadienes is through the use of an intramolecular [4 + 2] cycloaddition reaction.[15,30–34,95] A select set of thermal and Lewis acid-catalyzed intramolecular cycloaddition reactions of unactivated and electron-rich alkenes with α,β-unsaturated aldehydes and ketones has been detailed.[15] Two examples of the poorly matched intramolecular Diels–Alder reaction of an α,β-unsaturated aldehyde (4π component) with an α,β-unsaturated amide (2π component) have proven successful (190–160 °C) and may be attributed to the entropic assistance provided by the intramolecular reaction. These observations have been applied in

Table 5 1-Oxa-1,3-butadiene Substituent Effects on the π HOMO and LUMO[a]

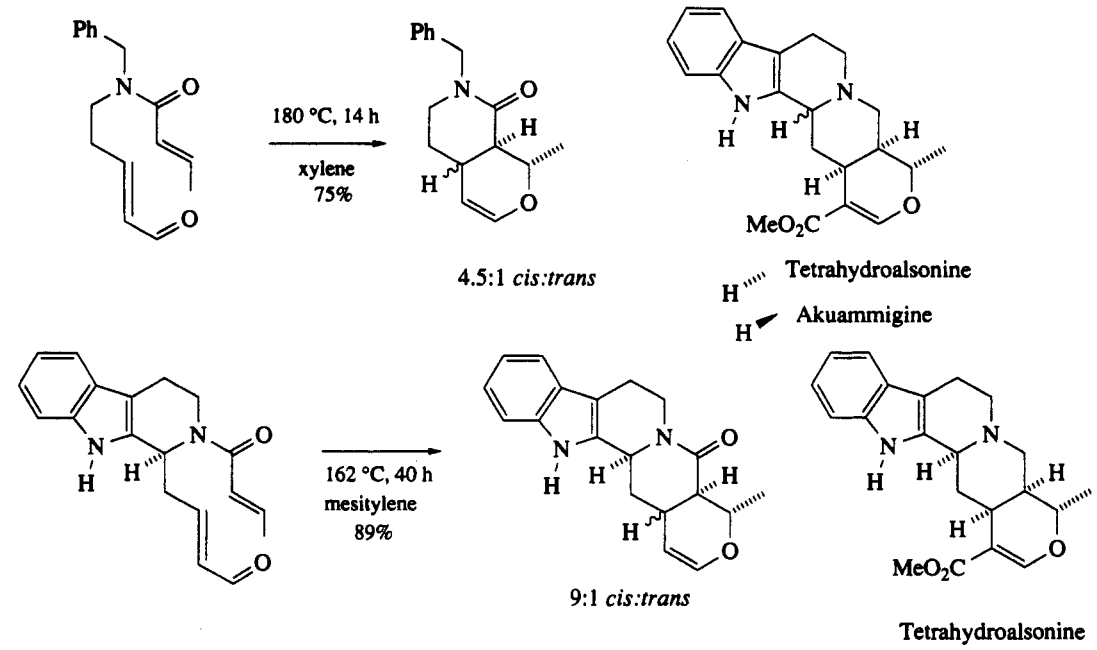
	E(LUMO)	*E(HOMO)*	*Coefficients* *O-1*	*C-2*	*C-3*	*C-4*	*CHO*
$H_2C{=}CH{-}CH{=}O$	–0.04	–10.9	LUMO: 0.42	–0.50	–0.43	0.63	—
			HOMO: –0.35	–0.05	0.68	0.65	—
$H_2C{=}CH{-}CH{=}OH^+$	–7.0	–16.6	LUMO: 0.36	–0.73	–0.03	0.58	—
			HOMO: –0.36	–0.23	0.73	0.53	—
$H_2C{=}C(CHO){-}CH{=}O$[b]	–0.8	–11.3	LUMO: 0.26	–0.27	–0.41	0.69	–0.34
			HOMO: –0.32	–0.05	0.64	0.61	–0.05
$H_2C{=}CH{-}C(CHO){=}O$[c]	–0.9	–11.1	LUMO: 0.47	–0.51	–0.20	0.43	–0.40
			HOMO: –0.34	–0.03	0.68	0.65	0.00
$HC(CHO){=}CH{-}CH{=}O$[b]	–1.1	–11.3	LUMO: 0.33	–0.34	–0.50	0.52	0.35
			HOMO: –0.32	–0.05	0.64	0.62	–0.06
	E(LUMO)	*E(HOMO)*	*O-1*	*C-2*	*C-3*	*C-4*	*CO_2Me*
$HC(OMe){=}CH{-}CH{=}O$	0.05	–9.9	LUMO: 0.39	–0.46	–0.38	0.66	—
			HOMO: –0.32	0.00	0.69	0.43	—
$HC(OMe){=}CH{-}C(CO_2Me){=}O$	–0.7	–10.2	LUMO: 0.46	–0.52	–0.22	0.52	–0.28
			HOMO: –0.31	0.02	0.69	0.41	–0.01
	E(LUMO)	*E(HOMO)*	*C-1*	*C-2*	*O-Me*		
$H_2C{=}CH{-}OMe$	1.4	–9.5	LUMO: 0.72	–0.66	0.21		
			HOMO: 0.48	0.69	–0.51		

[a]AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π orbital; values in eV. [b]*cis,trans* conformation. [c]*cis,trans* (dione) conformation (ref. 94).

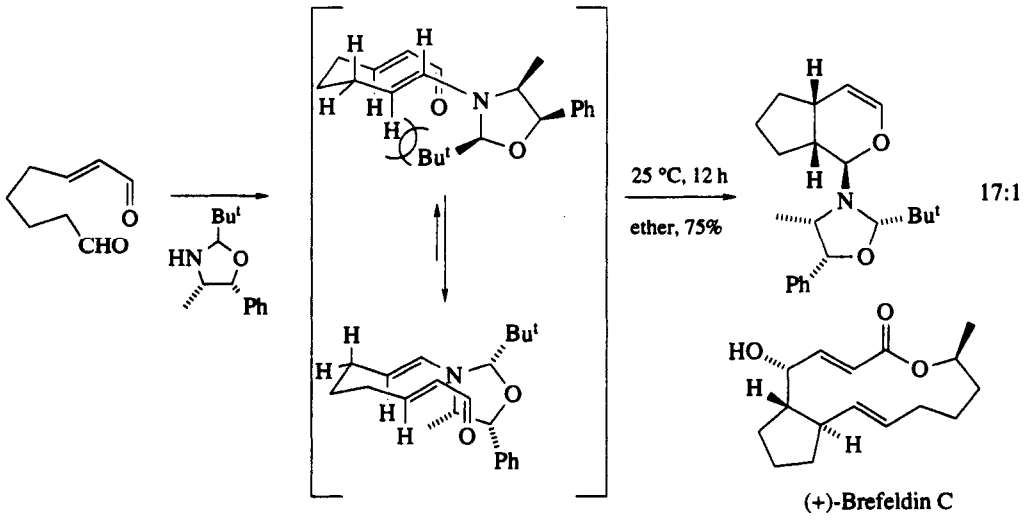
Table 6 Representative [4 + 2] Cycloaddition Reactions of Electron-rich 1-Oxa-1,3-butadienes

Reactants		*Conditions*	*Product*	*Yield (%)*	*Endo:exo ratio*	*Ref.*
				59		107
		180 °C, 3 h		95		109
		70–80 °C				110–114
R^1 = Me	R^2 = Et			98	>10:1	
R^1 = Me	R^2 = Bn			96	>10:1	
R^1 = CH_2OBn	R^2 = Et			96	>10:1	
R^1 = CH_2OPh	R^2 = Et			68	12.5:1	
R^1 = CO_2Me	R^2 = Et			57	*endo* only	
						
	R = Me	240 °C		60		119
	R = Bu^i			45		120

the total syntheses of heteroyohimboid and corynantheiod indole alkaloids (Scheme 2).[116,117] In a useful comparison, the intramolecular reaction of an electron-deficient α,β-unsaturated aldehyde (4π component) with an electron-rich enamine provided the [4 + 2] cycloadduct at room temperature (25 °C).[118] Use of an optically active amine provided predominantly one cycloadduct possessing the *cis* bicyclic dihydropyran relative stereochemistry and the absolute stereochemistry depicted in Scheme 3 derived from *si* face addition to the enamine.[119]



Scheme 2



Scheme 3

The combined use of the intramolecular version of the 1-oxa-1,3-butadiene [4 + 2] cycloaddition reaction with the use of α,β-unsaturated carbonyl compounds bearing a C-3 electron-withdrawing substituent provides effective room temperature, regio- and diastereo-selective [4 + 2] cycloaddition reactions. In a series of investigations, Tietze and coworkers have shown that alkylidene- or arylidene-1,3-dicarbonyl compounds may be obtained *in situ* through a Knoevenagel condensation (0–25 °C) catalyzed by ethylenediammonium diacetate. Without isolation, the resulting heterodienes undergo [4 + 2] cycloaddi-

tion at room temperature to provide Diels–Alder products with high or exclusive diastereocontrol (≥ 90%).[95] Asymmetric induction can be effected by a stereogenic center in the connecting chain[121–123] or in the dicarbonyl compound[124,125] with high induced diastereoselectivity, *i-de* > 90%. The intramolecular cycloaddition reactions proceed with full (100%) maintenance of the alkene geometry,[126] the rate of reaction increases as the nucleophilic character of the dienophile is increased, and the rate of cycloaddition does not show a pronounced dependency on the solvent polarity, demonstrating that such cycloadditions may be regarded as concerted.[95,126] The *E*/*Z* stereochemistry of the diene carbon–carbon double bond, the length and nature of the diene–dienophile linking chain, and the alkene substitution have a pronounced effect on the rate, diastereoselectivity and regioselectivity (fused *versus* bridged cycloadduct) of the intramolecular [4 + 2] cycloaddition reaction.[15] In cases with substrates bearing a definable diene (*E*/*Z*)-alkene geometry,[127] isomerization to the (*E*)-alkene precedes cycloaddition and 6,6-*trans*-fused [4 + 2] cycloaddition products are favored with preferential cyclization through an *exo-E-anti* transition state. When unfavorable steric interactions between the diene and the connecting chain preclude formation of the *exo-E-anti* transition state, cycloaddition proceeds through an *endo-E-syn* transition state, providing the 6,6-*cis*-fused [4 + 2] cycloaddition product (Scheme 4). In such instances the lack of observation of cycloaddition through the *exo-E-anti* transition state has been attributed principally to stereoelectronic effects in which dienophile approach to the diene along a trajectory angle of approximately 109° is not permitted.[128]

Application of these observations to the total synthesis of (–)-(3*R*)- and (+)-(3*S*)-hexahydrocannabinol (Scheme 5)[123] and (3*S*)-3-hydroxyhexahydrocannabinol (Scheme 6)[95] has been described.

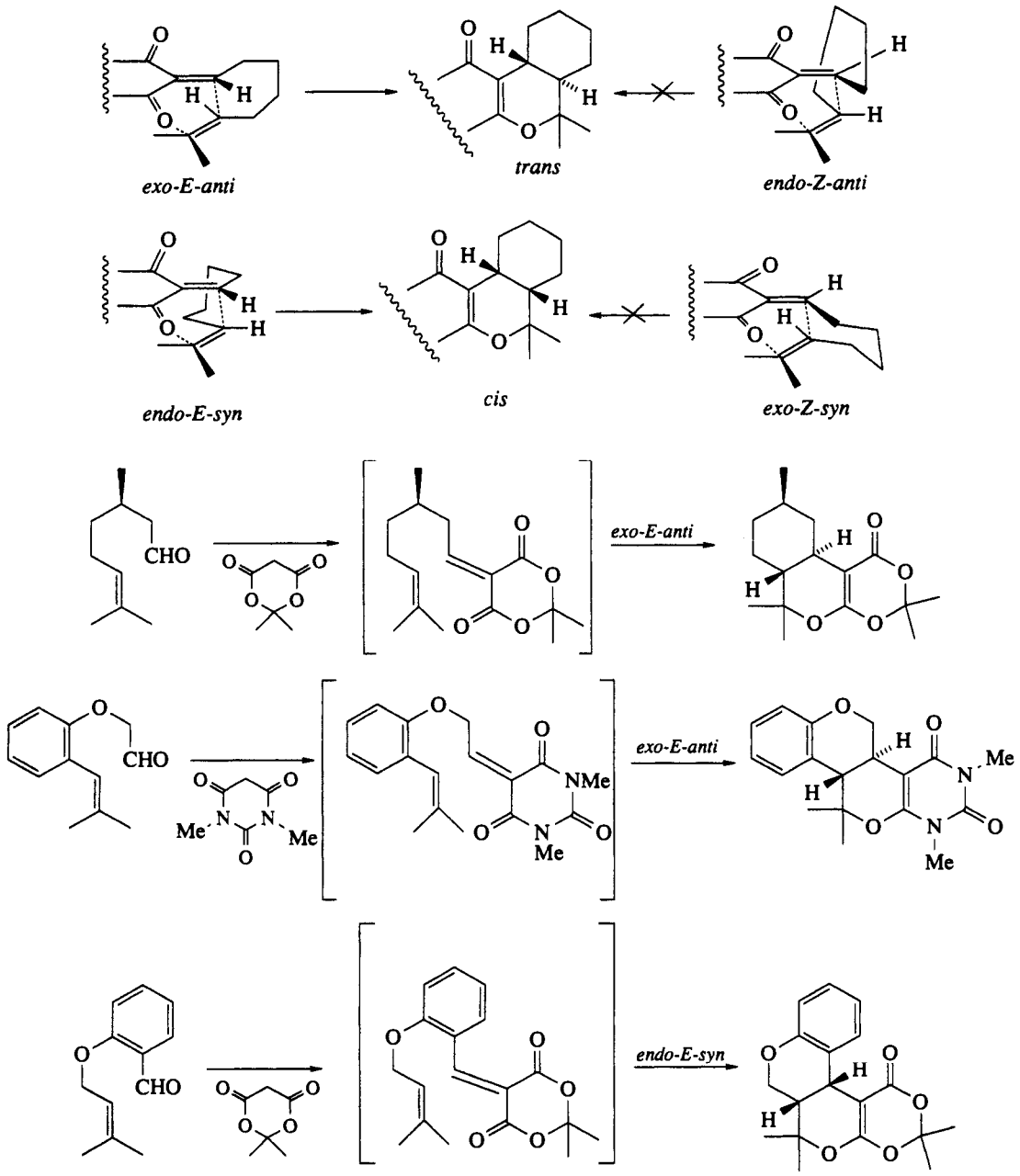
Although far less explored, the studies have been extended to the preparation of 6,5-fused cycloadducts. At present, the limited observations suggest that substrates bearing dienophile C-1 disubstitution or an *E*-1,2-disubstituted dienophile provide 6,5-*cis*-fused cycloaddition products with preferential cyclization through an *endo-E-syn* transition state. In contrast, substrates bearing a *Z*-1,2-disubstituted dienophile have been found to provide 6,5-*trans*-fused cycloadducts with preferential cyclization through an *exo-E-anti* transition state. Exceptions have been observed and have been related to the nature of the diene–dienophile linking chain.[128–131] The former observations have been applied in total syntheses of deoxyloganin from (*S*)-citronellal (Scheme 7),[128] (–)-kainic acid (Scheme 8)[129] and (–)-sesamolin, (–)-sesamin and (–)-acuminatolide (Scheme 9). In addition, these and related observations[132] have suggested that the biosynthesis of the loganins may proceed through a diastereoselective [4 + 2] cycloaddition reaction of the *E*-enol of a recognized biosynthetic precursor (equation 4).[133]

4.3.2.5 *o*-Quinones, *o*-Quinone Methides

The generation and subsequent [4 + 2] cycloaddition reactions of *o*-quinones (4π 1,4-dioxabutadiene participation)[14,24,44,134] and *o*-quinone methides[14,24,44,134] have been extensively reviewed.[15] Perhaps the most spectacular demonstration of the potential of such cycloadditions rests with the Chapman biomimetic total synthesis of carpanone (equation 5).[135] Palladium(II)-catalyzed generation and subsequent oxidation of an *o*-alkylphenol with intermediate generation of an *o*-quinone methide and *in situ* [4 + 2] cycloaddition through an *endo* transition state provided carpanone. The propensity for methide-substituted *o*-quinone methides to undergo rapid 1,5-hydrogen shift and rearomatization with *o*-hydroxystyrene generation has restricted their use to nontautomerizable *o*-quinone methides.[15] Even then the dimerization of the reactive *o*-quinone methides has proven problematic. In contrast, *in situ* generated *o*-quinone methides capable of tautomerization have been successfully employed in intramolecular [4 + 2] cycloaddition reactions,[15] and the observations have found application in the total synthesis of optically active cannabinoids (Scheme 10)[136,137] and citrans.[15] The exclusive generation of a single diastereomer possessing the *trans* ring fusion is consistent with [4 + 2] cycloaddition through an *exo-E-anti* transition state from a chair conformation possessing an equatorial methyl substituent.

4.3.2.6 Hetero 1-Oxabutadienes

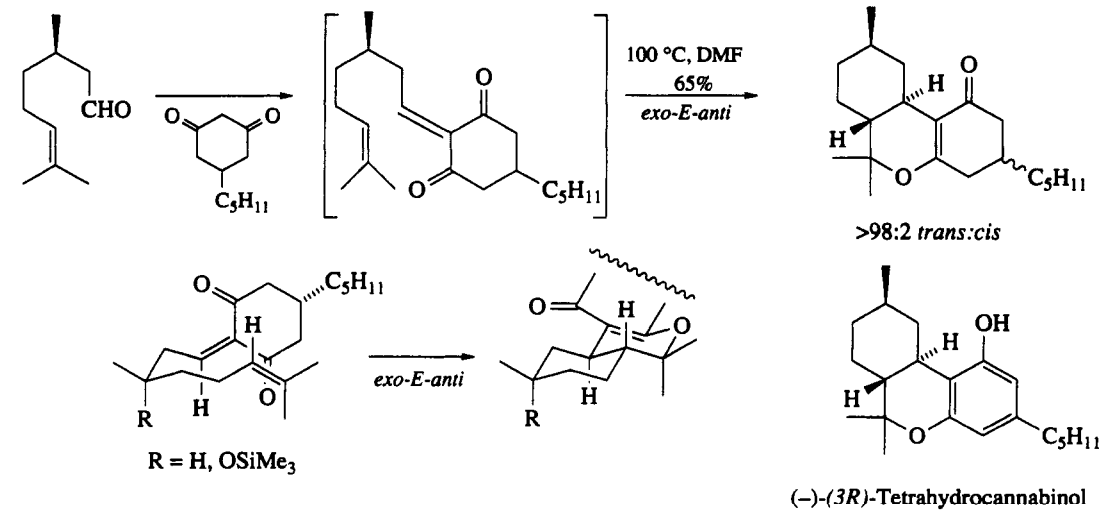
An extensive range of hetero 1-oxabutadiene systems containing nitrogen (Section 4.3.4) and sulfur (Section 4.3.3) have been investigated and found to function as 4π components of Diels–Alder reactions.[15] In general, the incorporation of an additional heteroatom into the 1-oxabutadiene system increases its electrophilic character and facilitates its 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions with electron-rich dienophiles. Examples of such systems are presented in Figure 4.[15]



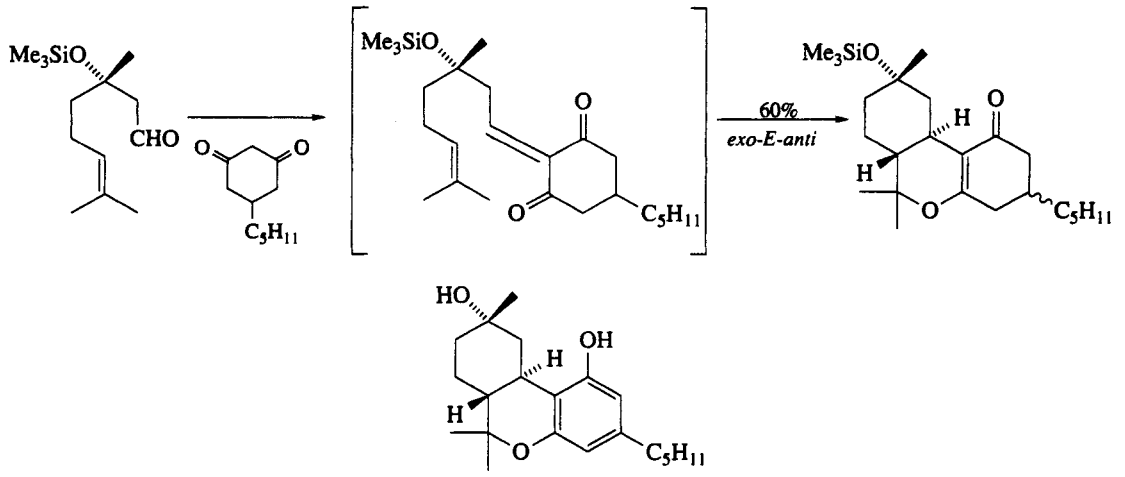
Scheme 4

4.3.3 THIABUTADIENES

In contrast to the thorough studies of the Diels–Alder reactions of oxa- and aza-butadienes, the [4 + 2] cycloaddition reactions of 1-thia-1,3-butadienes have not been studied extensively.[15,17,138] Although the general participation of thiabutadienes in $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions has been recognized and experimentally verified,[15] most investigations have detailed their 4π participation in $HOMO_{diene}$-controlled reactions with typical electron-deficient dienophiles. In such instances, the complementary C-2 or C-4 addition of electron-donating substituents to the 1-thia-1,3-butadiene increases the rate and regioselectivity of its 4π participation in $HOMO_{diene}$-controlled Diels–Alder reactions. With notable exceptions,[15] the $LUMO_{diene}$-controlled Diels–Alder reactions provide the expected 2-substituted 3,4-dihydro-2*H*-thiopyrans and, unlike simple 1-oxa-1,3-butadienes, the $HOMO_{diene}$-controlled Diels–



Scheme 5

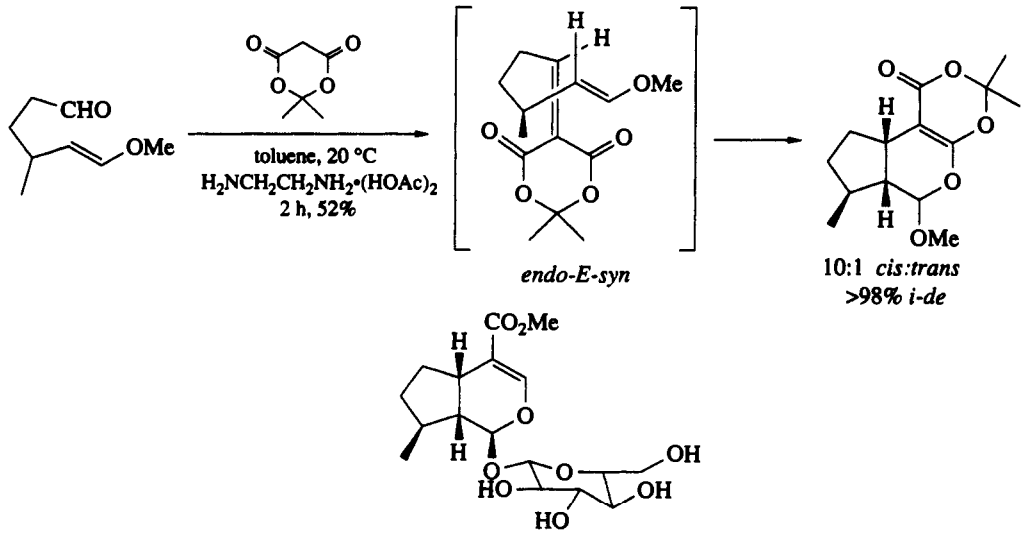


Scheme 6

Alder reactions of 1-thia-1,3-butadienes with electron-deficient or conjugated dienophiles provide 3-substituted 3,4-dihydro-2*H*-thiopyrans (equation 6). Representative Diels–Alder reactions of 1-thia-1,3-butadienes are presented in Table 7 and hetero-1-thiabutadienes that have been demonstrated to participate in [4 + 2] cycloaddition reactions are summarized in Figure 4.[15]

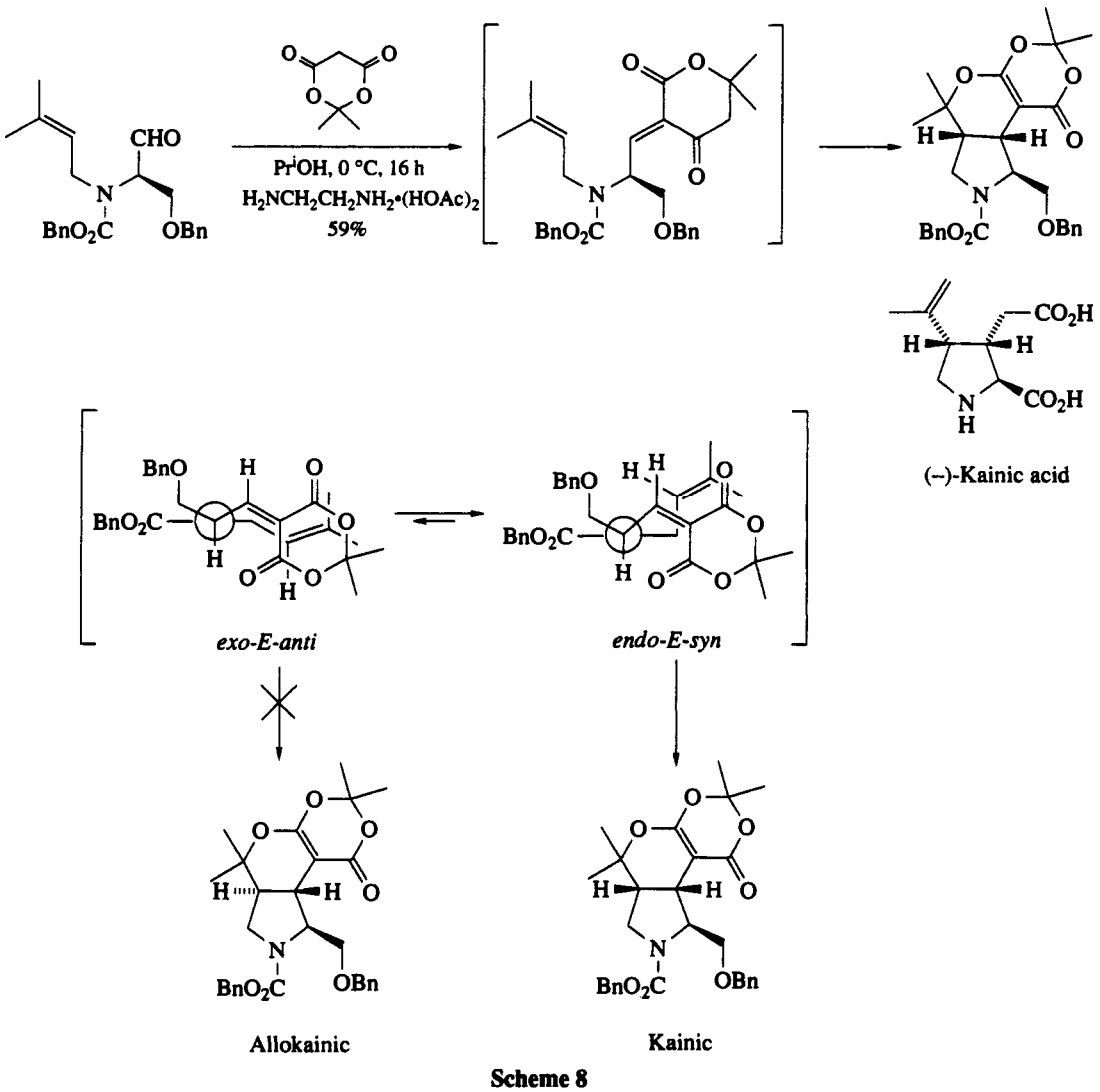
4.3.4 AZABUTADIENES

Comparable to the 1-oxabutadienes, the azabutadienes constitute a class of widely investigated heterodienes capable of productive 4π participation in [4 + 2] cycloaddition reactions. This work has been the subject of several comprehensive reviews[13–18,39–41] including recent accounts[15,21–23] that should be consulted for a thorough treatment of the mechanism, scope and applications of the [4 + 2] cycloaddition reactions of azabutadienes. Conjugated systems containing nitrogen characteristically are electron-deficient π-systems (Table 8) and exhibit an expected diminished Diels–Alder reactivity toward representative electron-deficient dienophiles and a modest Diels–Alder reactivity toward electron-rich dienophiles.

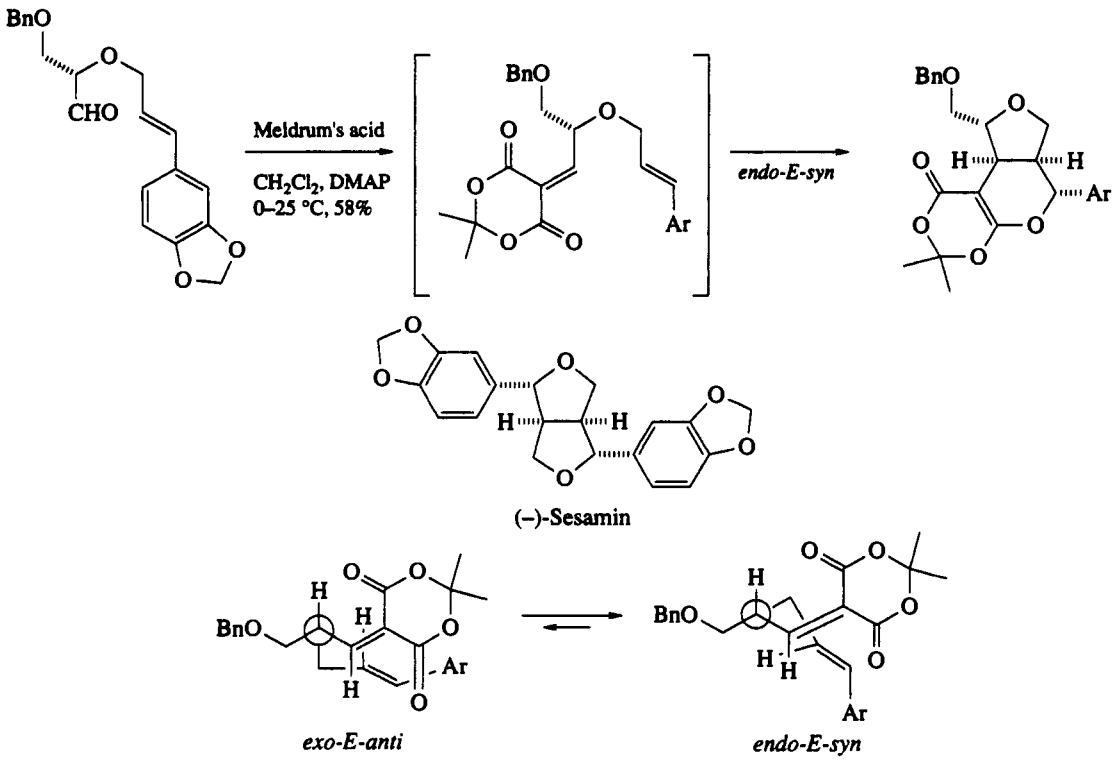


Deoxyloganin

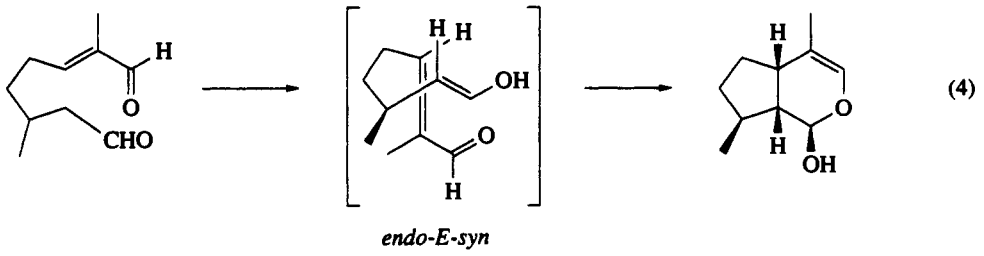
Scheme 7



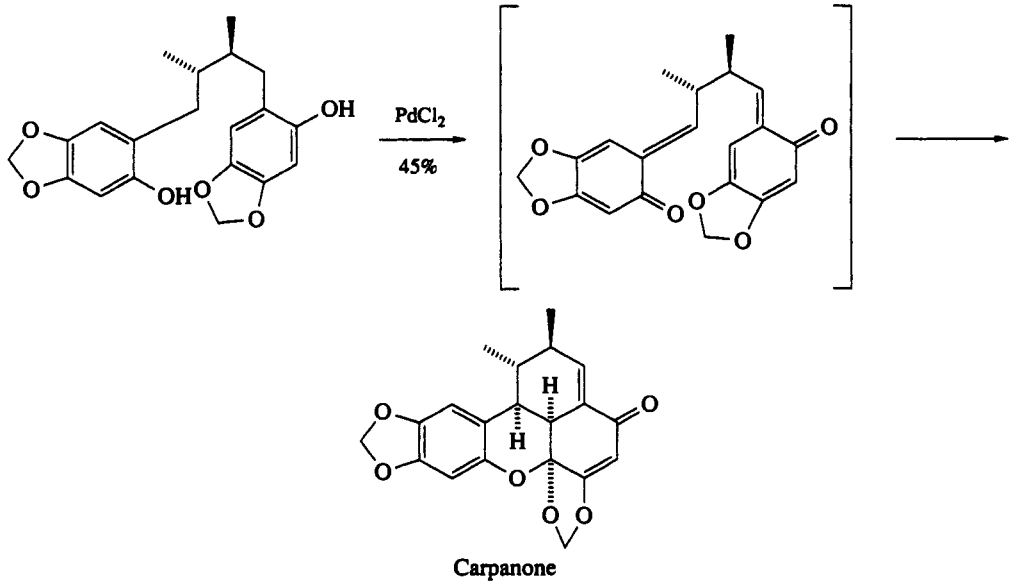
Scheme 8


BnO
CHO
Meldrum's acid
CH_2Cl_2, DMAP
0–25 °C, 58%
Ar
endo-E-syn
(–)-Sesamin
exo-E-anti
endo-E-syn

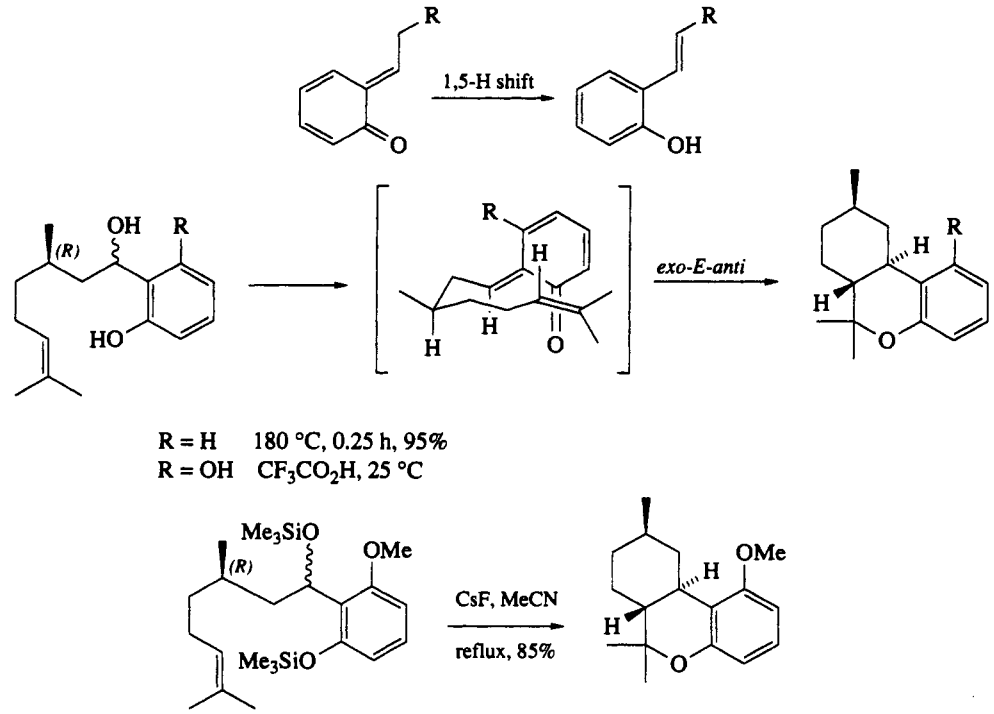
Scheme 9


CHO
OH
endo-E-syn

(4)


OH
$PdCl_2$
45%
Carpanone

(5)



Scheme 10

4.3.4.1 1-Aza-1,3-butadienes

α,β-Unsaturated imines, simple 1-aza-1,3-butadienes, participate in Diels–Alder reactions with typical electron-deficient dienophiles preferentially through their enamine tautomer;[149] in instances where tautomerization is not accessible, [2 + 2] cycloaddition usually intervenes (equation 7).[15] Consequently, the Diels–Alder 4π participation of simple α,β-unsaturated imines rarely is observed and typically suffers low conversions, competitive imine addition, and/or imine tautomerization precluding [4 + 2] cycloaddition. A limited number of 1-aza-1,3-butadiene structural variations and modified reaction conditions have been introduced that have permitted the productive 4π participation of 1-aza-1,3-butadienes in [4 + 2] cycloaddition reactions and include the intramolecular [4 + 2] cycloaddition reactions of *in situ* generated *N*-acyl-1-aza-1,3-butadienes[150] and *in situ* generated *o*-quinomethide imines,[151] the $HOMO_{diene}$-controlled Diels–Alder reactions of α,β-unsaturated *N,N*-dimethylhydrazones,[152,153] the Lewis acid-catalyzed intramolecular [4 + 2] cycloaddition reactions of *in situ* generated 2-*t*-butyldimethylsilyloxy- and 2-trimethylsilyloxy-1-aza-1,3-butadienes,[154] and the recently detailed general 4π participation of α,β-unsaturated *N*-phenylsulfonylimines in $LUMO_{diene}$-controlled Diels–Alder reactions.[155] Table 9 summarizes recent descriptions of the use of 1-aza-1,3-butadienes in [4 + 2] cycloaddition reactions.

The complementary N-1 or C-3 substitution of an α,β-unsaturated imine with an electron-withdrawing substituent accentuates the electron-deficient nature of the 1-aza-1,3-butadiene (Table 10), accelerates the rate of its [4 + 2] cycloaddition reaction with electron-rich dienophiles in $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions through substantial lowering of the 1-aza-1,3-butadiene E_{LUMO}, maintains the expected regioselectivity of the cycloaddition reaction, and enhances the *endo* selectivity of the cycloaddition reaction through a substantial increase in the LUMO C-2 coefficient. In addition, a bulky electron-withdrawing N-1 azabutadiene substituent preferentially decelerates 1,2-imine addition relative to [4 + 2] cycloaddition and conveys [4 + 2] cycloaddition product stability to the reaction conditions (deactivated enamine) while enhancing the electron-deficient nature of the diene. These expectations have been realized in the [4 + 2] cycloaddition reactions of *N*-phenylsulfonyl-1-aza-1,3-butadienes in which: (1) the Diels–Alder reactions have been shown to proceed predominately if not exclusively (≥ 95%) through an *endo* transition state (Figure 5); (2) there is full preservation of the dienophile alkene geometry; (3) the cycloaddition rate exhibits little solvent dependency; (4) *trans*-1,2-disubstituted dienophiles react more rapidly than *cis*-1,2-disubstituted dienophiles [$k(E)/k(Z)$ = 6–13 for (*E*)- and (*Z*)-1-ethoxypropene]; and (5) the diastereoselectivity of the reaction increases as the pressure of the reaction is increased and the re-

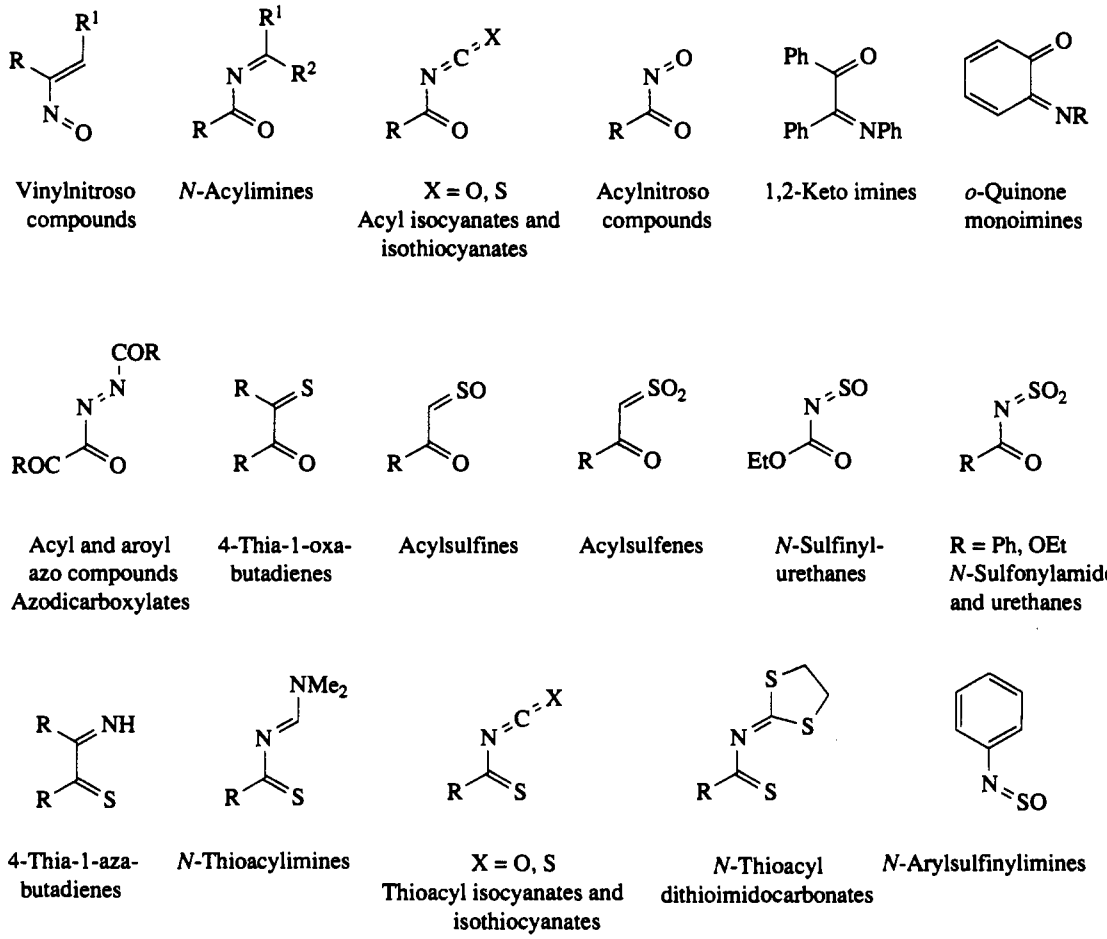
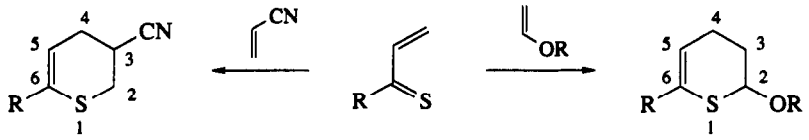


Figure 4



(6)

action temperature is decreased.[155,156] The observations are consistent with the 4π participation of the *N*-phenylsulfonyl-1-aza-1,3-butadiene in a concerted $LUMO_{diene}$-controlled Diels–Alder reaction (Scheme 11). *N*-Phenylsulfonyl aldimines (R^1 = H) have proven more reactive than *N*-phenylsulfonyl ketimines (R^1 = Me > R^1 = Ph), the complementary addition of a C-3 electron-withdrawing substituent ($R^2 = CO_2R$ >> R^2 = H) further accelerates the *N*-phenylsulfonyl-1-aza-1,3-butadiene participation in the $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction, and the observations have been successfully extended to include α,β-unsaturated *N*-phenylsulfonylimines that exist preferentially in the extended (*s*-*E*)-diene conformation.[155]

Similarly, the noncomplementary addition of a C-2 electron-withdrawing substituent to the *N*-phenylsulfonyl-1-aza-1,3-butadiene substantially lowers the 1-aza-1,3-butadiene E_{LUMO} (Table 10), accelerates its 4π participation in a $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction, maintains the expected regioselectivity of the cycloaddition reaction, and potentially enhances the *endo* diastereoselectivity of the [4 + 2] cycloaddition reactions through the introduction of a substantial increase in the magnitude of the LUMO C-2 coefficient (Table 10; equation 8).[157,158]

Table 7 Representative [4 + 2] Cycloaddition Reactions of Thiabutadienes

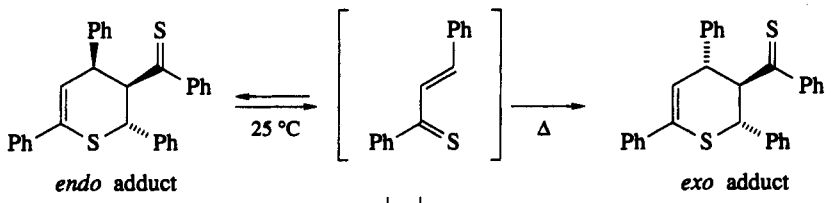
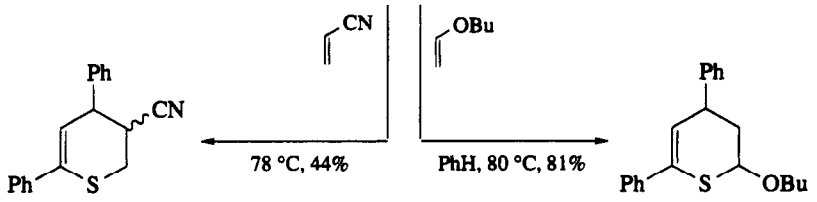
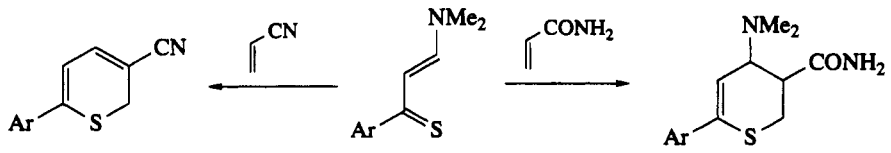
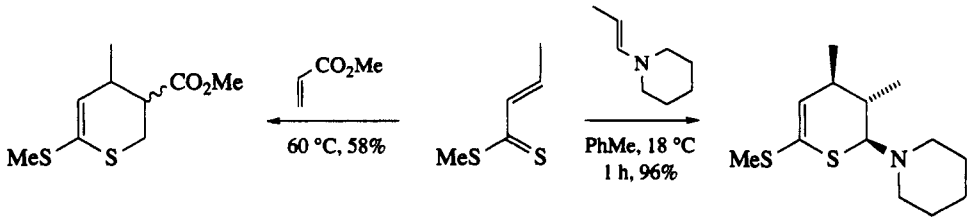
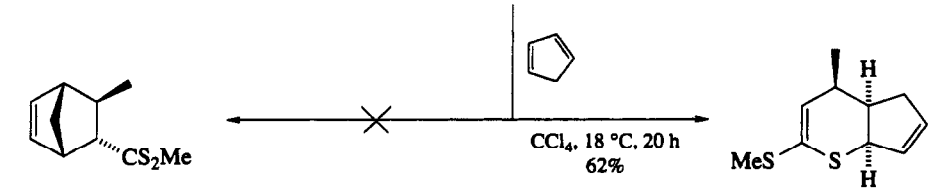
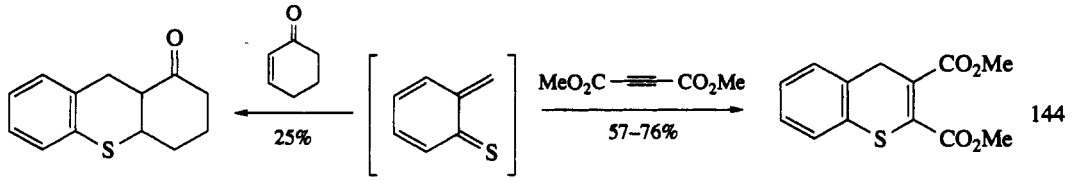
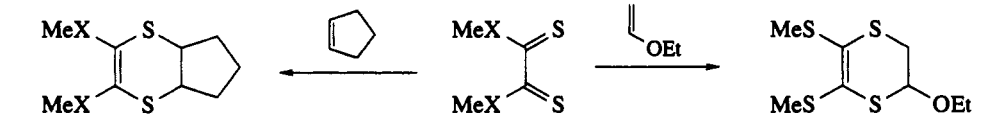
Diels–Alder reaction	*Ref.*
 *endo* adduct *exo* adduct	139
	140, 141
	142
	143
	
	144
 X = O, 67%, 3 days, 43 °C X = S, 95%, 3 days, 25 °C X = S, neat, 30 min, 25 °C 95%	145, 146

Table 7 *(continued)*

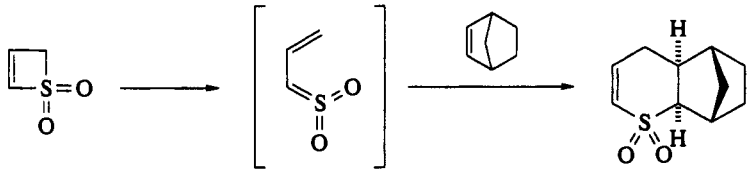
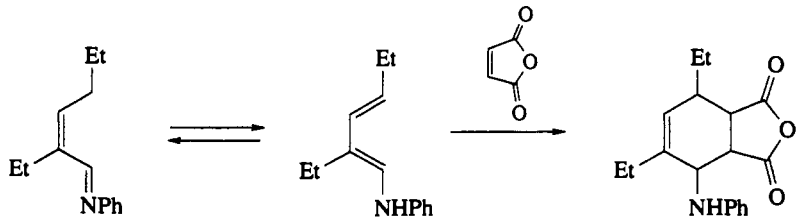
Diels–Alder reaction	*Ref.*
	147

Table 8 Theoretical Highest Occupied π Orbital (HOMO) and Lowest Unoccupied π Orbital (LUMO) of the Fundamental Aza-1,3-butadienes[a]

Azadiene	*E*(eV)	*Coefficients*			
$H_2C{=}CH{-}CH{=}NH$		*N-1*	*C-2*	*C-3*	*C-4*
LUMO	0.4	0.50	–0.45	–0.43	0.60
HOMO	–10.1	0.46	0.24	–0.59	–0.62
$H_2C{=}CH{-}CH{=}NH_2^+$					
LUMO	–6.3	0.47	–0.70	–0.11	0.53
HOMO	–15.9	0.41	0.05	–0.70	–0.59
$H_2C{=}CH{-}N{=}CH_2$		*C-1*	*N-2*	*C-3*	*C-4*
LUMO	0.3	0.58	–0.38	–0.43	0.56
HOMO	–9.8	0.36	0.41	–0.49	–0.62
$H_2C{=}CH{-}\overset{+}{N}H{=}CH_2$					
LUMO	–6.2	0.78	–0.49	–0.11	0.38
HOMO	–15.5	0.35	0.22	–0.66	–0.63
$H_2C{=}N{-}CH{=}NH$		*N-1*	*C-2*	*N-3*	*C-4*
LUMO	0.1	0.51	–0.46	–0.38	0.62
HOMO	–11.1	0.62	0.40	–0.45	–0.49
$H_2C{=}N{-}N{=}CH_2$		*C-1*	*N-2*	*N-3*	*C-4*
LUMO	0.8	0.52	–0.43	–0.43	0.52
HOMO	–12.4	0.45	0.44	–0.44	–0.45
$HN{=}CH{-}CH{=}NH$		*N-1*	*C-2*	*C-3*	*N-4*
LUMO	0.2	0.52	–0.37	–0.37	0.52
HOMO	–11.5	0.57	0.41	–0.44	–0.56
$HN{=}N{-}CH{=}CH_2$		*N-1*	*N-2*	*C-3*	*C-4*
LUMO	–0.1	0.55	–0.44	–0.40	0.60
HOMO	–10.5	0.38	0.17	–0.63	–0.66
$HN{=}N{-}N{=}CH_2$		*N-1*	*N-2*	*N-3*	*C-4*
LUMO	0.2	0.54	–0.49	–0.38	0.53
HOMO	–12.4	0.46	0.33	–0.60	–0.55
$HN{=}N{-}CH{=}NH$		*N-1*	*N-2*	*C-3*	*N-4*
LUMO	0.1	0.42	–0.50	–0.40	0.45
HOMO	–12.2	0.60	0.62	–0.57	–0.65
$HN{=}N{-}N{=}NH$		*N-1*	*N-2*	*N-3*	*N-4*
LUMO	0.0	0.52	–0.46	–0.46	0.52
HOMO	–13.6	0.52	0.44	–0.44	–0.52

[a]AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π-orbital.[148]



(7)

Table 9 Representative [4 + 2] Cycloaddition Reactions of 1-Aza-1,3-butadienes

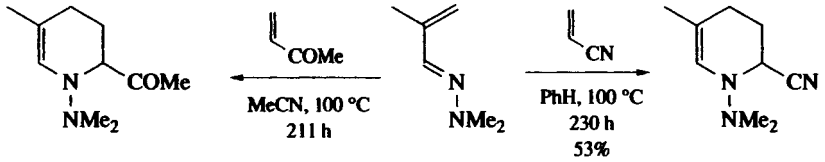
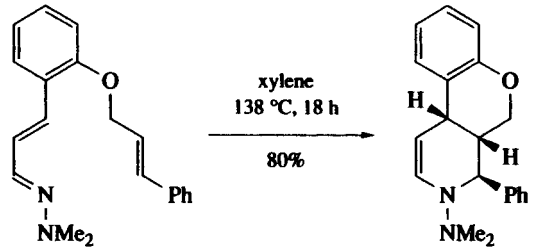
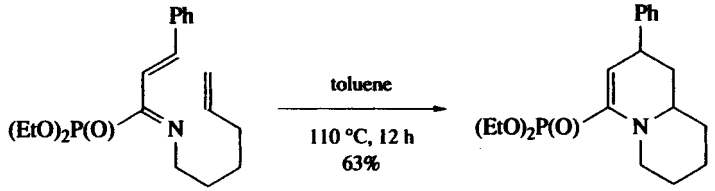
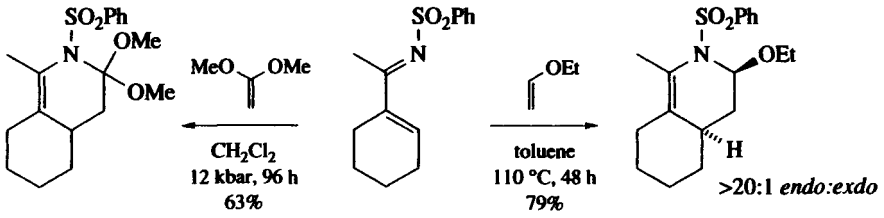
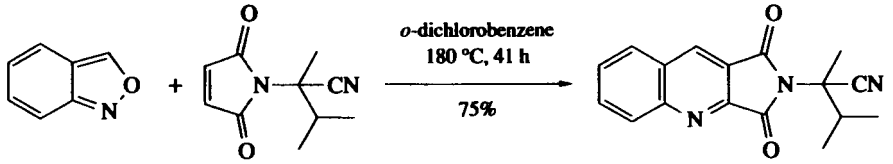
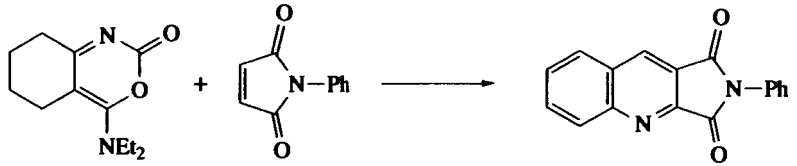
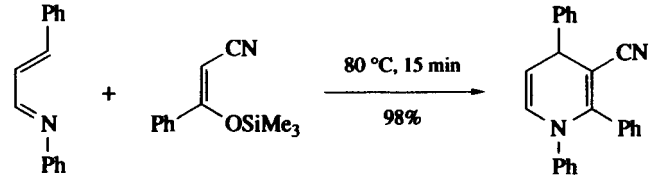
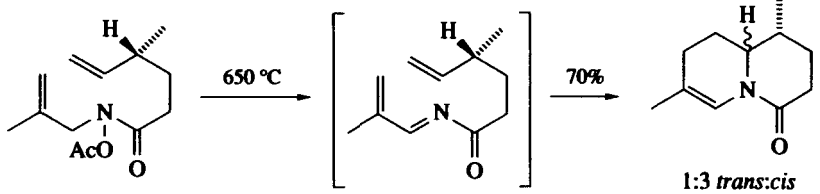
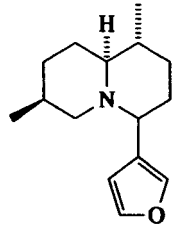
Diels–Alder reaction	*Ref. (application)*
	152, 153
	159
	160
	155

Table 9 *(continued)*

Diels–Alder reaction	*Ref. (application)*
	161, 162
	163
	164
 1:3 *trans*:*cis*	150



Deoxynupharidine

Table 9 *(continued)*

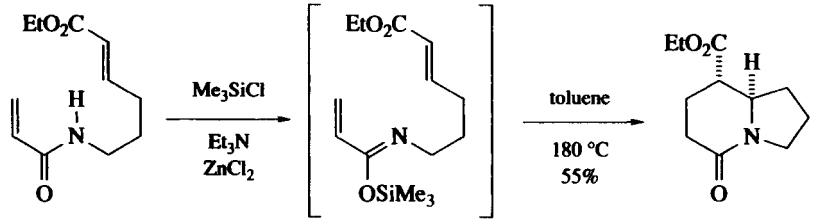
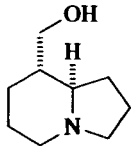
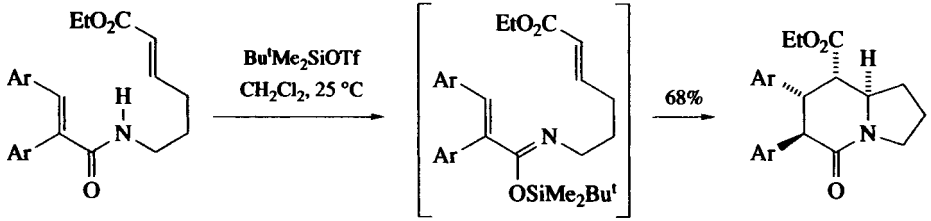
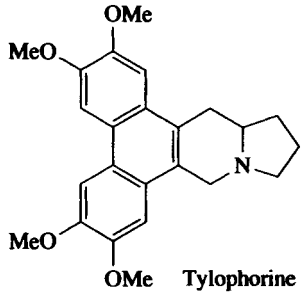
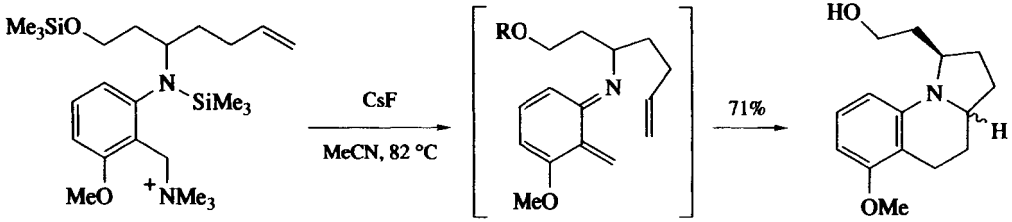
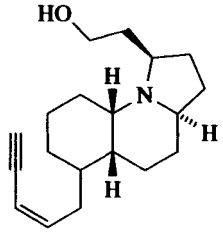
Diels–Alder reaction	*Ref. (application)*
	154  Epilupinine
	154  Tylophorine
 4:1 *cis*:*trans*	151  Gephyrotoxin

Table 10 1-Aza-1,3-butadiene Substituent Effects on the π HOMO and LUMO[a]

Azadiene	*E* (eV)	*Coefficients* N-1	C-2	C-3	C-4	
$H_2C{=}CH{-}CH{=}NH$						
LUMO	0.4	0.50	−0.45	−0.43	0.60	
HOMO	−10.1	0.46	0.24	−0.59	−0.62	
$H_2C{=}CH{-}CH{=}NSO_2Ph$						
LUMO	−0.9	0.50	−0.58	−0.30	0.53	
HOMO	−11.1	0.32	0.11	−0.47	−0.46	
$H_2C{=}C(CHO){-}CH{=}NSO_2Ph$						*CHO*
LUMO	−1.3	0.39	−0.37	−0.34	0.63	0.23
HOMO	−11.5	0.36	0.12	−0.52	−0.48	−0.10
$H_2C{=}CH{-}C(CO_2Me){=}NSO_2Ph$						*CO_2Me*
LUMO	−1.1	0.53	−0.60	−0.21	0.47	−0.10
HOMO	−11.2	0.32	0.12	−0.55	−0.55	0.05

[a]AM1, highest occupied (HOMO) and lowest unoccupied (LUMO) π orbital[148]

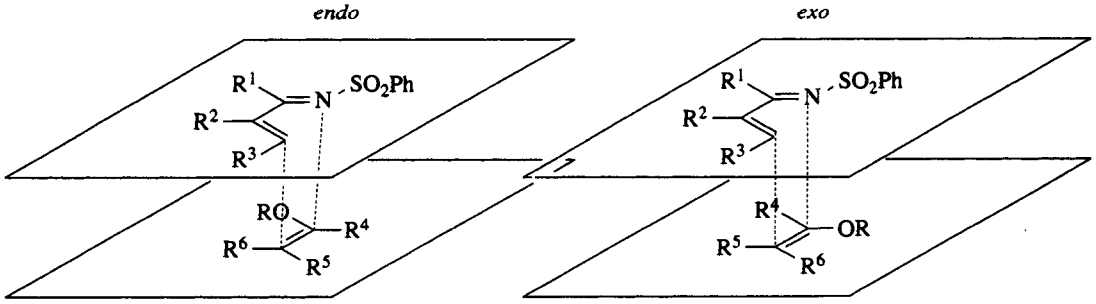
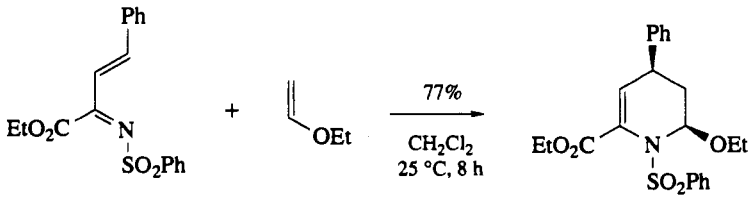


Figure 5



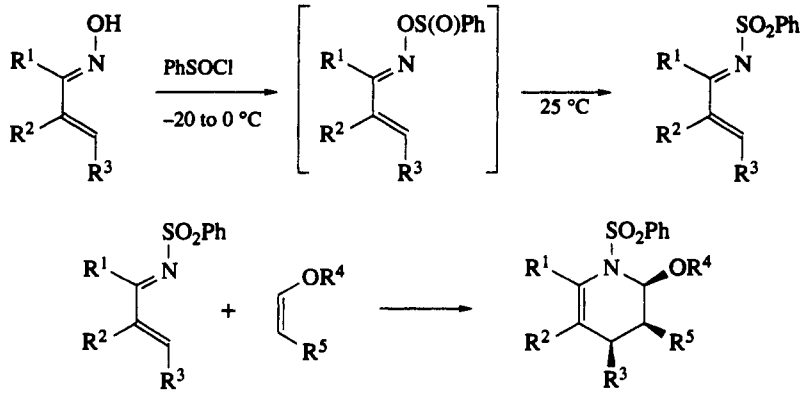
(8)

>20:1 *endo:exo*

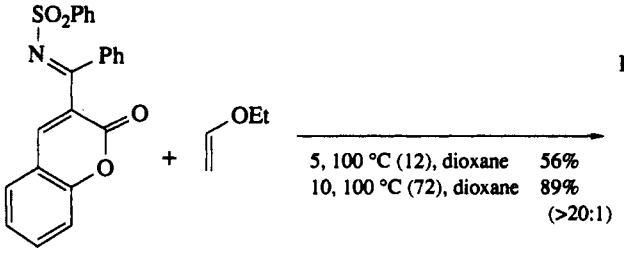
4.3.4.2 2-Aza-1,3-butadienes

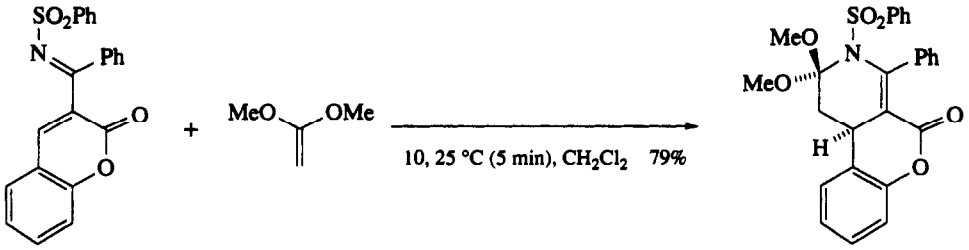
A select set of useful [4 + 2] cycloaddition reactions of simple 2-aza-1,3-butadienes have been detailed (Table 11),[170–176] and in most instances the 2-azadienes employed are substituted with strong electron-donating substituents responsible for enhancing its Diels–Alder reactivity toward electron-deficient dienophiles. The ease with which the 1,3-bis(t-butyldimethylsilyloxy)-2-aza-1,3-butadienes may be prepared from imides, and the demonstrated facility with which they participate in $HOMO_{diene}$-controlled [4 + 2] cycloaddition reactions, may prove exceptionally useful; their use constitutes the most general approach to implementing the 4π participation of 2-aza-1,3-butadienes (Scheme 12).[165–168] With the recent introduction of a convenient preparation of 3-trimethylsilyloxy-2-aza-1,3-butadienes, their comparable synthetic utility may be anticipated.[169]

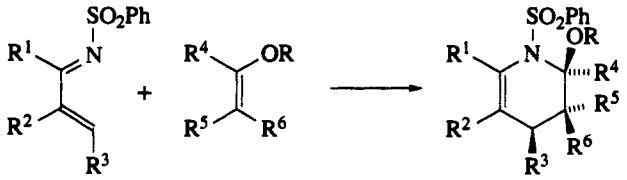
The protic acid and Lewis acid-catalyzed [4 + 2] cycloaddition reactions of electron-rich alkenes with imines derived from anilines and aryl aldehydes constitute an extensively explored class of 2-azadienes capable of providing the products of a formal Diels–Alder reaction (equation 9).[15,27,177] In a useful extension of these studies and in efforts to increase the rate of the 4π participation of simple 2-aza-1,3-butadienes in [4 + 2] cycloaddition reactions, Mariano and coworkers have examined the Lewis acid-catalyzed intermolecular reactions of (1*E*,3*E*)-1-phenyl-2-aza-1,3-pentadiene with electron-rich dienophiles, including enol ethers.[178] Reductive work-up of the cycloaddition reactions provided the pro-



R^1	R^2	R^3	R^4	R^5	*Equiv. of dienophile, temp. or pressure (time, h), solvent*	*% Yield (endo:exo)*
Me	H	H	Et	H	10, 60 °C (12), neat	73% (>20:1)
Me	H	Ph	Et	H	5, 12 kbar (80), CH_2Cl_2	69% (>20:1)
Ph	H	Ph	Et	H	5, 12 kbar (45), CH_2Cl_2	77% (>20:1)
H	H	Ph	Et	H	5, 12 kbar (45), CH_2Cl_2	72% (>20:1)
H	H	Ph	CH_2Ph	Me	5, 6 kbar (144), CH_2Cl_2	54% (>20:1)
H	Me	H	Et	H	5, 12 kbar (45), CH_2Cl_2	72% (>20:1)
					10, 40 °C (11), CH_2Cl_2	82% (>20:1)



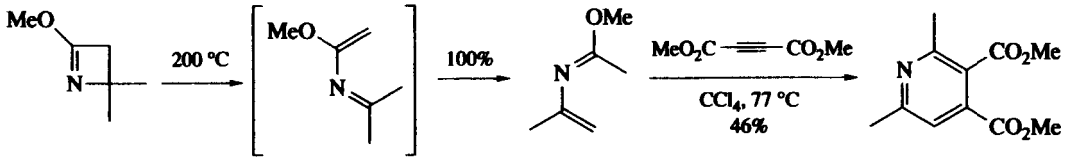
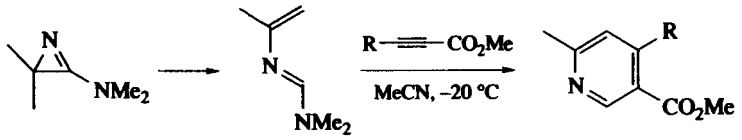
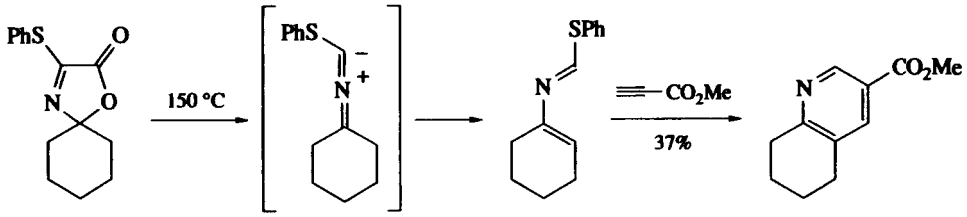
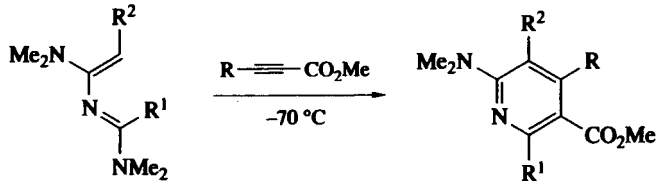




Scheme 11

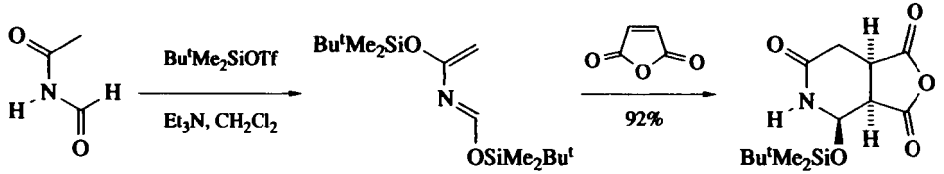
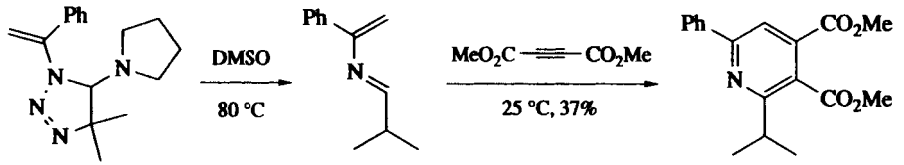
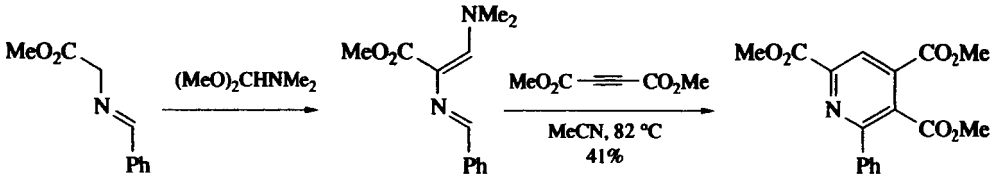
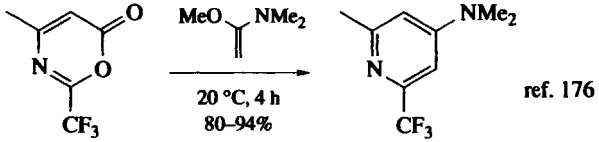
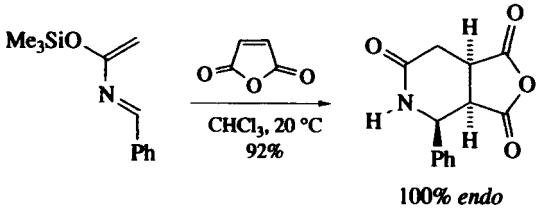
ducts of regio- and diastereo-selective [4 + 2] cycloaddition reactions derived from predominant cycloaddition through an *endo* transition state with full preservation of the dienophile and diene alkene geometries (equation 10). Although further studies are required to develop the scope of such reactions, the N-2 Lewis acid coordination or protic acid protonation of a 2-aza-1,3-butadiene would be expected to: (1) substantially lower the diene E_{LUMO} and thereby accelerate the rate of a $LUMO_{diene}$-controlled cycloaddition; (2) substantially increase the magnitude of LUMO N-2 coefficient and consequently enhance the

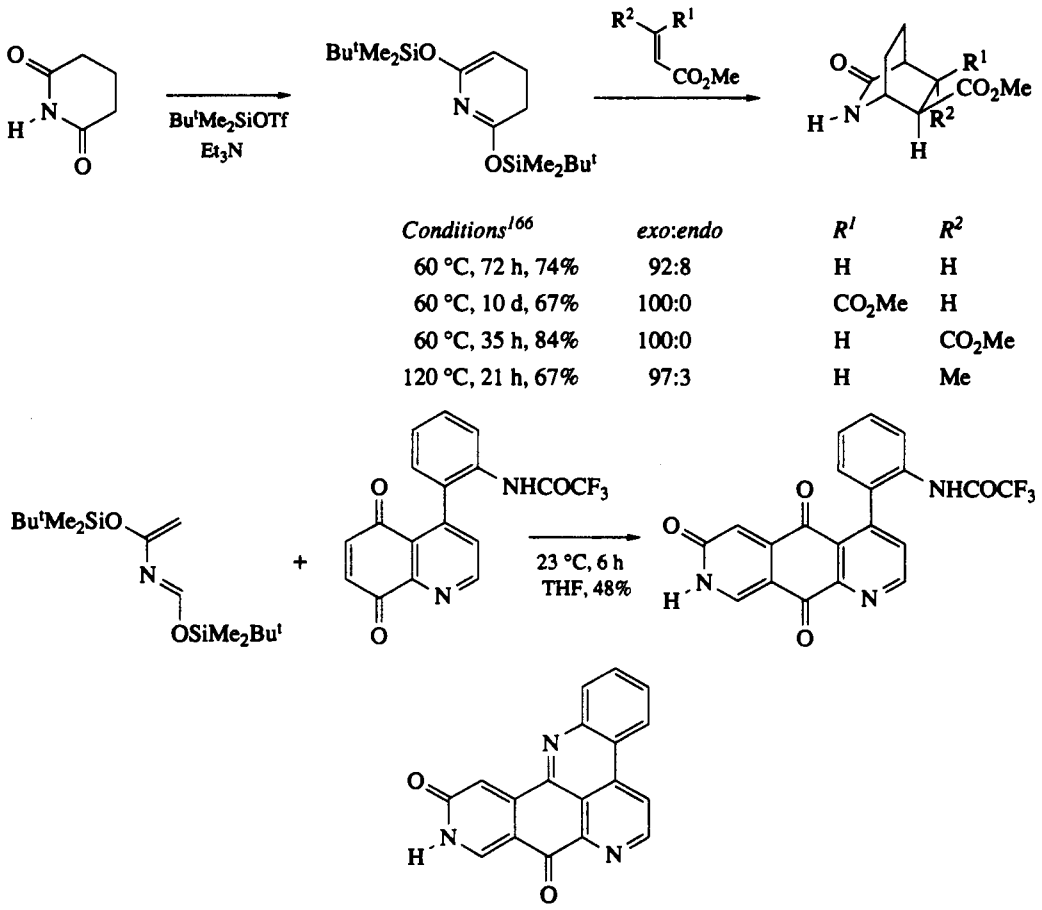
Table 11 Representative [4 + 2] Cycloaddition Reactions of 2-Aza-1,3-butadienes

Diels–Alder reaction	*Ref.*
	170
 R = H, 72%; R = CO_2Me, 57%	171
	172
	173

R^1	R^2	R	*Yield* (%)
H	H	CO_2Me	16
H	Ph	CO_2Me	50
H	Ph	H	29
Ph	H	H	12
Ph	H	CO_2Me	27

Table 11 *(continued)*

Diels–Alder reaction	*Ref.*
	165
	174
	175
 ref. 176	
 100% *endo*	169

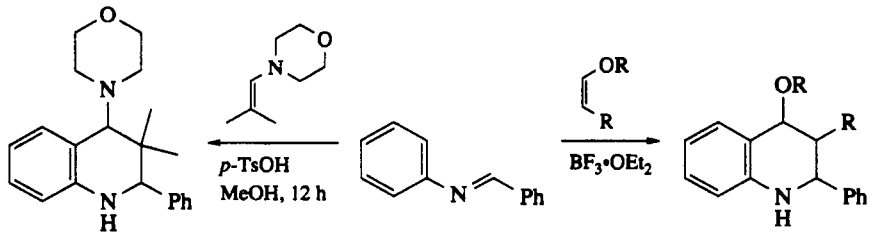


Conditions[166]	*exo:endo*	R^1	R^2
60 °C, 72 h, 74%	92:8	H	H
60 °C, 10 d, 67%	100:0	CO_2Me	H
60 °C, 35 h, 84%	100:0	H	CO_2Me
120 °C, 21 h, 67%	97:3	H	Me

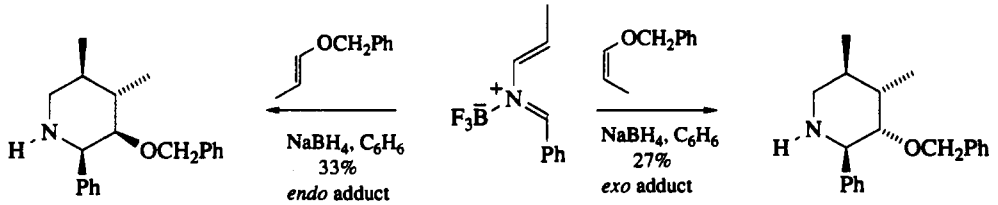
Amphimedine[167]

Scheme 12

endo diastereoselectivity; and (3) substantially increase the magnitude of the difference in the C-1/C-4 LUMO coefficients and thereby control the regioselectivity of the [4 + 2] cycloaddition reaction (*cf.* Table 8).[179] Additional discussion of this topic may be found in Section 4.3.6.1.



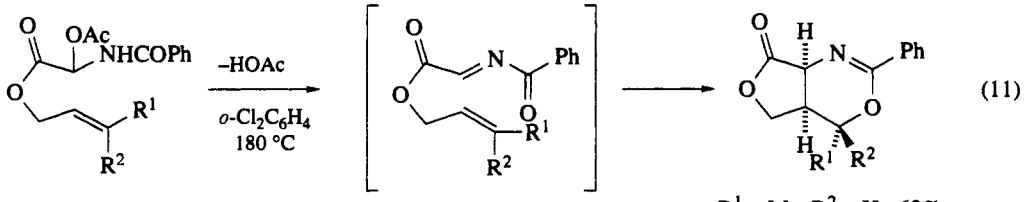
(9)



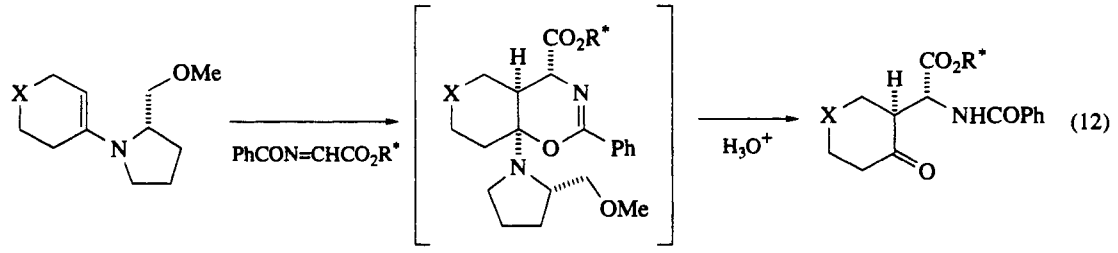
(10)

4.3.4.3 Hetero 2-Aza-1,3-butadienes

A wide range of hetero 2-aza-1,3-butadienes have been shown to participate as 4π components of Diels–Alder reactions (Figure 4). Perhaps the most widely recognized class of hetero 2-aza-1,3-butadienes is the *N*-acylimines (1-oxa-3-aza-1,3-butadiene)[15,24,39–43,180] and comprehensive reviews of their 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions are available. The recent disclosure of the 4π participation of *N*-acylimines in intramolecular [4 + 2] cycloaddition reactions (equation 11),[181] and the use of optically active *N*-acylimines in productive $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions, illustrate applications of the systems that have not been explored fully (equation 12).[182]

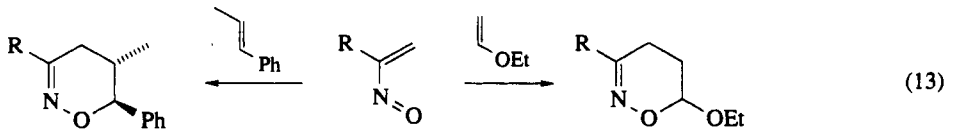


R^1 = Me, R^2 = H; 62%
R^1 = H, R^2 = Me; 75%



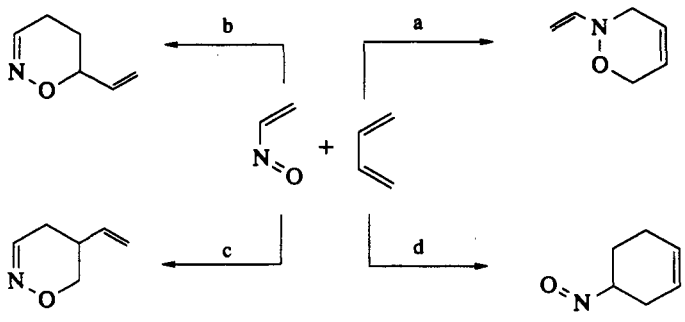
The Diels–Alder reactions of vinylnitroso compounds have been investigated extensively and they have been shown to participate productively as 4π components of $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions. The complementary C-3 substitution of the vinylnitroso compound with an electron-withdrawing substituent has proven sufficient to permit the observation of $LUMO_{diene}$-controlled Diels–Alder reactions with neutral dienophiles (equation 13).[183] In addition, vinylnitroso compounds may participate as 2π or 4π components in competitive [4 + 2] cycloadditions with typical dienes (Scheme 13). Experimentally it has been shown that vinylnitroso compounds possessing C-4 substituents react as 2π components in [4 + 2] cycloaddition reactions with dienes (path a) and that vinylnitroso compounds lacking C-4 substituents react as 4π components in [4 + 2] cycloaddition reactions with dienes (path b). To date, the potential that the 4π participation of vinylnitroso compounds in Diels–Alder reactions with dienes (path b) may be derived from the all-carbon Diels–Alder reaction (path d), followed by 3,3-sigmatropic rearrangement to the oxazine product, has not received experimental verification.

Similarly, acylnitroso compounds are recognized for their 2π participation in Diels–Alder reactions with dienes and these observations have found substantial application (Chapter 4.2). In addition, recent efforts have detailed the apparent 4π participation of an acylnitroso compound in a Diels–Alder reaction with a cyclopentadiene that suggests their potentially useful 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions (equation 14).[184]

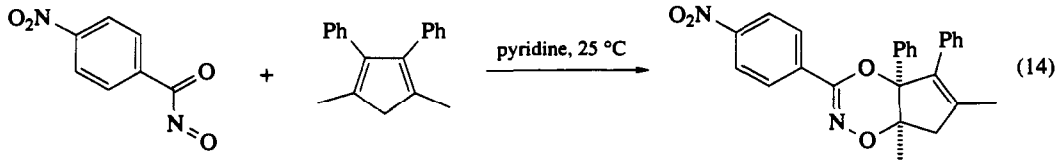


R = Ph; 26%
R = CO_2Et; 43%

R = Ph; 87%
R = CO_2Et; 82%



Scheme 13



(14)

4.3.4.4 1,2-Diaza-1,3-butadienes

Electron-deficient azoalkenes, 1,2-diaza-1,3-butadienes, participate as 4π components in regiospecific $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions with selected dienes or electron-rich and selected simple alkene dienophiles. The reactions studied in detail exhibit no rate dependency on the solvent polarity, proceed predominantly through an *endo* transition state, and have been suggested to represent concerted [4 + 2] cycloaddition reactions.[185] Table 12 summarizes representative examples of the inter- and intra-molecular [4 + 2] cycloaddition reactions of 1,2-diaza-1,3-butadienes.

4.3.4.5 Hetero 1,2-Diaza-1,3-butadienes

Azodicarboxylates are recognized for their ability to participate as 2π components of $HOMO_{diene}$-controlled Diels–Alder reactions with dienes and for their participation in ene reactions with reactive alkenes.[15,189] In addition, electron-rich or reactive simple alkenes that do not contain a reactive allylic hydrogen atom have been shown to participate in competitive [2 + 2] and [4 + 2] cycloaddition reactions with azodicarboxylates in which the observed course of the reaction is dependent upon the solvent polarity and nucleophilic character of the alkene (Table 13). As may be anticipated, alkoxycarbonylaroyldiimides (**4**), diaroyldiimides (**5**), and arylaroyldiimides (**6**) participate with increasing selectivity as 4π components of [4 + 2] cycloaddition reactions.

4.3.4.6 1,3-Diaza-1,3-butadienes

A surprisingly small group of 1,3-diaza-1,3-butadienes have been shown to participate in [4 + 2] cycloaddition reactions and the lack of additional efforts reflects the current difficulty in securing stable 1,3-diaza-1,3-butadienes for study (Table 12).

4.3.4.7 1,4-Diaza-1,3-butadienes

A select group of 1,4-diaza-1,3-butadienes have been demonstrated to participate as 4π components of Diels–Alder reactions (Table 12). Perhaps the most successful system described to date is the $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction of diiminosuccinonitrile, a 1,4-diaza-1,3-butadiene substituted with C-2 and C-3 electron-withdrawing groups, with electron-rich dienophiles (equation 15).[196] A common and competitive reaction of the α-diimines is [2 + 2] cycloaddition to afford azetidine cycloaddition products and many of the early reports of the [4 + 2] cycloaddition reactions are incorrect.

Table 12 Representative [4 + 2] Cycloaddition Reactions of Diaza-1,3-butadienes

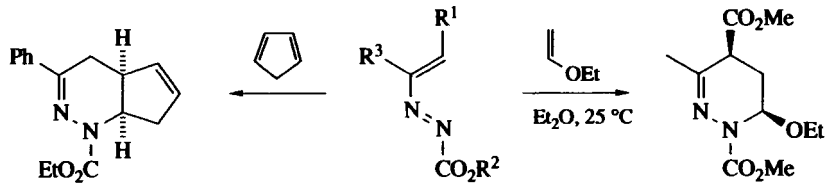
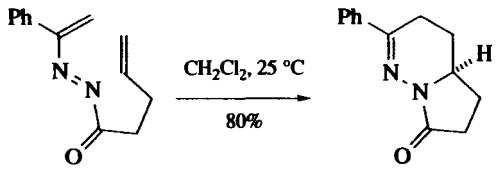
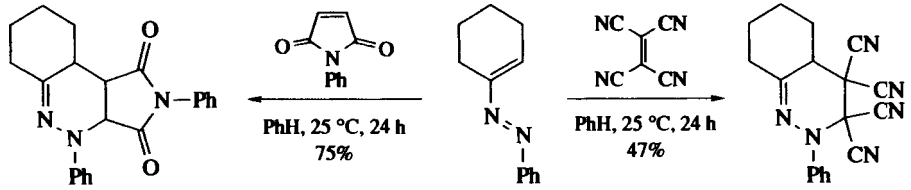
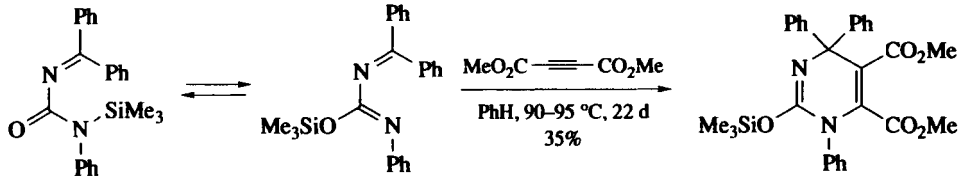
Diels–Alder reaction	*Ref.*
	185, 186
R^1 = H, R^2 = Et, R^3 = Ph; 96%	R^1 = CO_2Me, R^2 = Me, R^3 = Me; 70%
	187
	188
	193

Table 12 *(continued)*

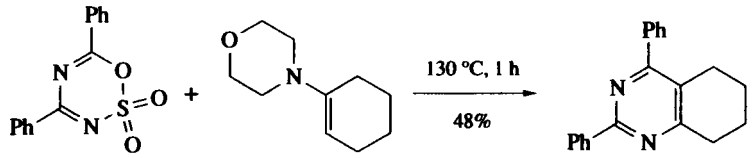
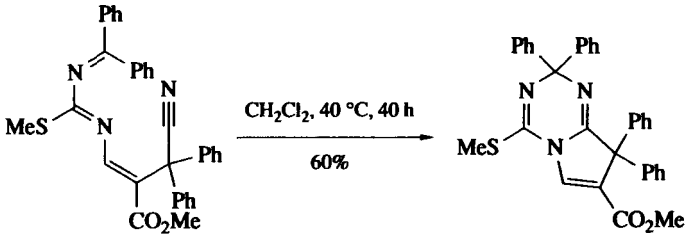
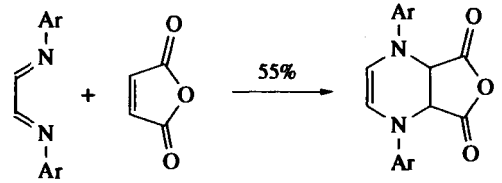
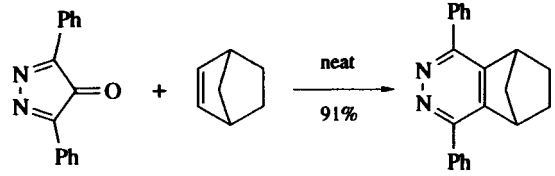
Diels–Alder reaction	*Ref.*
	194
	195
 Ar = 4-$MeOC_6H_4$	197
	198

Table 12 *(continued)*

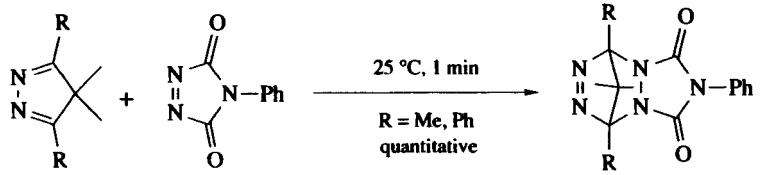
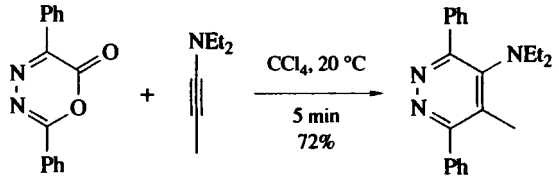
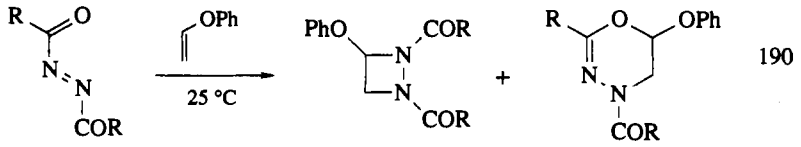
Diels–Alder reaction	*Ref.*
	199
	200

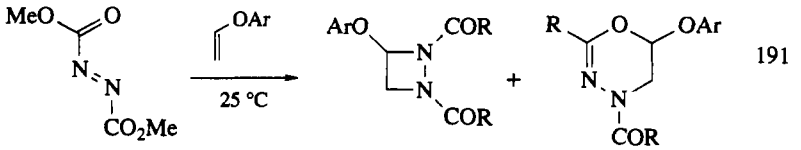
Table 13

Diels–Alder reaction	*Ref. (application)*



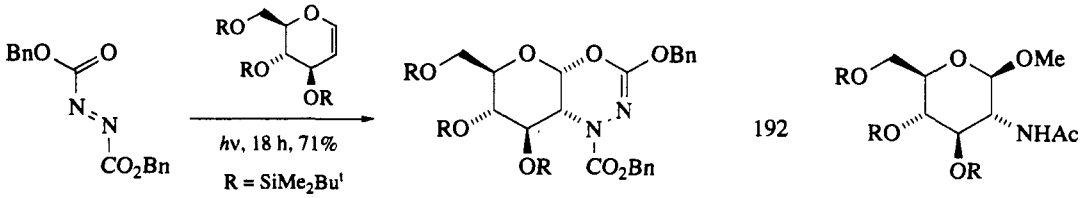
190

R	*Solvent*	*Yield (%)*	*Product ratio*
OMe	neat	73	77:23
Ph	neat	66	<5:95
OMe	MeCN	—	80:20
OMe	PhH	—	33:67



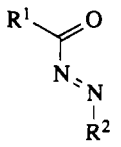
191

Ar	*Solvent*	*Yield (%)*	*Product ratio*
Ph	neat	73	77:23
4-$NO_2C_6H_4$	neat	40	5:95

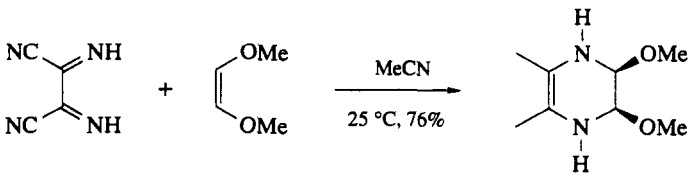


192

(4) R^1 = Ar, R^2 = OR
(5) $R^1 = R^2$ = Ar



(6) $R^1 = R^2$ = Ar



(15)

4.3.4.8 2,3-Diaza-1,3-butadienes

The examples of 2,3-diaza-1,3-butadienes participating as 4π components of Diels–Alder reactions are rare, and each successful case constitutes the reaction of a cyclic diene confined to an *s-Z* (cisoid) diene conformation (Table 12). Typical efforts to promote the Diels–Alder reactions of 2,3-diaza-1,3-butadienes provide simple imine addition products, *e.g.* 2:1 adducts, or [3 + 2] criss-cross products[26] that may be attributed to the strong preference for simple acyclic 2,3-diaza-1,3-butadienes to adopt an *s-E* (transoid) diene conformation.

4.3.5 HETEROAROMATIC AZADIENES

Since the initial demonstrations of the participation of substituted 1,2,4,5-tetrazines[201] and oxazoles[202,203] in [4 + 2] cycloaddition reactions with alkene and alkyne dienophiles, the investigation and application of the Diels–Alder reactions of heteroaromatic systems possessing reactive azadienes have been pursued extensively. A number of general reviews[15,21–23] have treated the spectrum of heteroaromatic azadienes that participate in [4 + 2] cycloaddition reactions and many of the individual heteroaromatic systems have been reviewed separately.[206,207] An extensive account was published recently and should be consulted for descriptions of the [4 + 2] cycloaddition reactions of the common heteroaromatic azadienes that have been observed to date.[15]

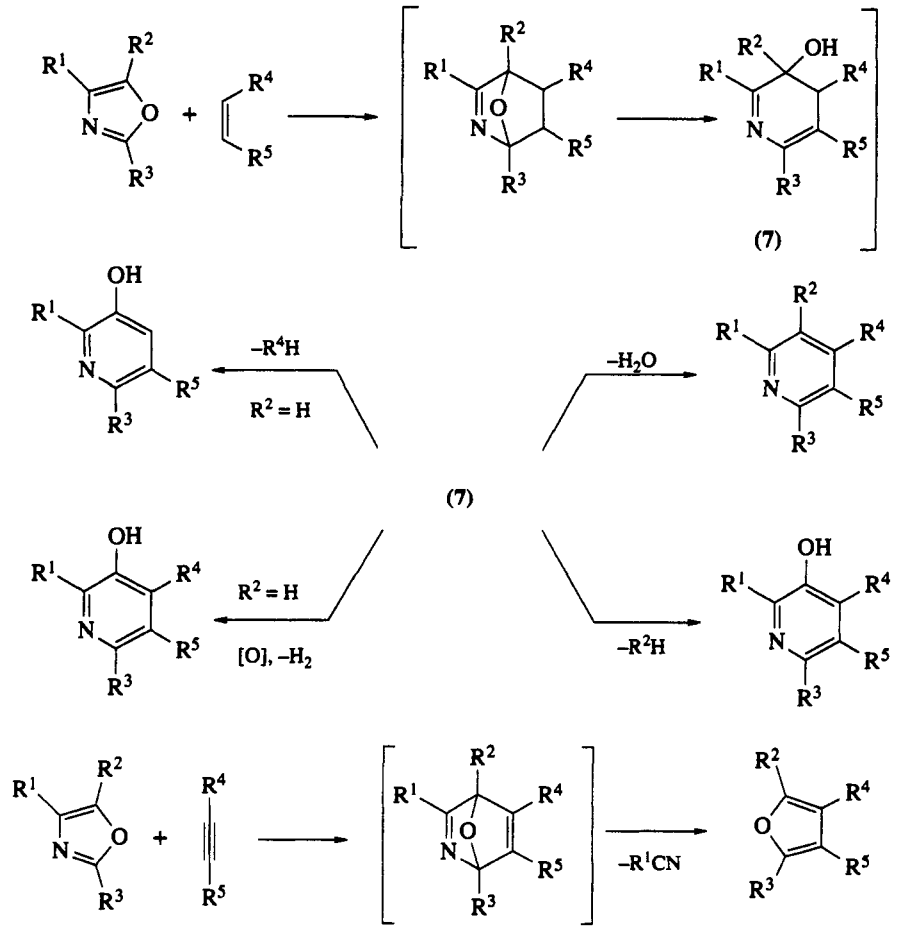
As with the simple heterodienes, the electron-deficient heteroaromatic azadienes have proven ideally suited for 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions. In fact, it was the recognition of this electron-deficient nature of heteroaromatic azadienes that led to the proposed[204] and demonstrated[205] rate acceleration that may accompany the reversal of the electronic properties of the Diels–Alder diene–dienophile partners and subsequently led to the full investigation of the $LUMO_{diene}$-controlled Diels–Alder reaction.

4.3.5.1 Five-membered Ring Heteroaromatic Azadienes

Oxazoles represent the most widely recognized heteroaromatic azadiene capable of [4 + 2] cycloaddition reactions.[206] The course of the oxazole Diels–Alder reaction and the facility with which it proceeds are dependent upon the dienophile structure (alkene, alkyne), the oxazole and dienophile substitution, and the reaction conditions. Alkene dienophiles provide pyridine products derived from fragmentation of the [4 + 2] cycloadducts which subsequently aromatize through a variety of reaction pathways to provide the substituted pyridines (Scheme 14). In comparison, alkyne dienophiles provide substituted furans that arise from the retro Diels–Alder reaction with loss of R^1CN from the initial [4 + 2] cycloadduct (Scheme 14).[15,206] Representative applications of the [4 + 2] cycloaddition reactions of oxazoles are summarized in Table 14. Selected examples of additional five-membered heteroaromatic azadienes participating in [4 + 2] cycloaddition reactions have been detailed and include the Diels–Alder reactions of thiazoles,[15,208] 1,3,4-oxadiazoles,[209] isoxazoles, pyrroles and imidazoles.[15]

4.3.5.2 Six-membered Ring Heteroaromatic Azadienes

Six-membered heteroaromatic azadienes, including pyridazines (1,2-diazines), pyrimidines (1,3-diazines), pyrazines (1,4-diazines), 1,2,3-triazines, 1,3,5-triazines, 1,2,4-triazines and 1,2,4,5-tetrazines, participate in characteristic $LUMO_{diene}$-controlled Diels–Alder reactions (Table 15), and this topic has been recently reviewed.[15] The regioselectivity and mode of the [4 + 2] cycloaddition reaction are dependent upon the heteroaromatic substitution pattern (electronic and steric substituent effects), the electronic and steric properties of the dienophile employed, as well as the reaction conditions. In most instances the proper selection of a matched diene–dienophile pair will permit the observation of a single cycloaddition product. The complementary substitution of the heteroaromatic azadiene with electron-withdrawing substituents accelerates its 4π participation in $LUMO_{diene}$-controlled Diels–Alder reactions, enhances or may control the observed regioselectivity of the [4 + 2] cycloaddition reaction, and in extreme cases will govern the mode of [4 + 2] cycloaddition, *e.g.* 1,2,4-triazine C-3/C-6 *versus* C-5/N-2 cycloaddition. The inherent reactivity of some heteroaromatic azadienes, *e.g.* 1,2,4,5-tetrazine and 1,3,5-triazine, or substitution of selected heteroaromatic azadienes with strong electron-donating substituents (OR, NR_2) are sufficient to overcome the characteristic electron-deficient nature of the heteroaromatic azadiene and permit the use of conventional electron-deficient dienophiles, presumably in $HOMO_{diene}$-controlled Diels–Alder



Scheme 14

reactions. In addition, the entropic assistance provided by the intramolecular Diels–Alder reaction has proven effective in promoting a number of heteroaromatic azadiene Diels–Alder reactions and selected examples of this widely used process may be found in the following schemes. Representative examples of the application of heteroaromatic azadiene Diels–Alder reactions include the total syntheses of streptonigrin (Scheme 15),[239] lavendamycin (Scheme 16),[240] OMP (Scheme 17),[238] prodigiosin (Scheme 18),[241] PDE-I, PDE-II and (+)-CC-1065 (Scheme 19),[242–244] pyrimidoblamic acid/bleomycin A_2 (Scheme 20),[245] actinidine (Scheme 21),[246] fabianine (Scheme 22),[247] guaipyridine (Scheme 23)[248] and DDATHF (Scheme 24)[249] and are summarized below.[22,23]

4.3.6 CATIONIC HETERODIENES, [4⁺ + 2] CYCLOADDITIONS

The past classification of the [4⁺ + 2] cycloaddition reactions involving the 4π participation of a cationic heterodiene among the 'polar' cycloadditions is derived not from an implied stepwise addition–cyclization reaction mechanism but was terminology introduced to distinguish cycloadditions employing cationic or anionic components from those employing dipolar or uncharged components.[29] Herein the reactions are simply referred to as [4⁺ + 2] cycloaddition reactions.

4.3.6.1 Cationic Azadienes

The preparation or *in situ* generation of azabutadienes bearing a formal positive charge, *i.e.* an immonium cation, provides a substantial enhancement of the electron-deficient character of the azadiene and in many instances such systems have proven to be effective 4π components in Diels–Alder reactions with electron-rich or neutral dienophiles. The most widely recognized class of cationic azadienes shown

Table 14 Representative [4 + 2] Cycloaddition Reactions of Oxazoles

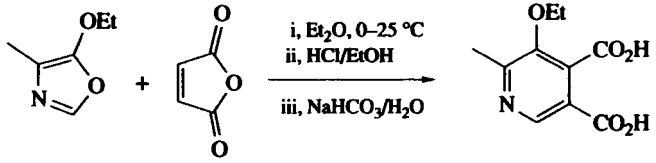
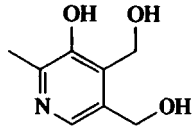
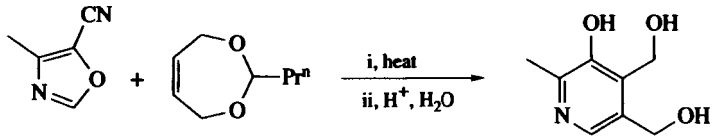
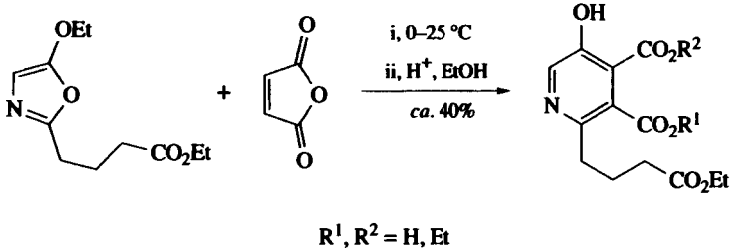
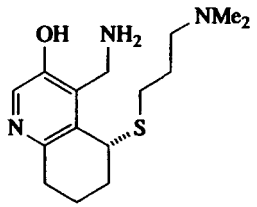
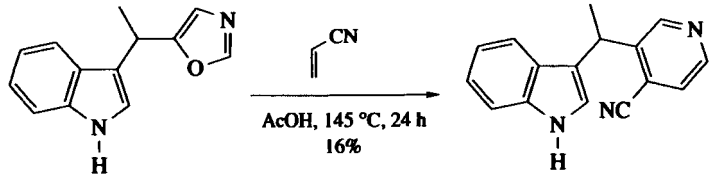
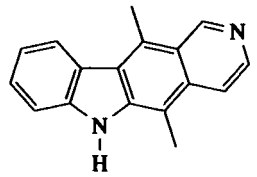
Diels–Alder reaction	*Application*	*Ref.*
	 Pyridoxol	210
	Pyridoxol	211
 R^1, R^2 = H, Et		212
	 Ellipticine	213

Table 14 *(continued)*

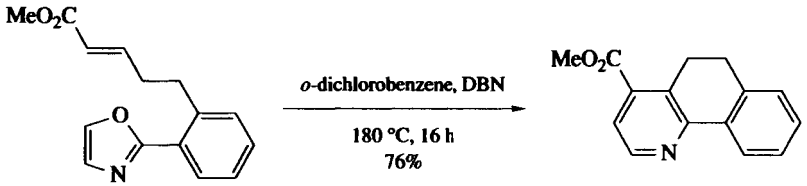
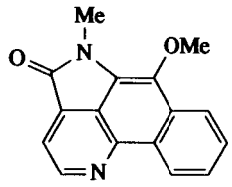
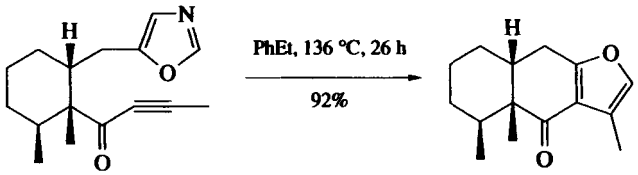
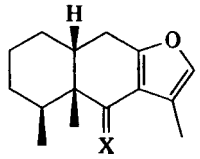
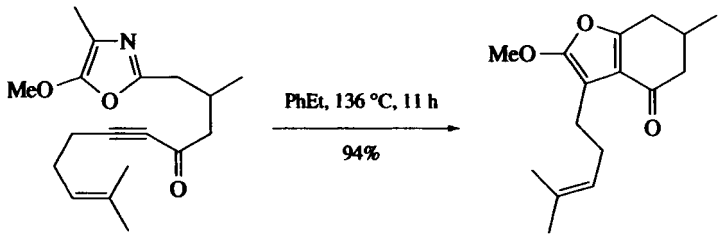
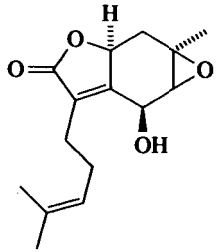
Diels–Alder reaction	*Application*	*Ref.*
	 Eupolauramine	214
	 X = O, Ligularone X = *cis* OH, H; Petasalbine	215 216
	 Paniculide-A	217

Table 14 *(continued)*

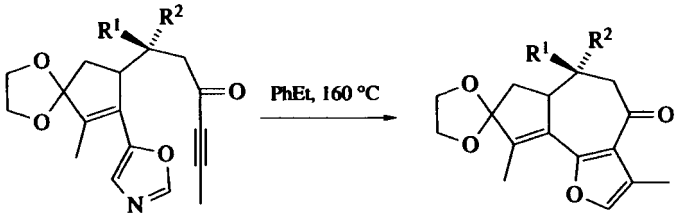
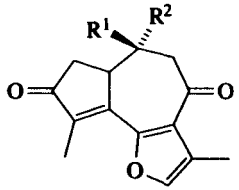
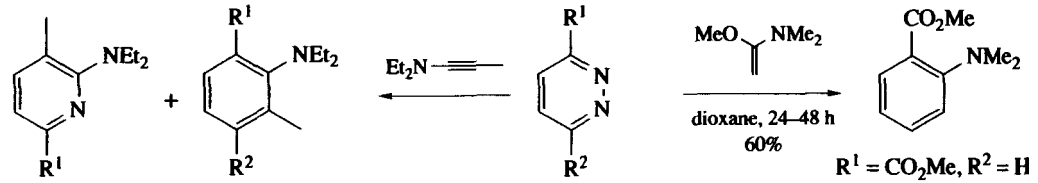
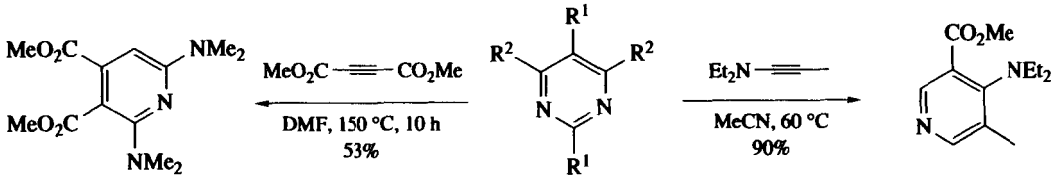
Diels–Alder reaction	*Application*	*Ref.*
		218
R^1 = Me, R^2 = H; 45% R^1 = H, R^2 = Me; 57%	Gnididione Isognididione	

Table 15 Representative [4 + 2] Cycloaddition Reactions of Six-membered Heteroaromatic Azadienes

Diels–Alder reaction					*Ref.*
1,2-Diazines (pyridazines)					
					219
		R^1	R^2		
23%	–	CO_2Me	H	xylene, 140 °C, 40 h	
–	75%	CO_2Me	CO_2Me	dioxane, 101 °C, 50 h	
1,3-Diazines (pyrimidines)					
					220, 221

$R^1 = H, R^2 = NMe_2$

$R^1 = CO_2Me, R^2 = H$

Table 15 *(continued)*

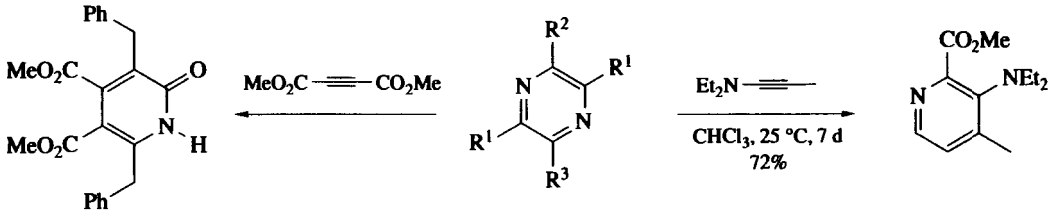
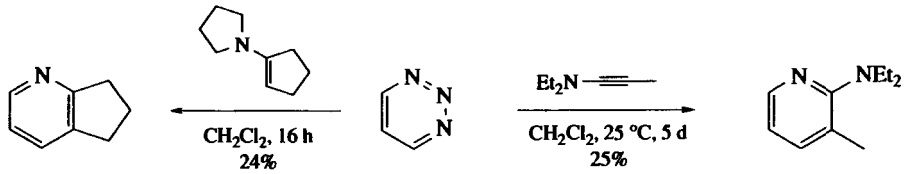
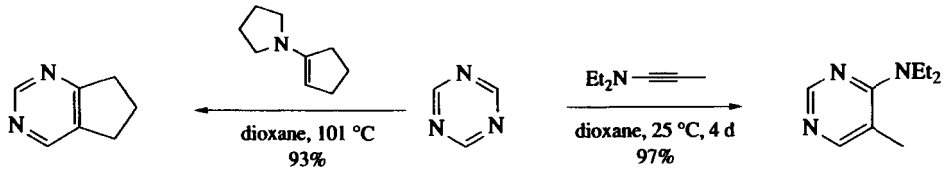
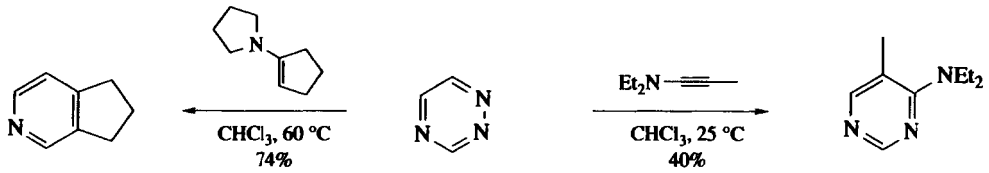
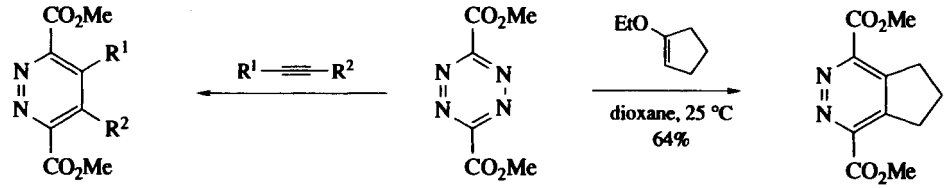
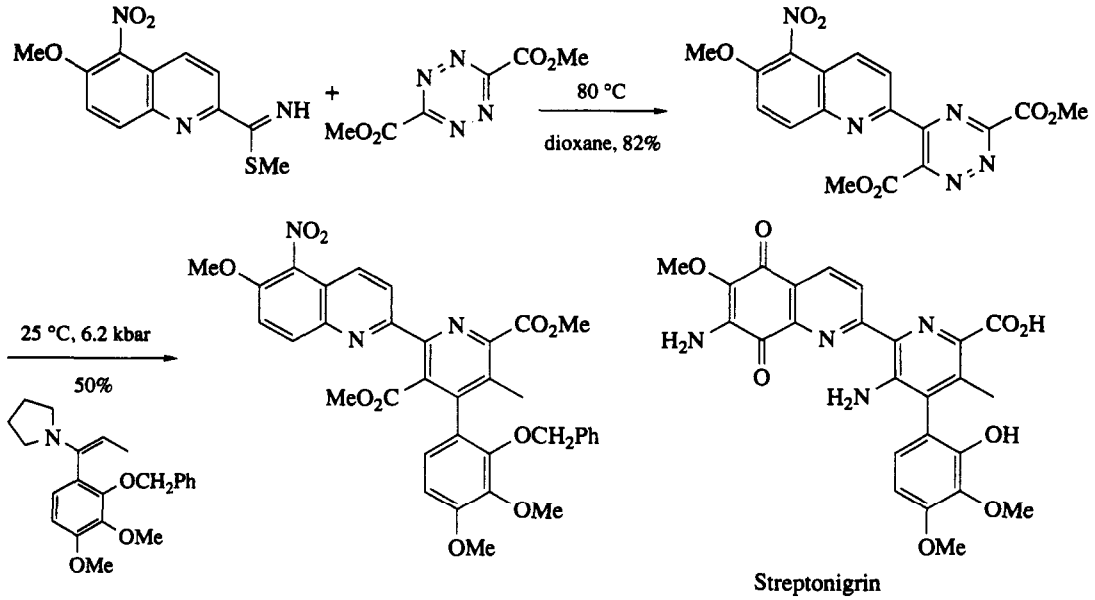
Diels–Alder reaction	*Ref.*
1,4-Diazines (pyrazines)	
	222, 223
$R^1 = OH, R^2 = R^3 = CH_2Ph$	$R^1 = CO_2Me, R^2 = R^3 = H$
1,2,3-Triazines	
	224, 225
1,3,5-Triazines	
	226, 227

Table 15 *(continued)*

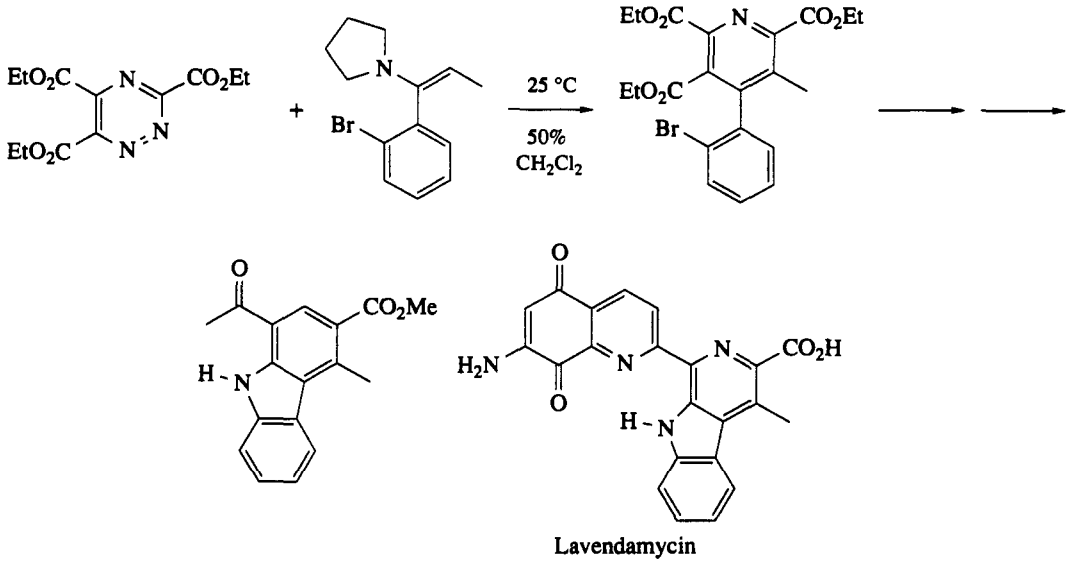
Diels–Alder reaction	*Ref.*
1,2,4-Triazines	
	228–235
1,2,4,5-Tetrazines	
	236–238

$R^1 = NEt_2$, $R^2 = Me$; 25 °C; 73%

$R^1 = R^2 = CO_2Me$; 140 °C; 53%

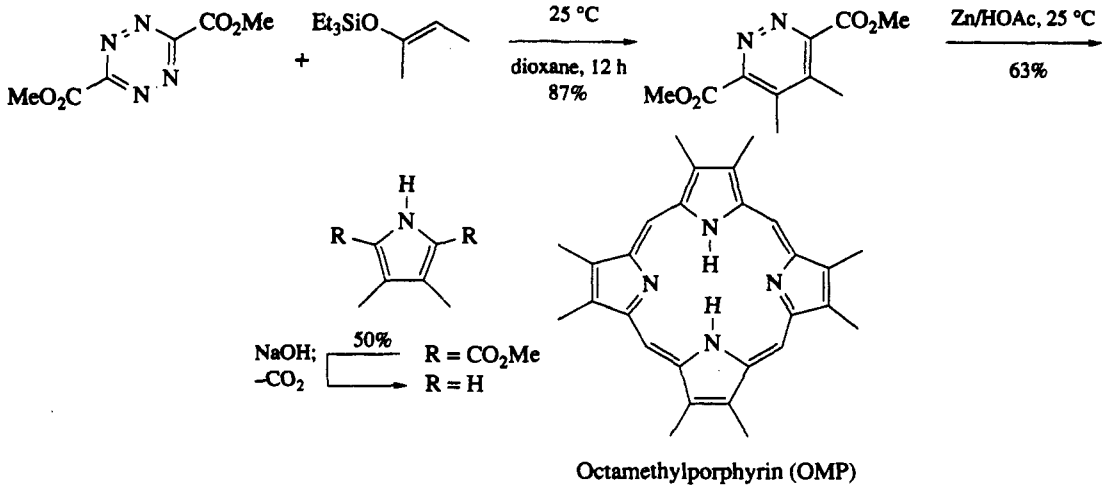


Scheme 15

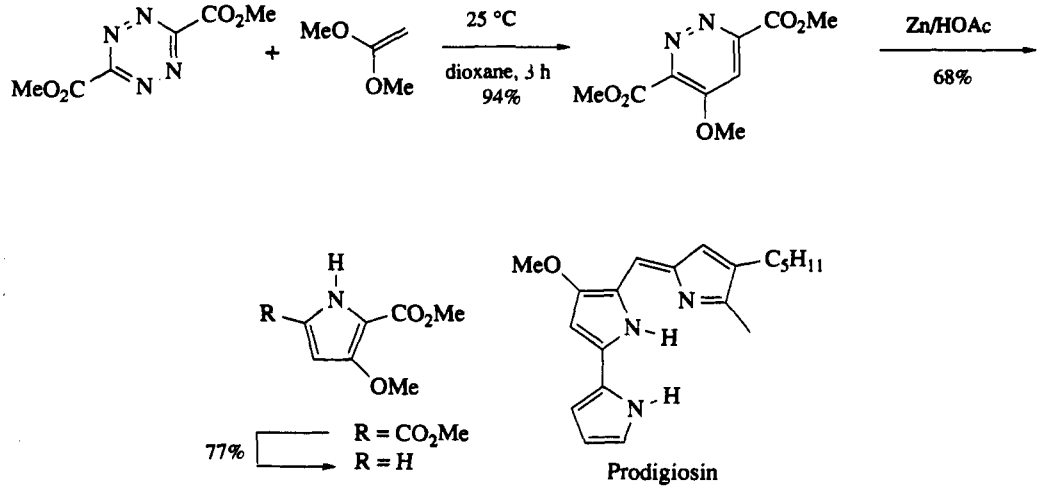


Scheme 16

to participate in effective [4⁺ + 2] cycloadditions is the heteroaromatic quaternary salts including the acridizinium and isoquinolinium cations.[15] The extensive studies of Bradsher and Fields and more recently Falck[250,251] and Franck[252] have been reviewed.[15,253–255] Nucleophilic alkenes including ketene acetals or enol ethers react at room temperature with the acridizinium or isoquinolinium cations but typical electron-deficient dienophiles require more vigorous reaction conditions (100–160 °C, 10–90 h) (Scheme 25). The reactions proceed with complete regiocontrol with the nucleophilic carbon of an electron-rich dienophile attaching to the expected aromatic quaternary salt electrophilic site (acridizinium C-6, isoquinolinium C-1). The rate of the reaction expectedly increases as the nucleophilic character of the dienophile is increased. The observed high diastereoselectivity may be best rationalized by developing electrostatic interactions at or *en route* to the transition state for the [4⁺ + 2] cycloaddition where dienophile electron-withdrawing substituents are found *cis* to the quaternary nitrogen in the cycloaddition products and dienophile electron-donating, alkyl or alkenyl substituents are found *trans* to the quaternary nitrogen, and the dienophile alkene geometry is maintained in the [4⁺ + 2] cycloaddition products. In addition, the recent interception of simple addition products, albeit under modified reaction conditions, and



Scheme 17



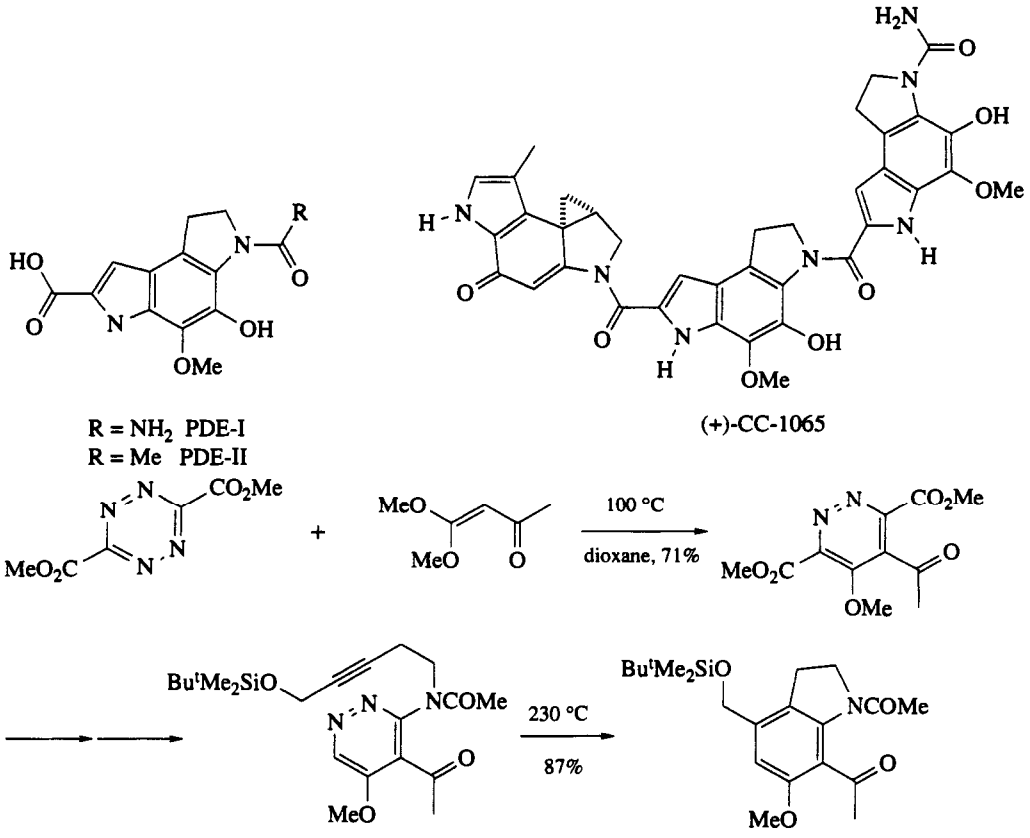
Scheme 18

their subsequent diastereoselective conversion to the observed [4⁺ + 2] cycloadducts[252] suggest the mechanism for the reaction may be represented as a stepwise addition–cyclization reaction in which the second bond formation need not proceed at a rate that exceeds that of simple bond rotation and in which electrostatic interactions control the regio- and diastereo-selectivity of the cycloaddition reaction.

The use of 2,4-dinitrophenyl aromatic quaternary salts prepared directly from the parent isoquinoline compound and 2,4-dinitrophenyl bromide or chloride enhances the electron-deficient nature of the isoquinolinium salts, accelerates the rate of their [4⁺ + 2] cycloaddition reactions with electron-rich alkenes, and has permitted the use of isoquinolinium salts previously regarded as unmanageable. The application of these observations in the total syntheses of methylarnottianamide and 14-epicorynoline is summarized in Scheme 26.[250,251]

The preparation of *N*-vinyl-2-ethoxypyrrolidinium tetrafluoroborate and its cycloaddition reactions with terminal alkenes, including electron-rich enol ethers, have been detailed. At present, the reported regioselectivity of this [4⁺ + 2] cycloaddition is not easily rationalized (equation 16).[256]

The acid-catalyzed or Lewis acid-catalyzed ($TiCl_4$, $BF_3{\cdot}OEt_2$; –78 °C) *in situ* generation of *N*-alkylarylimmonium ions in the presence of electron-rich or neutral alkenes has been shown to provide [4⁺ + 2] cycloadducts (*N*-methyltetrahydroquinolines) in excellent yields (Scheme 27).[257–260] More recent efforts have demonstrated that immonium ions derived from the condensation of aryl amines and aldehydes in the presence of cyclopentadiene participate as effective 4π components of [4⁺ + 2] cycloadditions and complement their demonstrated 2π participation in related [4 + 2⁺] cycloaddition reactions (Scheme 27).[261] Additional examples of the participation of cationic azadienes in [4⁺ + 2] cycloaddition reactions



Scheme 19

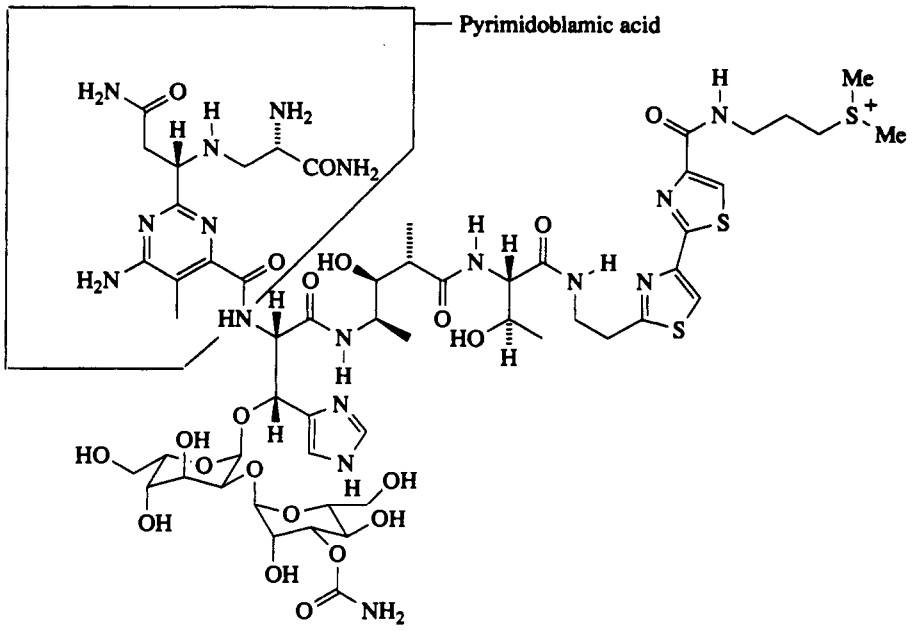
may be found in recent reviews[15,28] and within the discussion of the Lewis acid-catalyzed [4 + 2] cycloaddition reactions of azabutadienes (Section 4.3.4).

Two classes of cationic heteroazadienes have been shown to participate in effective [4⁺ + 2] cycloaddition reactions: (1) *N*-methyl-*N*-methylenium amide[262] cations and simple *N*-methylenium amides[263–267] and (2) vinyl nitrosonium cations[268–270] (Scheme 28). *N*-Methyl-*N*-methylenium cations and the simple *N*-methylenium benzamide cation have been shown to participate in regio- and stereo-specific [4⁺ + 2] cycloaddition reactions with a range of representative electron-rich, neutral or electron-deficient dienophiles in which the alkene geometry is maintained in the cycloaddition products. As noted by investigators in this area, the clean preservation of dienophile alkene geometry, and the lack of observed rearrangement products potentially derived from polar intermediates susceptible to carbocation rearrangement, satisfy important criteria required of a concerted cycloaddition reaction but do not exclude a two-step addition–cycloaddition reaction in which the subsequent cyclization of a polar intermediate is more rapid than carbon–carbon bond rotation or carbocation rearrangement.[29,253]

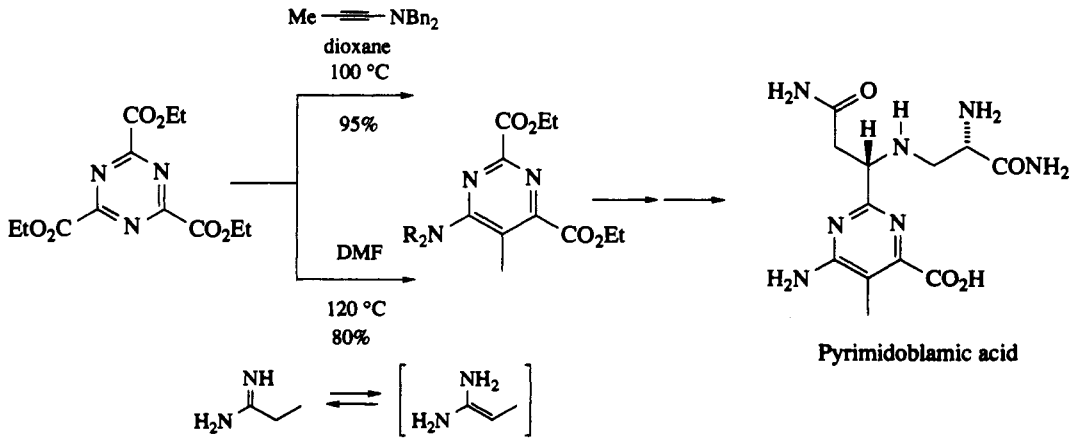
Similarly, *in situ* generation of *N*-vinyl-*N*-cyclohexylnitrosonium cations and their 4π participation in regio- and stereo-specific [4⁺ + 2] cycloaddition reactions with the full range of electron-rich, neutral and electron-deficient alkenes continue to be extensively investigated.[15,268–270]

4.3.6.2 Cationic Oxabutadienes

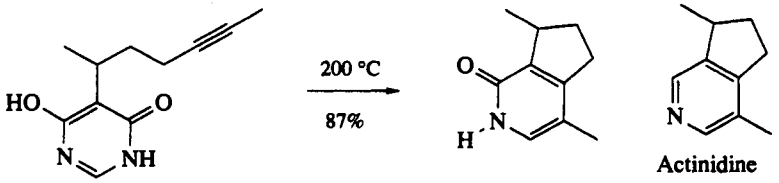
The most extensively explored class of cationic oxabutadienes are the 3-aza- and 2-aza-1-oxabutadienes including the *N*-methyl-*N*-methylenium and simple *N*-methylenium amides and *N*-vinyl-*N*-cyclohexylnitrosonium cation detailed in the preceding section.[15] In addition, the *o*-hydroxybenzyl carbocation generated *in situ* has been shown to participate in regio- and stereo-specific [4⁺ + 2] cycloaddition reactions in which the alkene geometry of the dienophile is maintained in the cycloaddition reaction (Scheme 29).[271] Schmidt has described the presumed 4π participation of *in situ* generated



Bleomycin A_2

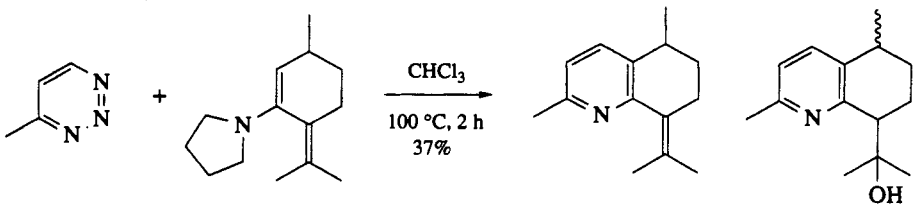


Scheme 20



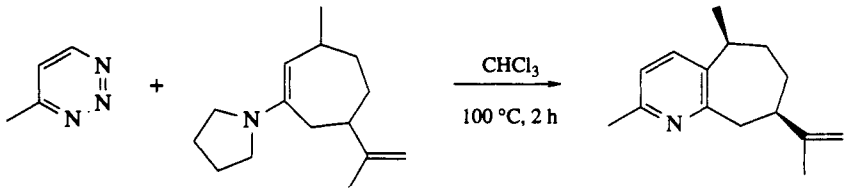
Scheme 21

β-acylvinyl carbocations in a [4⁺ + 2] cycloaddition reaction providing pyrylium salts (equation 17).[272,273]



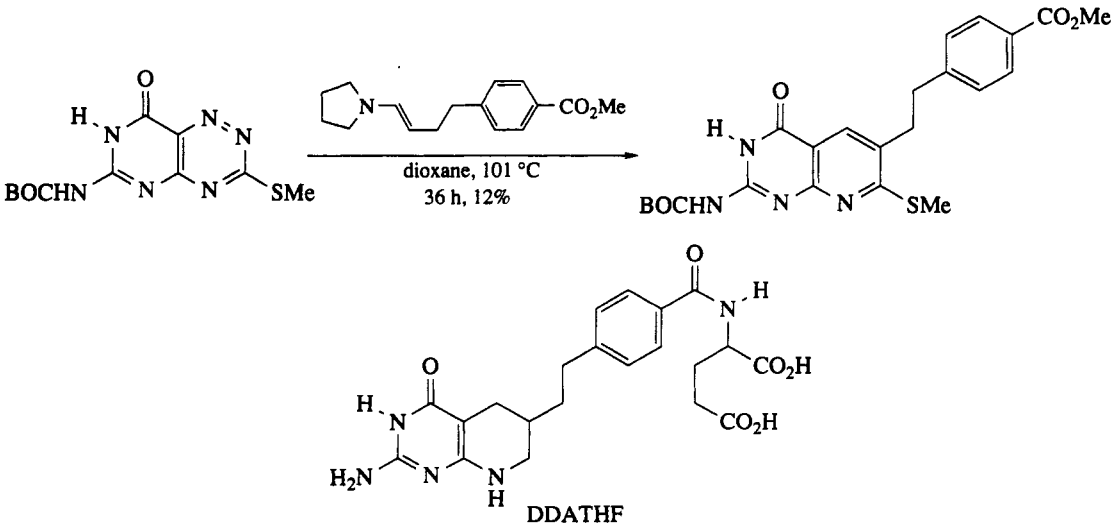
Fabianine

Scheme 22



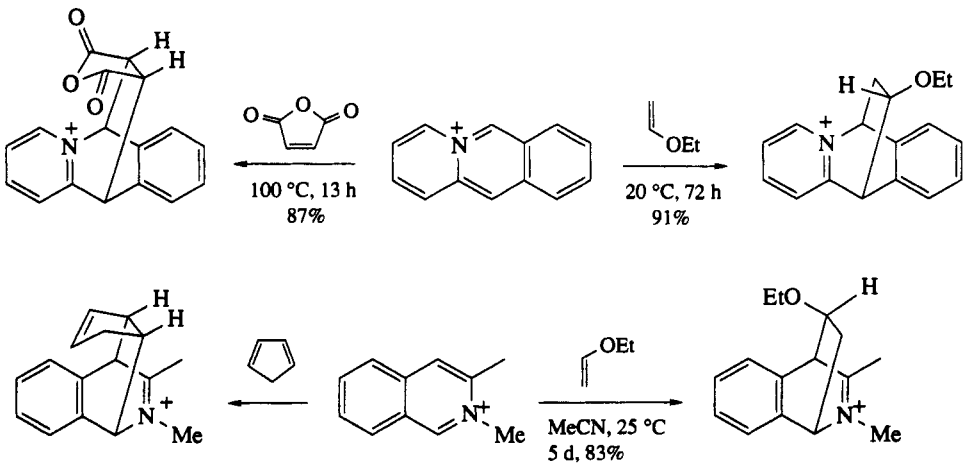
Guaipyridine

Scheme 23

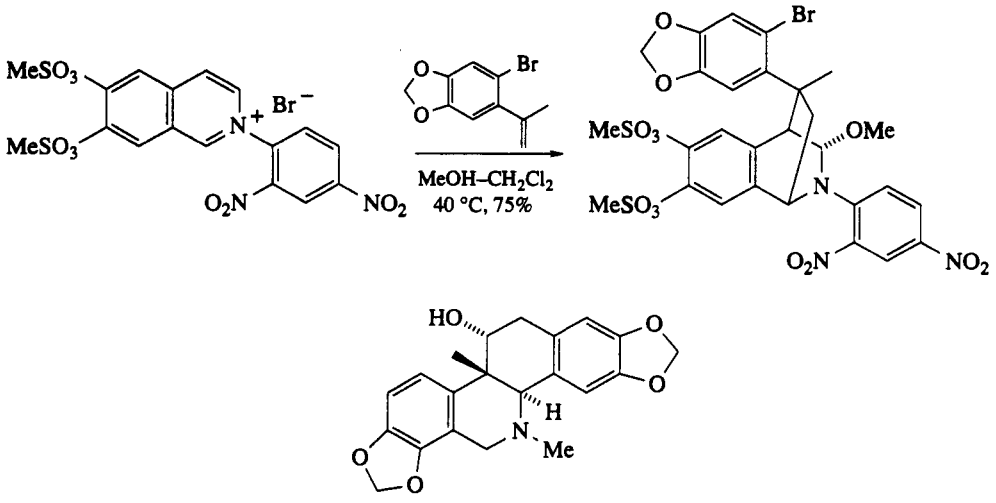


DDATHF

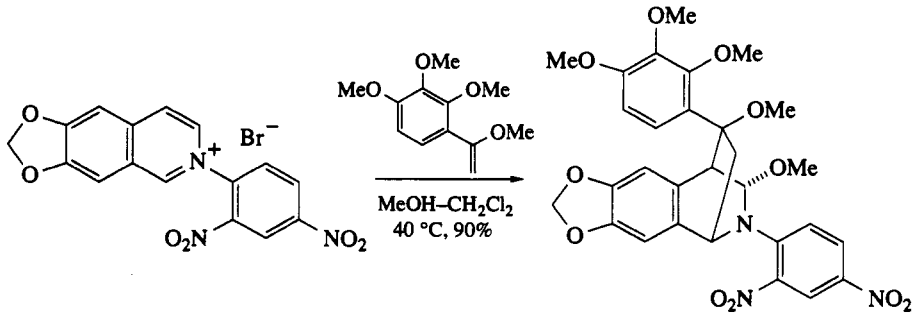
Scheme 24

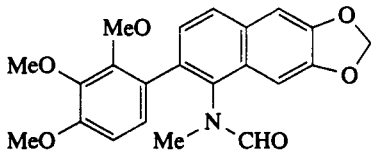


Scheme 25



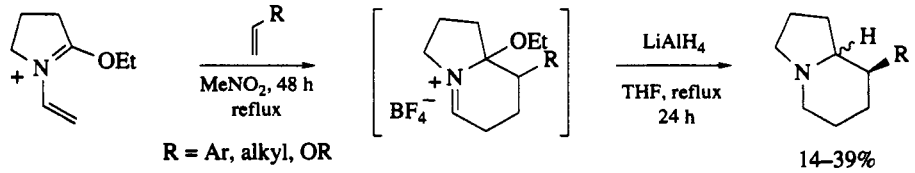
14-Epicorynoline





Methylamottianamide

Scheme 26



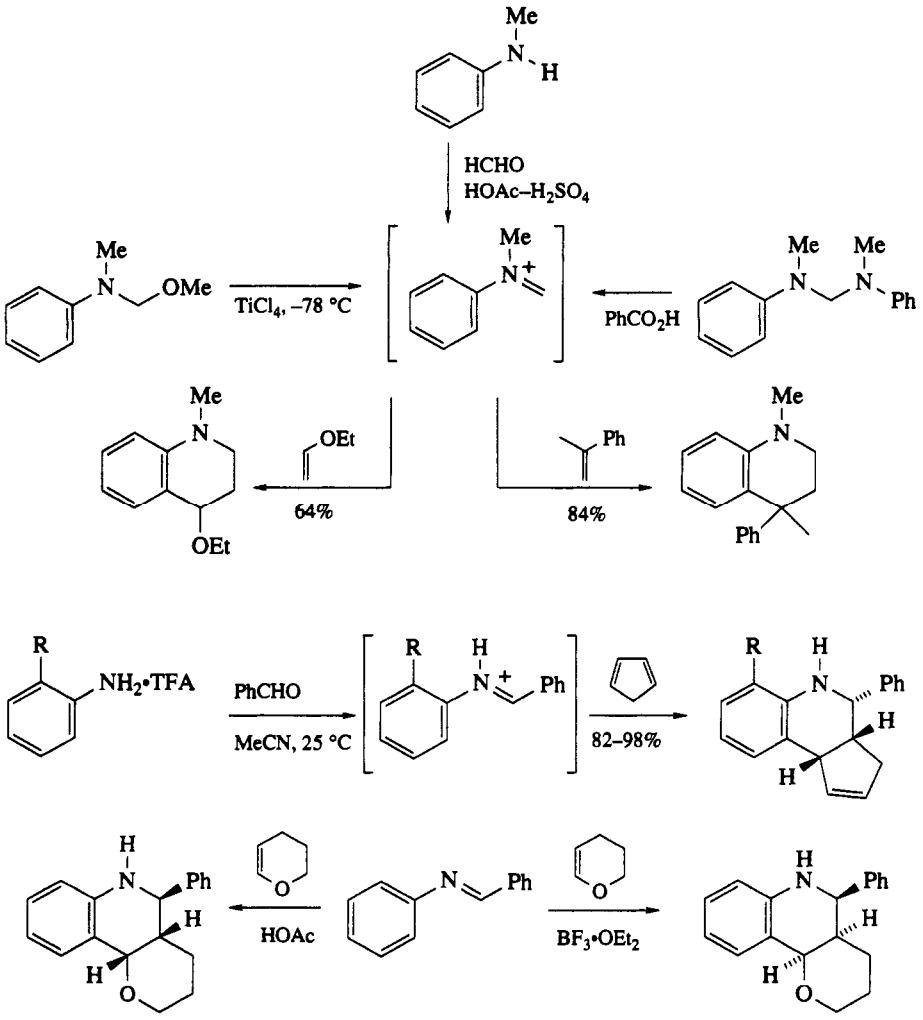
R = Ar, alkyl, OR

14–39%

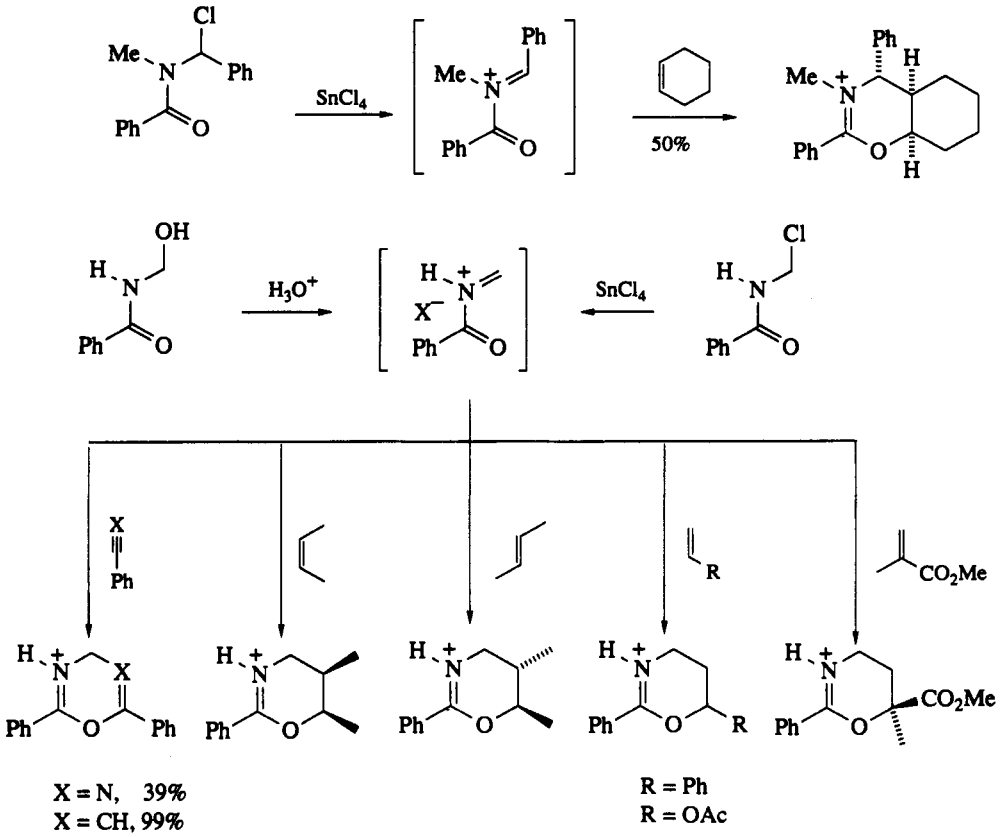
(16)

4.3.6.3 Cationic Thiabutadienes

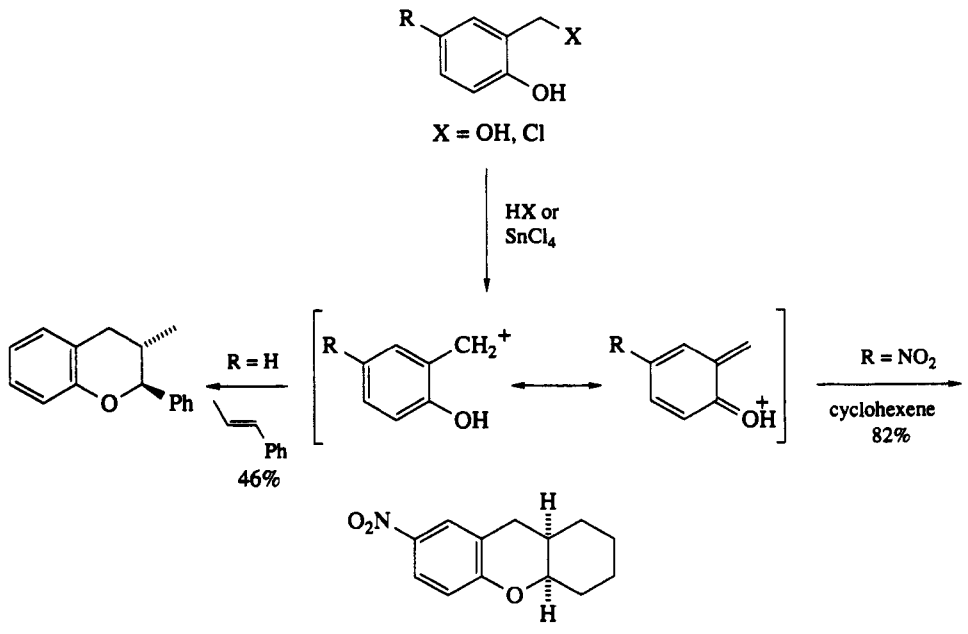
A growing class of useful [4⁺ + 2] cycloadditions based on the use of *in situ* generated 2-thieniumbutadienes have been detailed.[274–277] The 4π participation of arylthienium salts in [4⁺ + 2] cycloaddition reactions with alkenes, alkynes and nitriles[274–276] complements the 2π participation of simple thienium salts in [4 + 2⁺] cycloadditions (Scheme 30). Thioamidomethylenium cations generated *in situ* from hydroxymethylthioamides have been shown to participate in regio- and stereo-specific [4⁺ + 2] cycloadditions to provide 5,6-dihydro-4*H*-1,3-thiazinium salts, although the conversions are lower than that observed with amidomethylenium cations (equation 18).[277]


Me
N
H
HCHO
HOAc–H2SO4
Me
N
OMe
TiCl4, –78 °C
Me
N+
PhCO2H
Me
N
N
Ph
Me
N
OEt
OEt
64%
Ph
84%
Me
N
Ph
R
NH2•TFA
PhCHO
MeCN, 25 °C
R
H
N+
Ph
82–98%
R
H
N
Ph
H
H
H
N
Ph
H
H
O
HOAc
N
Ph
BF3•OEt2
H
N
Ph
H
H
O

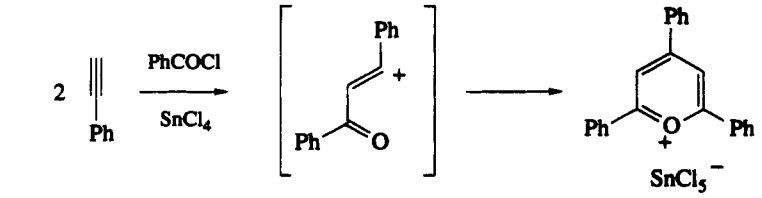
Scheme 27



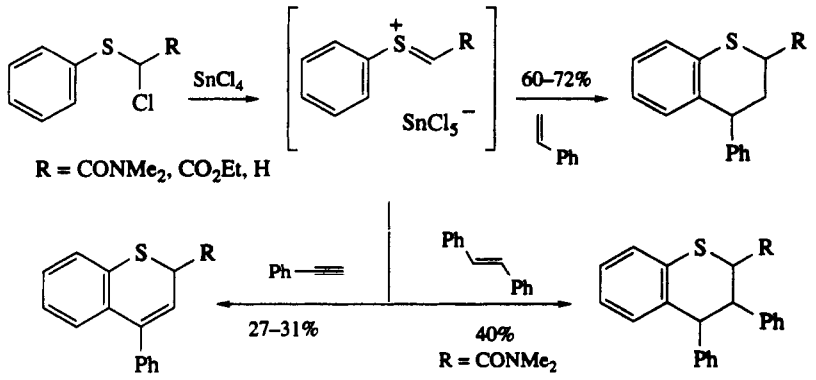
Scheme 28



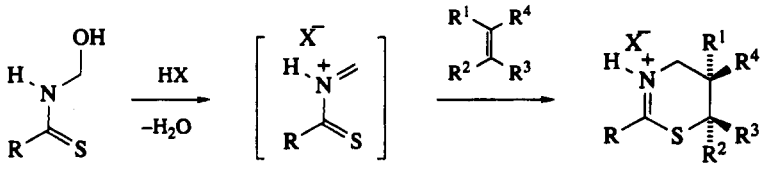
Scheme 29



(17)



Scheme 30



(18)

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4.4
Intramolecular Diels–Alder Reactions

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4.4.1 INTRODUCTION

The Diels–Alder reaction, first described in 1928,[1] has enjoyed widespread use in organic synthesis.[2] This [4 + 2] cycloaddition is particularly valuable in that it forms two bonds in a cyclohexenyl system with simultaneous creation of up to four new stereocenters. Curiously, the intramolecular version in which the diene and dienophile are tethered by a connecting chain was not investigated for many years. Alder and Schumaker reported the first example of the intramolecular reaction in 1953,[3] but it was not until the early 1960s that additional examples began to appear in the literature.[4] Since the mid-1970s, however, a virtual explosion of interest in this reaction has occurred.[5] The increased reactivity (due to favorable entropy considerations) and heightened regioselectivity (due to constraints posed by the connecting chain), as well as the potential for the synthesis of stereochemically complex polycyclic ring systems, account for the growth of applications of this reaction in organic and particularly natural products synthesis.

Two major classes of intramolecular Diels–Alder (IMDA) reactions may be identified based on the point of connection of the diene to the dienophile (Figure 1). Type I reactions involve trienes with the connecting chain attached to the diene terminus, while type II substrates have the dienophile tethered *via* one of the internal diene positions.

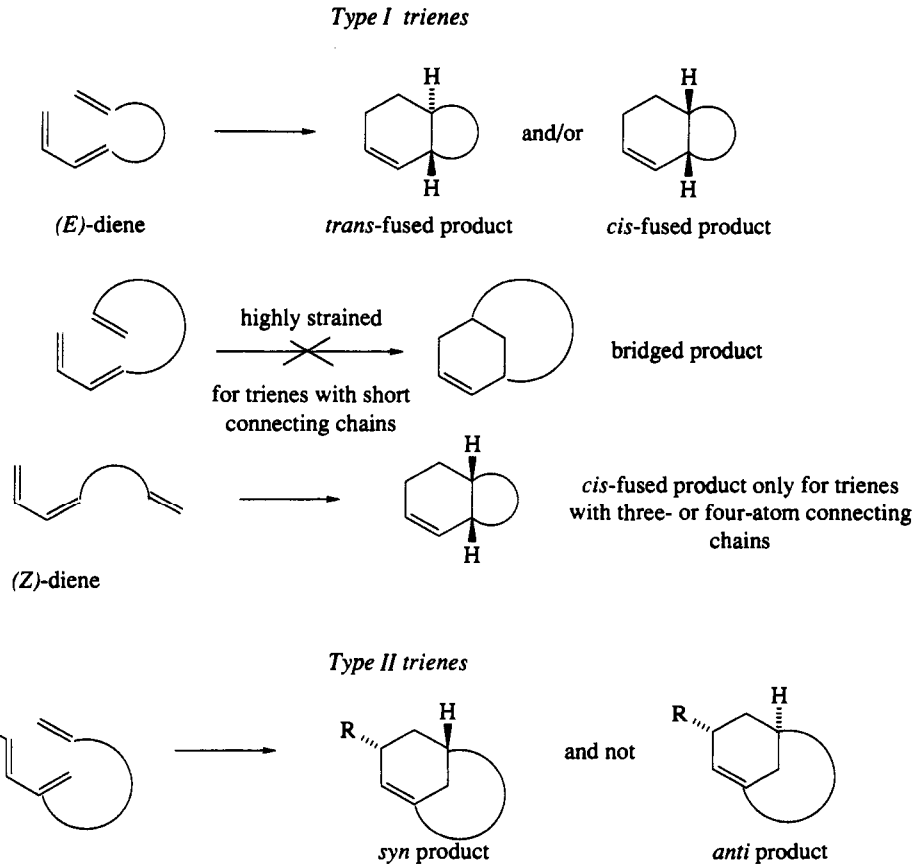


Figure 1

The ability to control the stereo- and regio-selectivity of these cycloadditions is critical for their successful application in synthesis. Except for some specialized cases,[3,6] type I IMDA reactions are feasible only if the connecting chains contain three or more atoms.[4e] In the vast majority of successful cases the fused rather than the bridged product is obtained, even when (*Z*)-dienes are employed. The only reported examples of bridged product formation involving type I (*E*)-diene substrates occur with connecting chains of 10 or more atoms.[7] The most significant issue with type I trienes is that of stereoselectivity, as mixtures of *cis* and *trans*-fused cycloadducts are accessible from (*E*)-dienes, the most frequently encountered class of substrates. This problem of simple diastereoselection is not an issue with type I (*Z*)-dienes with three or four atom connecting chains, however, as the transition states leading to the *trans*-fused products are highly strained.[4e,8]

Simple diastereoselection is also a potential concern for type II IMDA reactions. However, type II substrates with bridging chains of three or four members cyclize exclusively to the *syn* cycloadduct, since the transition state leading to the *anti* diastereomer is more strained than that leading to the *syn* diastereomer.[9] It should be noted as well that type II cycloadditions are restricted to substrates with bridging chains of at least three members owing to the strain that develops in the transition state.[10]

Another selectivity issue that influences the applicability of all IMDA reactions in synthesis is that of relative diastereoselection if the substrate is chiral. This problem is encountered whenever the substrate contains one or more stereocenters on the chain linking the diene and dienophile, or is chiral by virtue of stereocenters associated with a substituent anywhere else in the Diels–Alder substrate. Conventional asymmetric synthesis involving removable chiral auxiliaries falls into the latter category.

The purpose of this review is to assess critically the stereoselectivity of the IMDA reaction. Owing to the number of exhaustive reviews that have appeared,[5] no effort has been made to provide yet another comprehensive survey here. Rather, our focus is on the selectivity issues that define the utility of this reaction in synthesis, and only a carefully selected number of examples will be provided to illustrate each point. Attempts have been made, however, to include examples published since 1987, the date that the last major review appeared.[5i] The literature coverage extends through the end of 1988.

This chapter is organized along three distinct stereoselectivity issues: (i) simple diastereoselection, (ii) relative diastereoselection and (iii) absolute stereochemical induction. Because the greatest number of examples involve type I trienes with three- or four-atom connecting chains, the review is heavily slanted towards the IMDA reactions of functionalized 1,6,8-nonatrienes and 1,7,9-decatrienes. Factors that are examined include the role of dienophile activating groups, the influence of nonbonded interactions involving substituents on the diene or the connecting chain, and the influence of heteroatom substituents on IMDA diastereoselectivity.

4.4.2 SIMPLE DIASTEREOSELECTION

4.4.2.1 All-carbon Nona- and Deca-trienes

4.4.2.1.1 Effect of dienophile activating group

It has been recognized for many years that the presence of a dienophile activating group has a significant effect on the stereoselectivity of IMDA reactions. The results in Figure 2 show that *trans*-fused cycloadducts are favored in the cyclizations of terminally activated nonatrienes such as (**1**) or (**2**),[11] while with internally activated systems such as (**5**)–(**7**) it is the *cis*-fused cycloadduct that is favored.[12–15] While the results with (**1**), (**6**) and (**7**) are superficially consistent with *endo* stabilization of the predominant reaction transition state, the results with (**2**) and (**5**) are not; in these cases the major product diastereomers arise *via* transition states in which the dienophile activating group occupies an *exo* orientation relative to the diene. In contrast to these results in the nonatriene series, introduction of a terminal CO_2Me activating group in the 1,7,9-decatriene system has a very minor effect on stereoselectivity relative to the unsubstituted triene (**10**).[13a,16] A significant shift in stereoselectivity favoring the *cis*-fused product, however, occurs with internal dienophile activation, *e.g.* (**11**) (Figure 3).[17,18]

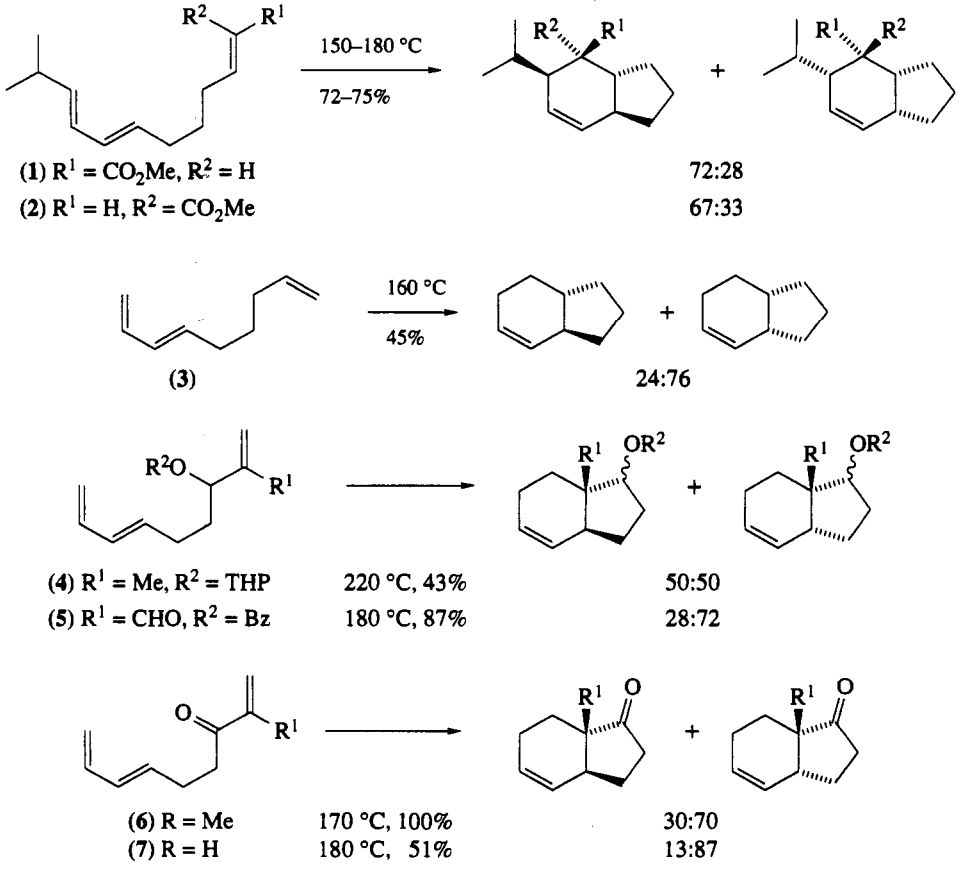


Figure 2 1,6,8-Nonatriene cyclizations

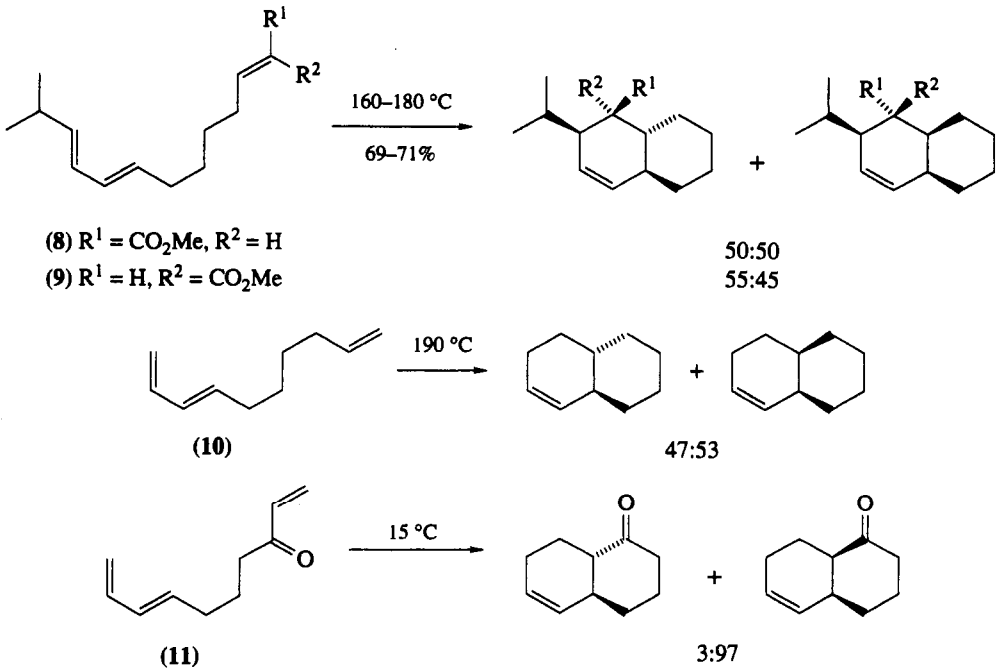


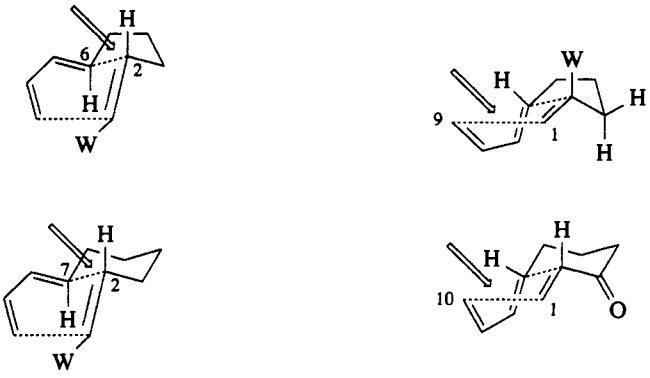
Figure 3 1,7,9-Decatriene cyclizations

The currently accepted interpretation of these data involves the concept of concerted but asynchronous transition states.[2i,19] Boeckman was first to apply this idea to IMDA reactions,[20] but shortly thereafter White,[21] Taber[12b] and Roush[12a] also invoked this model to rationalize stereochemical results. Houk further expanded this theory by introducing the concept of 'twist asynchronicity' to rationalize differences between pairs of similarly substituted nona- and deca-trienes.[22]

According to this model, stereoselectivity is governed by the timing of bond formation in the transition states. It is clear that in the absence of overriding steric or substituent effects the *cis*-fused nonatriene transition state (for **3**) is favored enthalpically by *ca.* 1 kcal mol^{-1}.[13a] The parent nonatriene transition states, further, are assumed to be rather symmetrical.[22] Addition of a terminal dienophile activating group, CO_2Me for (**1**) or (**2**) (Figure 2), shifts selectivity by at least 1.3 kcal mol^{-1} relative to (**3**) and the *trans*-fused product is then favored by 0.3–0.5 kcal mol^{-1}. This effect is attributed to the polarization of the dienophilic C=C bond that causes the LUMO coefficient at C(2) to be larger than at C(1). Consequently, bonding between C(2) and C(6) will be somewhat more advanced than between C(1) and C(9) in the transition state. Under these circumstances, steric or other nonbonded interactions involving the chain separating diene and dienophile develop at an early stage of the reaction, and the transition state that has more *trans*-disubstituted cyclopentanoid character becomes the more stable one (due to 'twist asynchronicity' resulting from torque applied to the developing C(2)—C(6) bond by the three-carbon connecting chain).[22] Similarly, introduction of a substituent at the diene terminus C(9) that increases the HOMO coefficient at C(6) should also lead to increased *trans* stereoselectivity in the Diels–Alder reaction (Figure 4).

For trienes like (**5**)–(**7**) with dienophile activating groups located at C(2) ('internally' activated systems), however, the situation is reversed. The LUMO coefficient at C(1) is greater than at C(2) and so bonding between C(1) and C(9) should be more advanced early in the transition state. This form of twist asynchronicity, however, is probably less significant than that involving the C(2)—C(6) bond for terminally activated nonatrienes (**1,2**) since the selectivity of the IMDA reactions of (**5**)–(**7**) is comparable with that obtained with the unsubstituted nonatriene (**3**) (also compare results with (**4**), Figure 2).

This model also predicts that selectivity for the *trans*-fused cycloadducts in nonatriene ($n = 0$) or decatriene ($n = 1$) cyclizations should increase as size of the coefficients at C(2)/C(6 + n) are increased relative to those at C(1)/C(9 + n), that is, as the polarization of the dienophile or diene is increased.[23] Tables 1 and 2 summarize results of intramolecular Diels–Alder reactions that provide a test of this proposal.[24,25] First, it is clear that an electron-releasing Et_2N group at C(9) of the nonatrienoate system leads to a substantial increase in selectivity for the *trans*-fused product (compare entries 4–6, Table 1).[26] Increased *trans* stereoselectivity also occurs with C(9)-alkoxy-substituted nonatrienes.[28] A similar effect



Terminally activated nona- and deca-trienes

Bonding is more advanced at the indicated position in the transition state; *trans*-fused product is favored

Internally activated nona- and deca-trienes

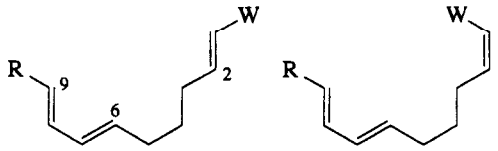
Bonding is more advanced at the indicated position in the transition state; *cis*-fused product is favored

Figure 4 Asynchronous transition states

may be involved in the increased selectivity of triene (**1**) in entry 5 compared with the C(9)-unsubstituted triene in entry 4, since the alkyl substituent at C(9) of (**1**) is expected to increase the size of the HOMO coefficient at C(6).[23,25c] Second, for trienes with *trans* dienophiles, stereoselectivity for the *trans*-fused cycloadduct increases as the dienophile activating group is changed along the series $CONR_2$ < CO_2Me < COMe < CHO;[24,29] further increases in selectivity occur when Lewis acid catalysis is employed.[11a,24] This trend exactly parallels the ability of these groups to activate alkenes towards β-nucleophilic attack, and is consistent with the predictions made above regarding the increased polarization of the dienophile double bond.

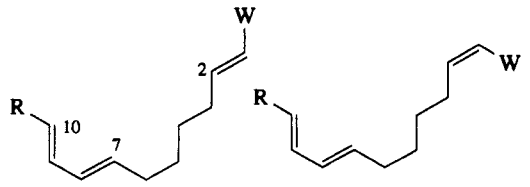
Similar trends, albeit less pronounced in several instances, are apparent in the data summarized in Table 2 for (*E,E,E*)-decatrienes. Houk has attributed the smaller effect of the Et_2N substituent in the deca- compared to the nona-triene series to the smaller requirement for twist asynchronicity in the deca-triene transition state. It is argued that this transition state is essentially unstrained by the four-carbon connecting chain and that less torque is applied to the developing C(2)—C(7) bond.[22,26] Although the

Table 1 Substituent Effects in Cyclizations of Terminally Activated Nonatrienes



Entry	*R*	*W*	*Temp.* (°C)	*trans:cis*	*Temp.* (°C)	*trans:cis*	*Ref.*
1	H	H	160	24:76	—	—	13a
2	EtO_2C	H	180	43:57	—	—	13b
3	Pr^i	$CO(NC_4H_8)$	150	51:49	—	—	24
4	H	CO_2Me	150	60:40	180	65:35	11a
5	Pr^i	CO_2Me	150	72:28	180	67:33	11a
6	Et_2N	CO_2Et	60	85:15	—	—	26
7	Pr^i	COMe	120	85:15	—	—	24
8	Me	NO_2	80	89:11	23	53:47	27
9	Pr^i	CHO	110	92:8	—	—	24
10	H	$CO_2Me{\cdot}AlEtCl_{2AlEtCl}$	23	>99:1	23	52:48	11a
11	Pr^i	$CO_2Me{\cdot}AlEtCl_{2AlEtCl}$	23	>99:1	23	63:37	11a
12	Pr^i	$COMe{\cdot}AlEt_{2AlEtCl}$	−78	>99:1	—	—	24
13	Pr^i	$CHO{\cdot}AlEt_{2AlEtCl}$	−78	>99:1	—	—	24

Table 2 Substituent Effects in Cyclizations of Terminally Activated Decatrienes



Entry	*R*	*W*	*Temp.* (°C)	*trans:cis*	*Temp.* (°C)	*trans:cis*	*Ref.*
1	H	H	190	47:53	—	—	13a
2	EtO_2C	H	180	50:50	—	—	13b
3	H	CO_2Me	155	51:49	155	51:49	16b
4	Pr^i	CO_2Me	160	50:50	180	55:45	16a
5	Et_2N	CO_2Et	40	55:45	—	—	26
6	Pr^i	COMe	150	67:33	—	—	24
7	Pr^i	CHO	150	75:25	—	—	24
8	Pr^i	$CO_2Me{\cdot}AlEtCl_{2AlEtCl}$	23	88:12	23	<8:92	16a
9	Pr^i	$COMe{\cdot}AlEtCl_{2AlEtCl}$	23	97:3	—	—	24
10	Pr^i	$COMe{\cdot}AlEtCl_{2AlEtCl}$	−78	>99:1	—	—	24
11	Pr^i	$CHO{\cdot}AlEtCl_{2AlEtCl}$	23	>98:2	—	—	24
12	Pr^i	$CHO{\cdot}AlEtCl_{2AlEtCl}$	−78	>99:1	—	—	24

CO_2Me group increases *trans* selectivity by only 0.1 kcal mol^{-1} in the decatriene series (compare entries 1–3, Table 2) *versus ca.* 1.3 kcal mol^{-1} with the nonatrienes, the additional increases in selectivity due to the COMe and CHO activating groups are comparable in the two series: 0.6–0.7 kcal mol^{-1} for COMe and 0.3–0.4 kcal mol^{-1} for CHO.[24]

The behaviors of the (*Z,E,E*)-nona- and deca-trienes are different, however. The data in Table 1 indicate that (*Z,E,E*)-nonatriene stereoselectivity is unaffected by changes in the dienophile activating group, while the more limited data available for (*Z,E,E*)-decatrienes in Table 2 suggest that increased dienophile activation increases selectivity for the *cis*-fused, and not the *trans*-fused, product. Two factors presumably contribute to these results: twist asynchronicity and Alder *endo* stabilization that undoubtedly becomes increasingly important as the dienophile activation increases. It is a well established trend in bimolecular Diels–Alder reactions that increased amounts of *endo* product are obtained as dienophile activation is increased.[2] Although *endo* stabilization is apparently not an important stereochemical control element of the IMDA reactions of CO_2Me activated trienes like (**1**), (**2**), (**8**) and (**9**) (Figures 2, 3), it is necessary to invoke this factor in order to develop an internally consistent rationalization of the data summarized in Tables 1 and 2:

For terminally activated (*E,E,E*)-trienes in both series, twist asynchronicity and *endo* stabilization of the transition state are cooperative and increased selectivity for the *trans*-fused product occurs with increased dienophile activation. The dienophile activating group occupies an *endo* position in the transition state as long as the dienophile geometry is (*E*).

For (*Z,E,E*)-nonatrienes, however, twist asynchronicity favors the *trans*-fused adduct and Alder *endo* stabilization favors the *cis*-fused product. These effects evidently cancel such that no significant change in selectivity occurs with increased dienophile activation.

Increased *endo* stabilization of the *cis*-fused transition state must be invoked to account for the increased selectivity in the Lewis acid catalyzed cyclization of the (*Z,E,E*)-decatrienoate recorded in Table 2, entry 8.[16a] Because twist asynchronicity is believed to be less important in the decatriene transition state,[22,26] Alder *endo* stabilization apparently dominates twist asynchronicity in this case.

The increased stereoselectivity of decatrien-3-ones relative to the nonatrien-3-ones[14,15,17] may also be the consequence of cooperativity between twist asynchronicity and *endo* stabilization that both favor the *cis*-fused product. The decatrien-3-one transition state is considerably less strained than the nonatrien-3-one transition state, and the uncatalyzed decatrienone cyclizations occur at or near ambient temperature.[17] Consequently, one expects greater *endo* stabilization, and hence also greater *cis* stereoselectivity, in the decatrienone intramolecular Diels–Alder reactions.

4.4.2.1.2 Lewis acid and other catalyzed intramolecular Diels–Alder reactions

The use of Lewis acid catalysis is a powerful method of increasing the rates and diastereoselectivity of many IMDA reactions. Several examples involving terminally activated nona- and deca-trienes are summarized in Tables 1 and 2. Examples illustrating rate and stereoselectivity improvements in the cyclizations of functionalized decatrien-3-ones appear in Figure 5.[30–32] The most striking of these is the cyclization of (**12**) when performed in the presence of trifluoroacetic acid at –78 °C, providing (**13**) with 94% stereoselectivity.[30]

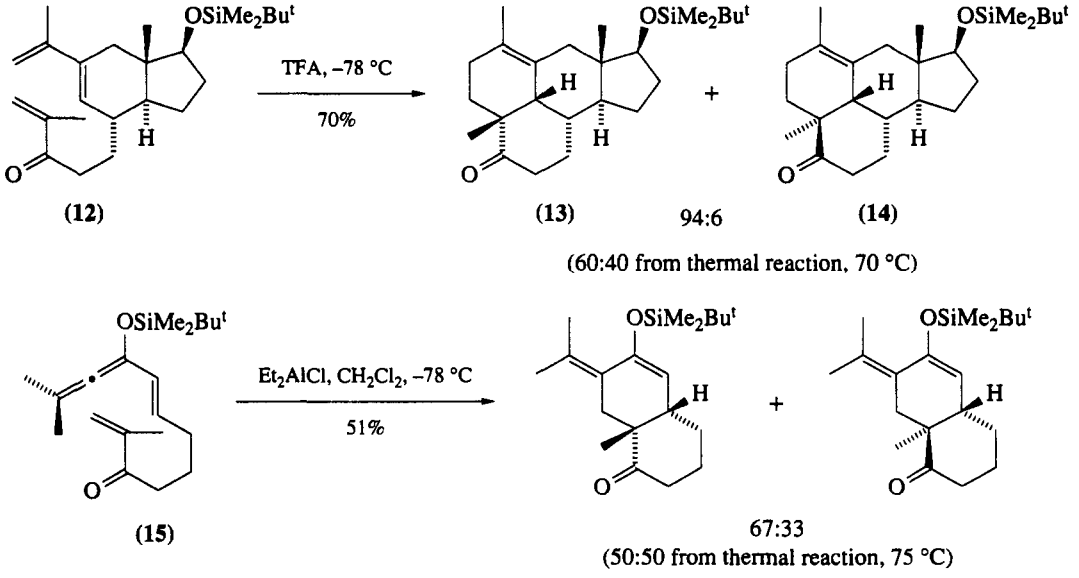
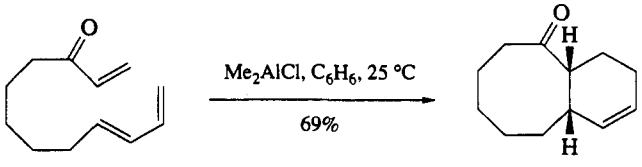


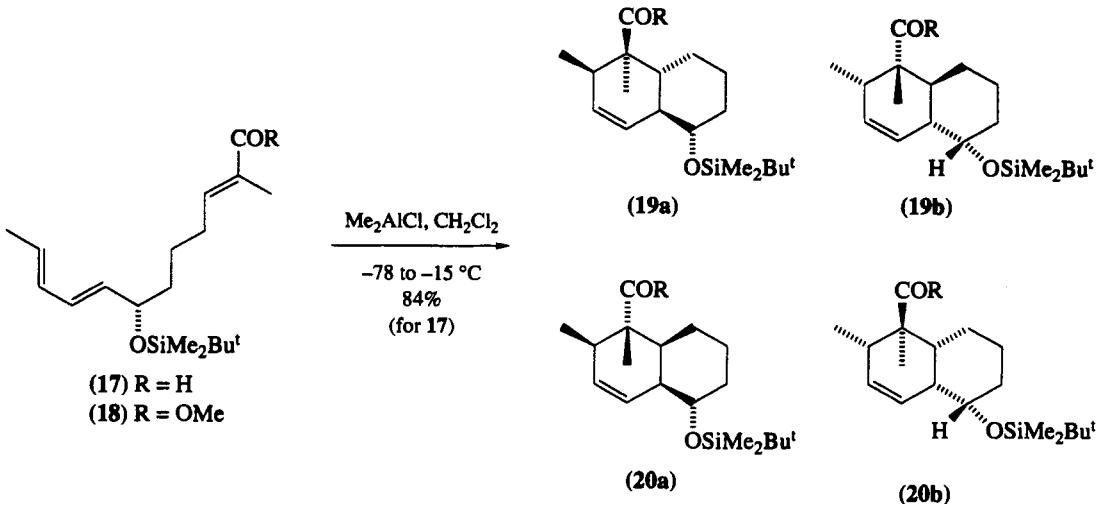
Figure 5

Several examples of IMDA reactions that are successful with Lewis acid or alumina catalysis, but which are not preparatively useful or fail altogether under thermal conditions, have been reported.[15,33,34] Among the former group are trienones such as (**16**).[15,33] More frequently encountered, however, are substrates that fail to cyclize in the presence of Lewis acids. Polymerization of the diene is a frequently encountered problem, and consequently relatively mild Lewis acids such as the alkylaluminum chlorides (*e.g.* $EtAlCl_2$ or Et_2AlCl) are generally recommended.[35] Another group of problematic functionality are alkoxy substituents allylic to the diene that readily ionize to pentadienyl carbonium ions upon exposure to Lewis acids.[11a] In such cases it is necessary to use a highly activated dienophile so as to accelerate the rate of cycloaddition relative to the pentadienyl carbonium ion decomposition pathway. This point has been demonstrated in several studies by Marshall, who has shown that alkoxy-substituted trienals such as (**17**) smoothly cyclize in the presence of Lewis acids,[29] whereas the corresponding methoxycarbonyl activated triene (**18**) fails to cyclize under analogous conditions.[16b] Comparison of the stereoselectivities of the IMDA reactions of (**17**) and (**18**) provides another set of data that demonstrates the tendency of terminally activated 1,7,9-decatrienes to cyclize with increasing selectivity to *trans*-fused cycloadducts upon increased dienophile activation (Figure 6). Lewis acid catalysis may be used with alkoxy-substituted trienoates, however, as long as the alkoxy substituent is not in a dienylic position (see cyclization of **21**[102]).

The reactive species in Lewis acid catalyzed IMDA reactions of α,β-unsaturated ester dienophiles is formally a Lewis acid stabilized dioxolenium ion. It stands to reason that other allylic species bearing positive charges, such as dioxolenium ion (**22**) and allyl cations (**23**), should also function as highly reac-



(**16**) *cis* isomer only



Substrate	*Conditions*	(19a)	(19b)	(20a)	(20b)	*trans:cis*
(17)	Me_2AlCl, as above	15	75	10	0	90:10
(17)	thermal (150 °C)	27	27	33	13	54:46
(18)	thermal (150 °C)	15	13	49	23	28:72

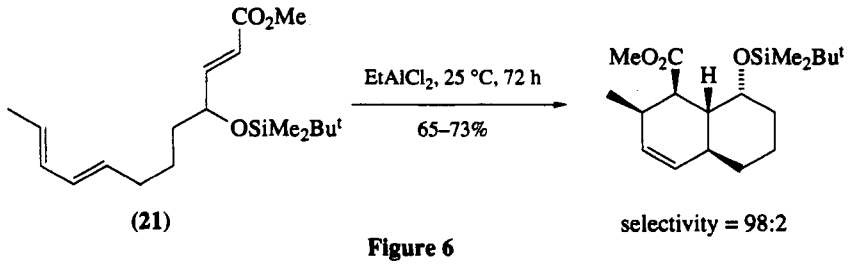
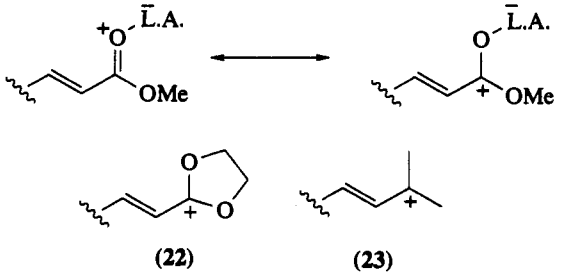


Figure 6

tive dienophiles. Dioxolenium ions (**22**) were encountered as reactive intermediates in studies of trienes such as (**24**) and (**25**) (Figure 7).[36] Recent studies by Gassman have shown that α,β-unsaturated dioxolenium ions, generated by treatment of triethyl orthoacrylate with trimethylsilyl triflate in CH_2Cl_2 at −78 °C, are excellent dienophiles for intermolecular Diels–Alder reactions.[37] Similarly, acetals of α,β-unsaturated aldehydes are precursors to alkoxy-substituted allyl cations that are also excellent ionic Diels–Alder dienophiles.[38]

Gassman first observed the intermediacy of allyl cations as dienophiles in connection with efforts to extend the aminium cation-radical catalyzed Diels–Alder reaction[39] to intramolecular cases.[40] It was found that the cyclization of tetraene (**26**) performed in the presence of 0.2 equiv. of tris(*p*-bromophenyl)aminium hexachloroantimonate [$Ar_3N^{+}\cdot Cl_6Sb^{-}$] was in fact catalyzed by protic acid.[40,41] A better means of catalyzing the cyclization of (**26**) involves use of 4 mol % trifluoromethanesulfonic acid at −23 °C for 6 min, which provides the *trans*-fused cycloadduct in 88% yield (98% isomeric purity). Similar treatment of (**27**), however, provided a mixture of *cis*- and *trans*-fused products. A subsequent report revealed that allylic alcohols and allylic ethers are useful precursors to the allyl cation dienophiles with



(**22**) (**23**)

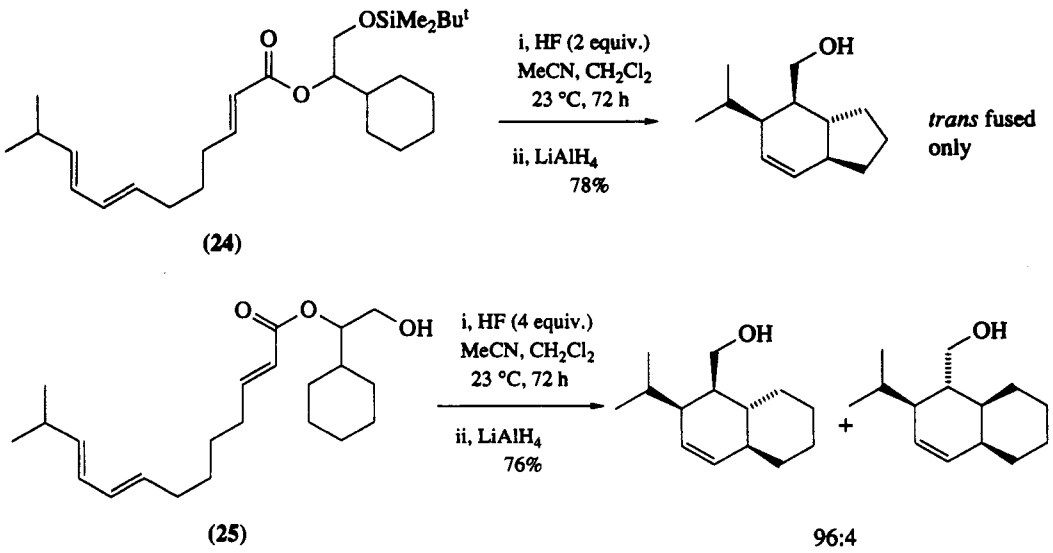


Figure 7 Dioxolenium ion mediated IMDA reactions

CF_3SO_3H as catalyst.[42] This method has been applied successfully to several highly functionalized trienes including (**29**) (Figure 8). While the outcome of these reactions is consistent with the IMDA paradigm, it is unclear whether these reactions are actually concerted or stepwise. For example, the acid catalyzed cyclization [$Ar_3N^{+}\cdot Cl_6Sb^{-}$ conditions] of the (*E*,*Z*)-isomer of (**27**) provided the same products as obtained from (*E*,*E*)-(**27**), albeit in altered ratio, suggesting that the cyclization of (*E*,*Z*)-(**27**) is not concerted.

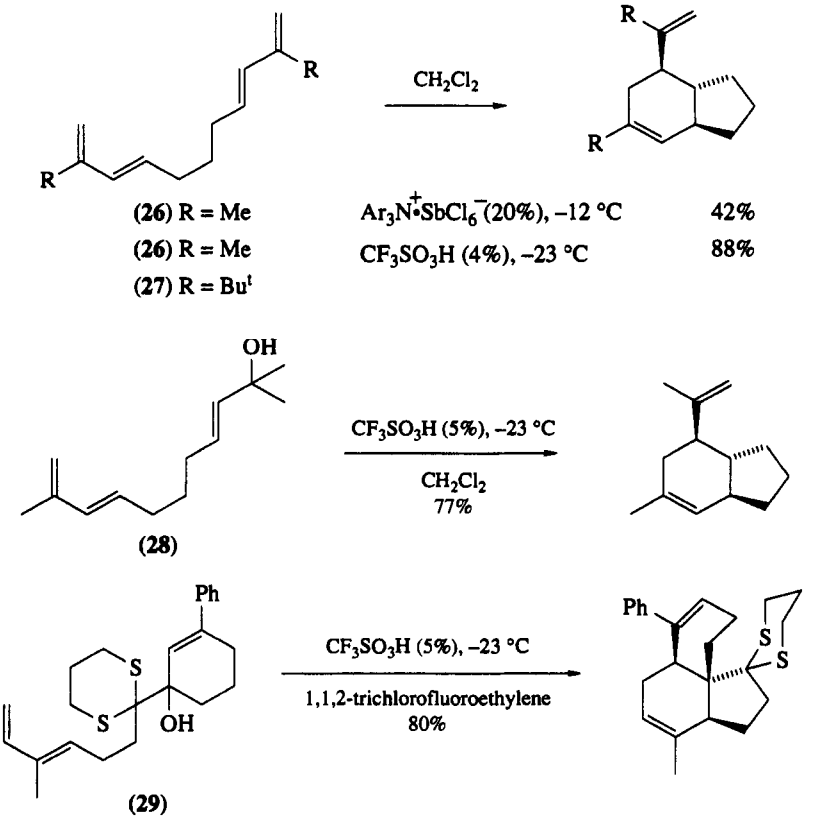


Figure 8 Allyl cation mediated IMDA reactions

Cation radical Diels–Alder reactions catalyzed by $Ar_3N^{+}\cdot Cl_6Sb^{-}$ occur when the reactions are performed in the presence of 2,6-di-*t*-butylpyridine (in excess, based on aminium cation salt) to scavenge protic acids generated either from loss of protons from initially generated cation radicals or from dimerization of cation radical intermediates.[41] Bauld has applied these modified conditions to the cyclizations of (**30**) and (**31**), and both show very high selectivity for the *trans*-fused product.[43] The (*Z*)-dienophile isomer of (**30**) also undergoes cyclization, but with prior isomerization of the dienophile from (*Z*) to (*E*). Attempts to apply this method to trienes with less easily ionized dienophiles, *e.g.* (*E,E*)-1,6,8-decatriene or (*E,E*)-2-methyl-2,7,9-undecatriene, were unsuccessful. Nevertheless, in combination with the acid catalyzed cyclizations *via* allyl cation intermediates and conventional Lewis acid mediated cyclizations of carbonyl activated trienes, a wide range of trienic systems are viable substrates for catalyzed, rate accelerated cyclizations with impressive increases of selectivity relative to the uncatalyzed, thermal cycloadditions.

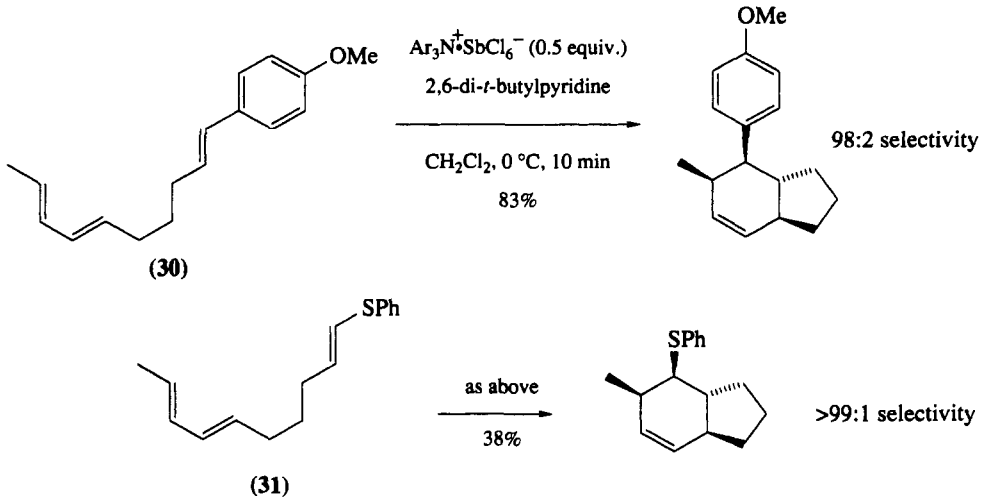


Figure 9 Cation radical catalyzed IMDA reactions

4.4.2.1.3 Influence of steric effects on diastereoselectivity

While the electronic effects discussed in Section 4.4.2.1.1 certainly play a significant role in determining the stereochemical outcome of IMDA reactions, steric and conformational effects, discussed in Section 4.4.2.1.4, also exert a significant influence on the course of these reactions. Figure 10 summarizes two sets of data that illustrate that steric effects are capable of overriding the usual preference of terminally activated nona- and deca-trienes to cyclize to *trans*-fused products.[44,45] Sulfonyl activated 1,7,9-decatriene (**32**) cyclizes exclusively to the indicated *cis*-fused octalin, while the nonatriene analogue provides a 1:1 mixture of *trans*- and *cis*-fused products.[44] The bulky $PhSO_2$ group apparently experiences repulsive nonbonded interactions with the diene in the *trans*-fused ($PhSO_2$ *endo*) transition state for (**32**), thereby prompting this cyclization to proceed by way of a *cis*-fused transition state with the $PhSO_2$ unit in a less sterically demanding *exo* position. The twist asynchronicity encountered in the cyclizations of terminally activated nonatrienes (Table 1), however, is sufficient to counterbalance the $PhSO_2$ steric effect in the IMDA reactions of the analogous sulfonyl activated 1,6,8-nonatriene.[44] Steric effects evidently are much more serious with substituted nonatriene (**33**), which provides the indicated *cis*-fused cycloadduct as a single stereoisomer.[45] The ordinarily favored (*cf.* Table 1) *trans*-fused transition state (**34**) is destabilized by nonbonded interactions between the diene and the cyclopentenone unit, and the IMDA reaction thus proceeds *via* the less sterically crowded *cis*-fused transition state (**35**).

Geminal substitution at C(3) introduces destabilizing nonbonded interactions in the *cis*-fused transition states for both nona- and deca-trienes (Figure 11), resulting in enhanced selectivity for the *trans*-fused diastereomer.[14a,46,47] These examples are instructive particularly when compared with the results discussed previously for (**6**) and (**11**) (Figures 2, 3). The destabilizing nonbonded interactions are presumably more significant in the 1,7,9-decatriene series (**36**) owing to the greater conformational flexibility of the nonatriene transition state (developing five-membered ring).

Substituents on C(8) of the decatriene skeleton also enhance selectivity for the *trans*-fused cycloadduct by destabilizing the *cis*-fused transition state (Figure 12). A classic example is provided by Wilson, who

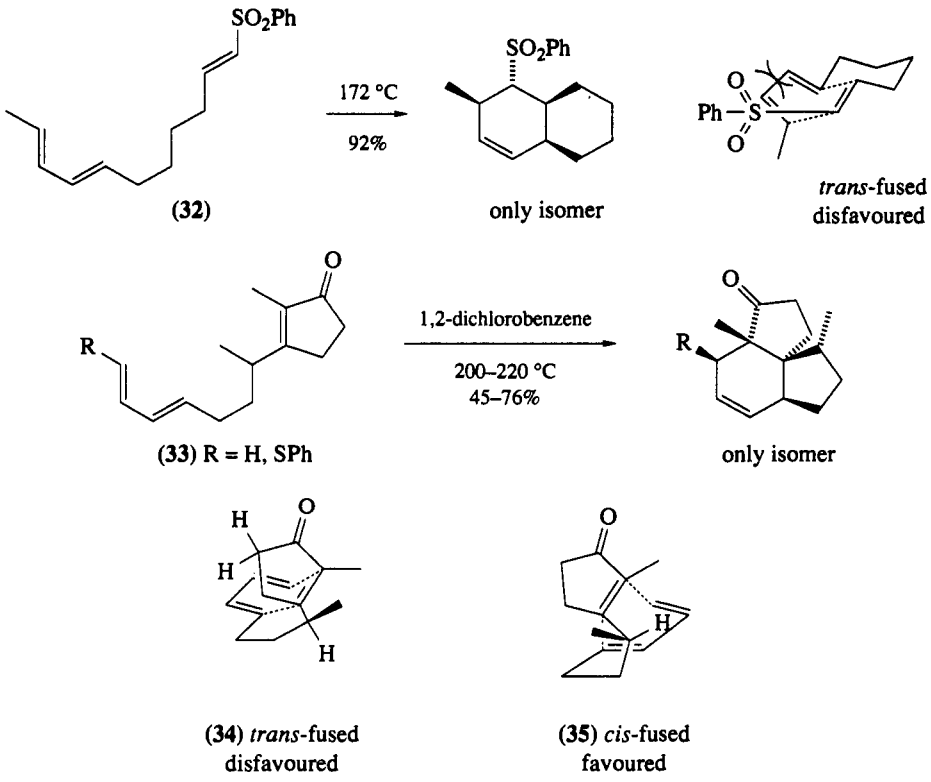


Figure 10

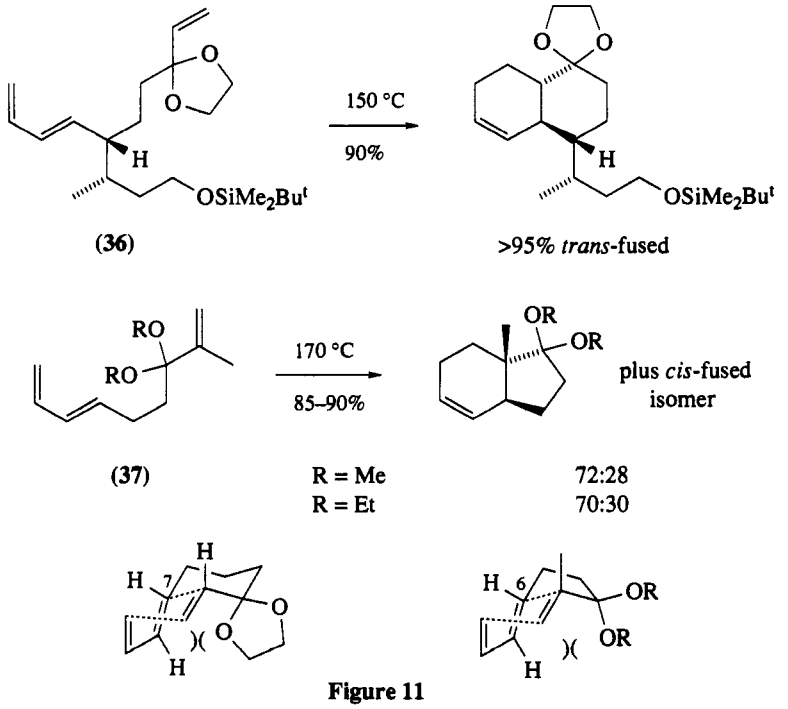


Figure 11

observed that (**38**) with a C(8)-Me substituent cyclized almost exclusively to *trans*-fused products, while the C(8) unsubstituted triene (**39**) provided a 55:45 mixture of the *trans*- and *cis*-fused products.[48] The increased selectivity with (**38**) is attributable to interactions between the C(8)-Me group and the axial C(5)-H that prohibitively destabilize the *cis*-fused transition state. In fact, the majority of unactivated

1,7,9-decatrienes that cyclize with high selectivity to *trans*-fused products, including most IMDA reactions involving *o*-diquinomethanes,[5c,e] possess substituents at C(8). With this effect in mind, several groups have explored the use of removable C(8) substituents (so called steric directing groups) as a strategy to enhance the diastereoselectivity of otherwise poorly selective IMDA reactions.[49,50] One example involves the Me_3Si-substituted triene (**40**) that undergoes a thermal IMDA reaction with 95% *trans* selectivity (compare results with (**8**), Figure 3).[51] Although a C(8)-Me_3Si substituent exerts a greater influence than a C(8)-Br group,[50] the C(8)-Br substituted trienes are more easily synthesized, especially in structurally complex cases, and thus are likely to find numerous applications in synthesis.[50b,52]

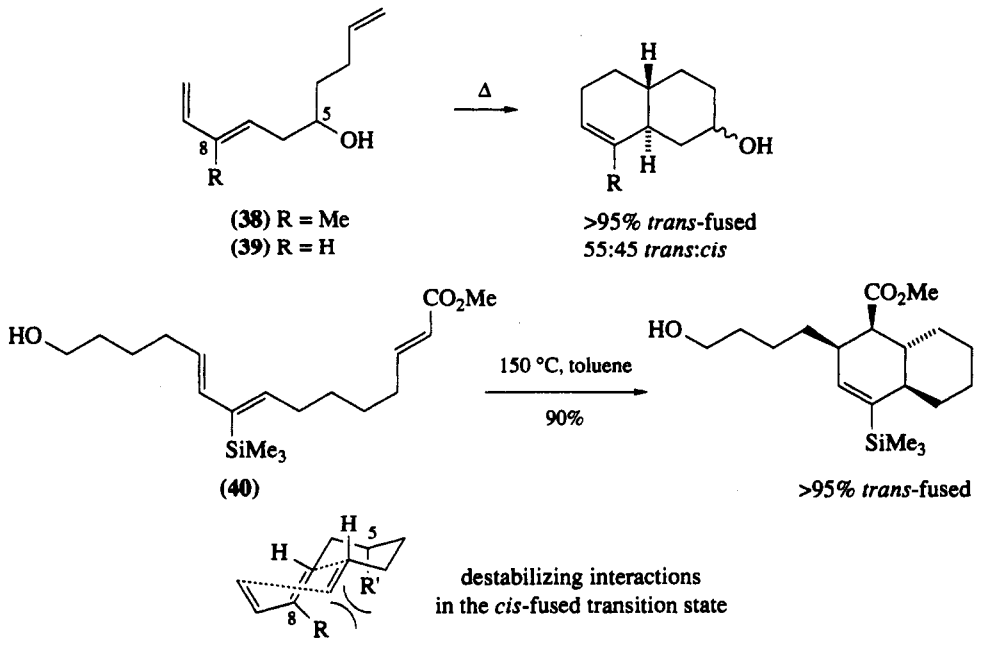
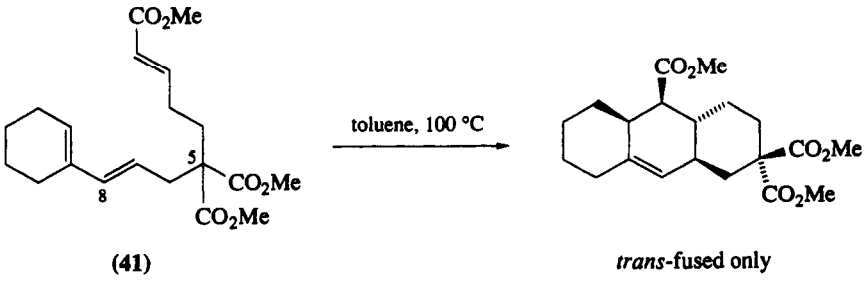


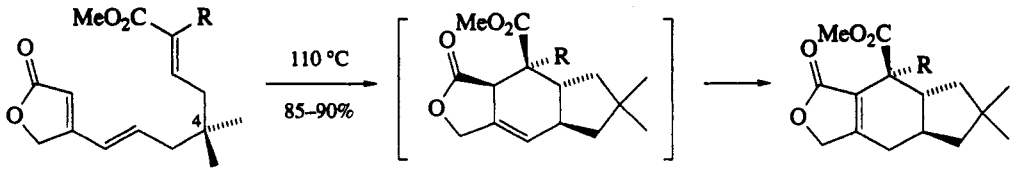
Figure 12

1,7,9-Decatrienes with geminal substituents at C(5), or C(5)-monosubstituted trienes constrained to cyclize *via* transition states with the C(5) substituent in an axial position, also display excellent stereoselectivity for the *trans*-fused product, *e.g.* triene (**41**).[53]

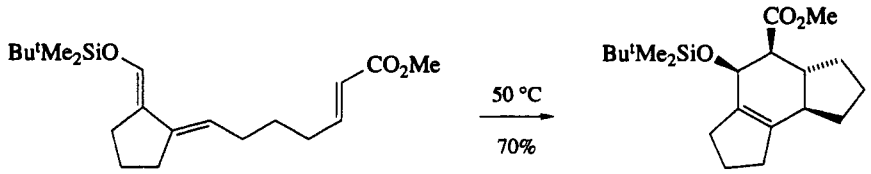


Similar nonbonded interactions occur between C(4) and C(7) substituents in the *cis*-fused 1,6,8-nonatriene transition state (Figure 13).[20,53,54] The very high *trans* selectivity exhibited by trienes (**42**), (**43**), (**44**) and (**46**) is striking in view of the data summarized in Figure 2 for less highly substituted systems. The results with (**44**) and (**45**) imply that the extent of destabilization of the *cis*-fused transition state depends on the steric requirements of the C(7) substituent, a conclusion also supported by other examples cited in the references.[54e-g] Nevertheless, these interactions are large enough to reverse the stereoselectivity of the IMDA reactions of internally activated nonatrienes (**44**) and (**47**)[55] relative to the usually observed *cis* manifold (compare (**5**) and (**7**), Figure 2).

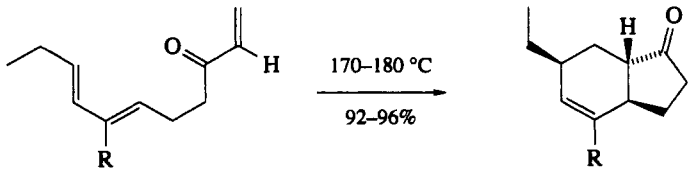
Finally, it is worthy of brief mention that the presence of C(6)-alkoxy substituents in decatriene substrates leads to an increase in selectivity for the *cis*-fused products, *e.g.* (**48**) (Figure 14).[16] This effect may result from eclipsing interactions involving H(8) in the *trans*-fused transition state, an interaction



(42) R = H, CO_2Me *trans* only

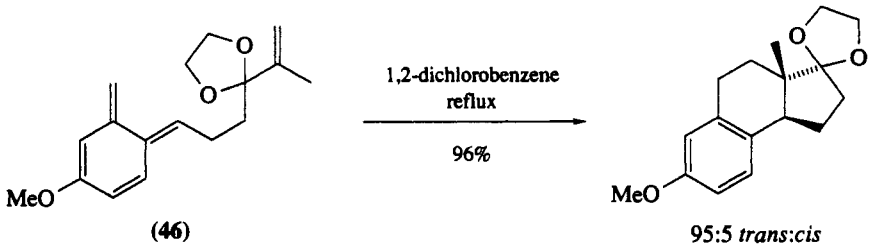


(43) plus *cis*-fused isomer >16:1



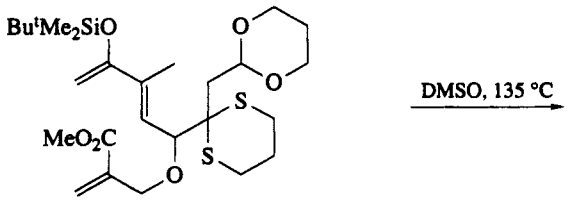
(44) R = *trans* only

(45) $R = CO_2Et$ 60:40 *trans*:*cis*

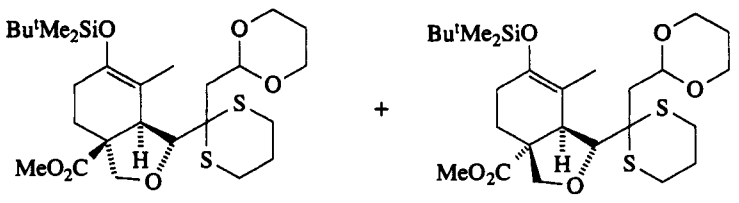


(46) 95:5 *trans*:*cis*

Figure 13



(47)



trans:*cis* 71:29

that is less severe in the *cis*-fused transition structure. A single C(6)-alkoxy substituent also increases selectivity for the *cis*-fused product, so the effect may not be entirely steric in origin.[16b,56] Interestingly, the same substitution pattern leads to a slight increase in *trans* stereoselectivity with nonatriene substrates.[11]

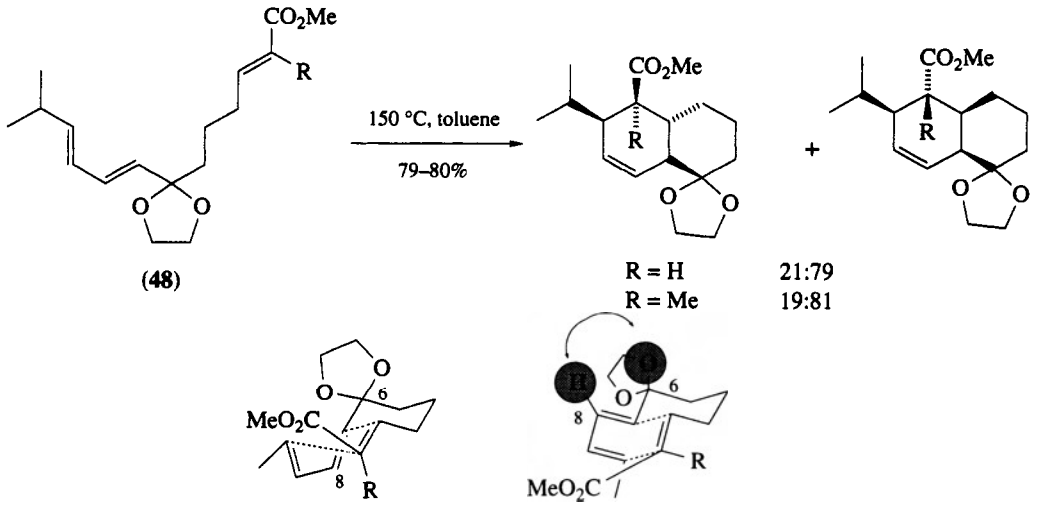


Figure 14

4.4.2.1.4 Influence of conformational effects on diastereoselectivity

Conformational effects also play an important role in determining IMDA diastereoselectivity. For example, trienes like (**49**) and (**50**) with two sp^2 hybridized atoms within the connecting chain cyclize preferentially to *cis*-fused rather than the *trans*-fused products that would be expected based on the presence of the C(8)-methyl substituent (Figure 15).[57] The benzo fusion forces the bridging chain to adopt boat-like conformations in the transition states, and the 1,3-diaxial interactions that the C(8)-methyl ordinarily experiences in the *cis*-fused, chair-like transition state are thus relieved (refer to Figure 12). The preferential formation of the *cis*-fused diastereomer may then be the consequence of a favored skew butene rotamer at C(6)—C(7) in (**51**) compared with a less favorable *gauche* butene rotamer at this position in the *trans*-fused transition state.[58] This effect is discussed in more detail in Section 4.4.3.2 concerning relative diastereoselection in the IMDA reactions of substituted decatrienones.

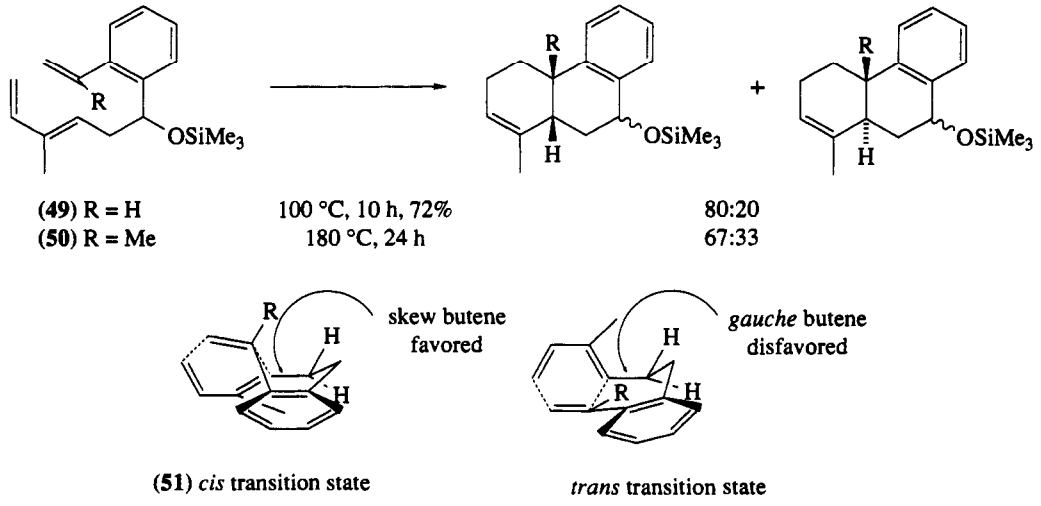
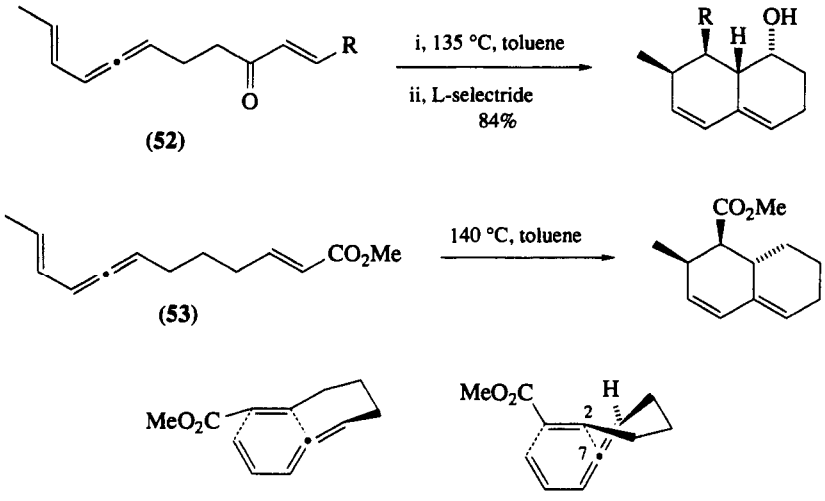


Figure 15

A variety of IMDA reactions have been reported for which only one set of transition states are accessible due to strain in the other. This factor is responsible for the exclusive production of *cis*-fused cy-

cloadducts in the IMDA reactions of (*Z*)-nona- and deca-trienes,[4e,8] and of the *syn* cycloadducts in type II IMDA cycloadditions (refer to Figure 1).[9] This conformational effect is probably also involved in the thermal isomerizations of allenic tetraenes (**52**)[59] and (**53**)[60] that cyclize *via* the same transition state even though the two substrates differ in terms of internal (**52**) *vs.* external (**53**) dienophile activation (Figure 16). An *exo* folding of the connecting chain in transition state (**54**) is much more easily accommodated than the *endo* folding in (**55**) owing to strain in the connecting chain that develops as C(2) and C(7) approach reasonable bonding distances.



(**52**)

(**53**)

(**54**) *exo* fold

(**55**) *endo* fold, strained

Figure 16

4.4.2.2 Heteroatom-substituted Nona- and Deca-trienes

Numerous IMDA reactions of heteroatom-substituted systems have been described.[5] In this section we provide an overview of the factors that influence diastereoselectivity of these cycloadditions, in comparison with the behavior of similarly functionalized all-carbon nona- and deca-trienes.

4.4.2.2.1 Heteroatom substituents on the bridging chain

Replacement of one of the CH_2 groups of the chain bridging the diene or dienophile with an amine, ether or thioether unit has a relatively minor effect on the IMDA diastereoselectivity, at least with relatively simple trienes such as (**56**)–(**58**) (Figure 17). Thus the stereoselectivities of the IMDA cyclizations of (**56**)[8b] and (**57**)[61] are comparable with that for (**8**) (Figure 3 and Table 2), and the cyclizations of (**58**) and (**59**) also give very similar product mixtures.[61]

A significant alteration of diastereoselectivity occurs with C(8)-substituted trienes like (**60**), however, since replacement of the C(5)-methylene by an NH group greatly reduces steric interactions in the *cis*-fused transition state that are important in enhancing stereoselectivity for the *trans*-fused product (refer to Figure 12). The results with (**61**) are more typical of all-carbon cases (Figure 18).[62]

Stereoselectivity in the IMDA reactions of heteroatom-substituted nonatrienes series sometimes shows a much greater departure relative to all-carbon analogs (Figure 19).[63–65] This is especially so in the case of (**63**)[64] compared to (**3**) in Figure 2, perhaps due to the reduced 1,3-interactions between C(7)-H and N(4) in the *cis*-fused transition state. The more highly activated triene (**64**), however, displays excellent selectivity for the *trans*-fused product, a result that may be due to the presence of the two dienophile activating groups and the electron-releasing *p*-methoxyphenyl unit at the diene terminus (nonsynchronous transition state hypothesis).[65]

The presence of an amide linkage on the connecting chain exerts a significant influence on IMDA diastereoselectivity (Figures 20 and 21). These effects, first observed by Oppolzer,[62,66] are related to conformational preferences exerted by the amide unit. Thus urethane (**65**) presumably cyclizes exclusively through transition state ($\mathbf{71}_{cis}$) since ($\mathbf{71}_{trans}$) is destabilized by an eclipsing interaction between H(8) and

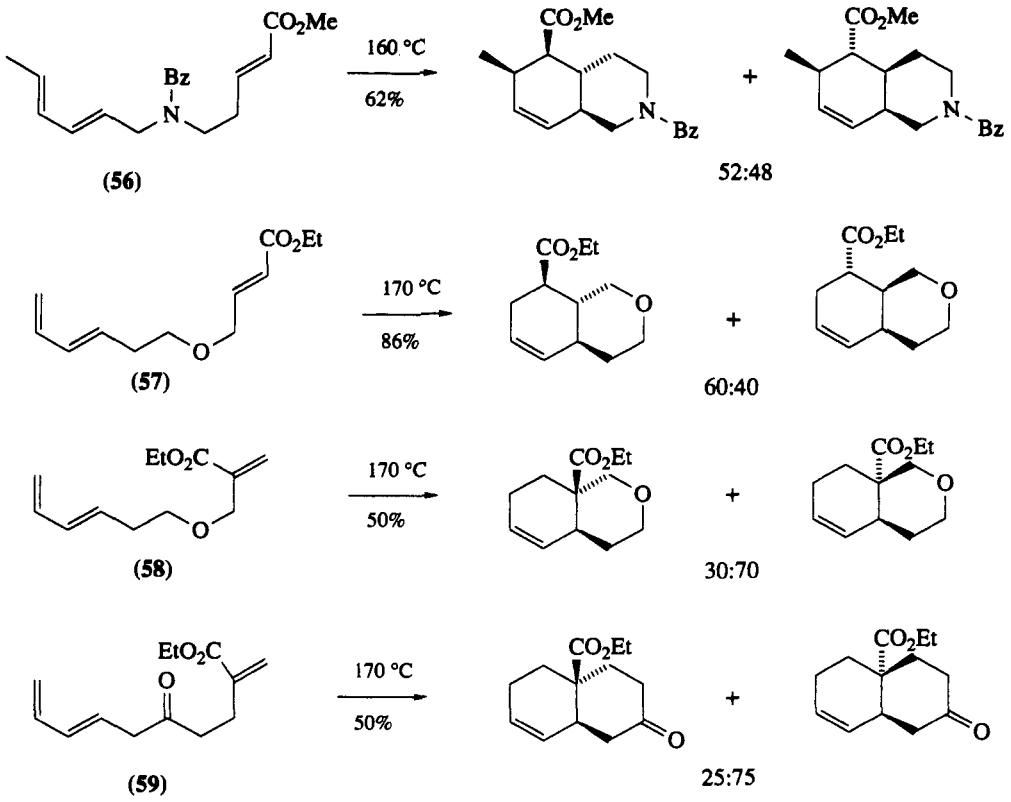


Figure 17

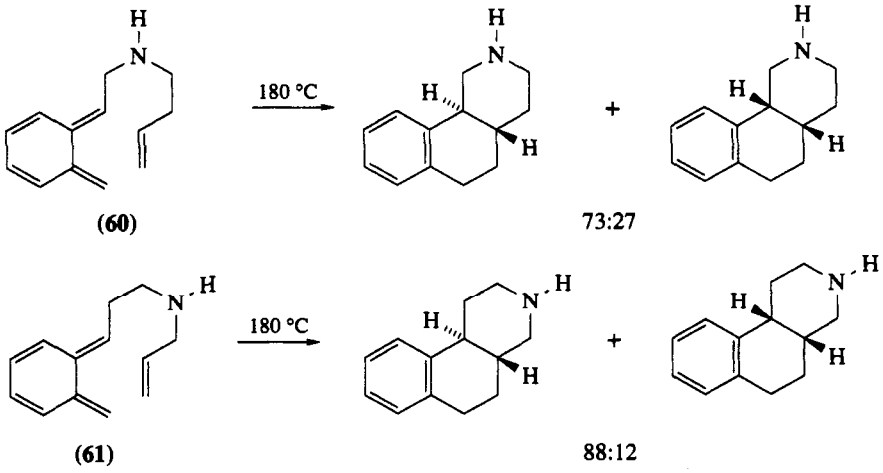


Figure 18

the CO_2Me unit.[66a] Triene (**66**), on the other hand, exhibits a modest preference for the *trans*-fused cycloadduct.[66a] Comparison of this result with the exclusive *trans* selectivity observed with (**67**)[67] supports the thesis that transition state ($\mathbf{72}_{trans}$) is intrinsically favored over ($\mathbf{72}_{cis}$) because the amide unit remains coplanar with the diene in ($\mathbf{72}_{trans}$),[66a] and because the C(3)-methylene unit interacts strongly with the diene in ($\mathbf{72}_{cis}$). Stereoselectivity with (**66**) is lower than with (**67**) presumably since ($\mathbf{72}_{trans}$) for (**66**) is destabilized by a 1,3-interaction between H(8) and the *N*-propyl unit. The only other triene that exhibits significant stereoselectivity in this series is (**70**),[68] and this IMDA reaction most likely proceeds through a boat-like transition state analogous to (**51**) of Figure 15. Consistent with this analysis is the report that a triene related to (**70**) but containing a C(8)-OTBDMS substituent also cyclizes to a 4:1 mixture of *cis*- and *trans*-fused products.[69] A C(8) substituent is not expected to influence significantly the relative en-

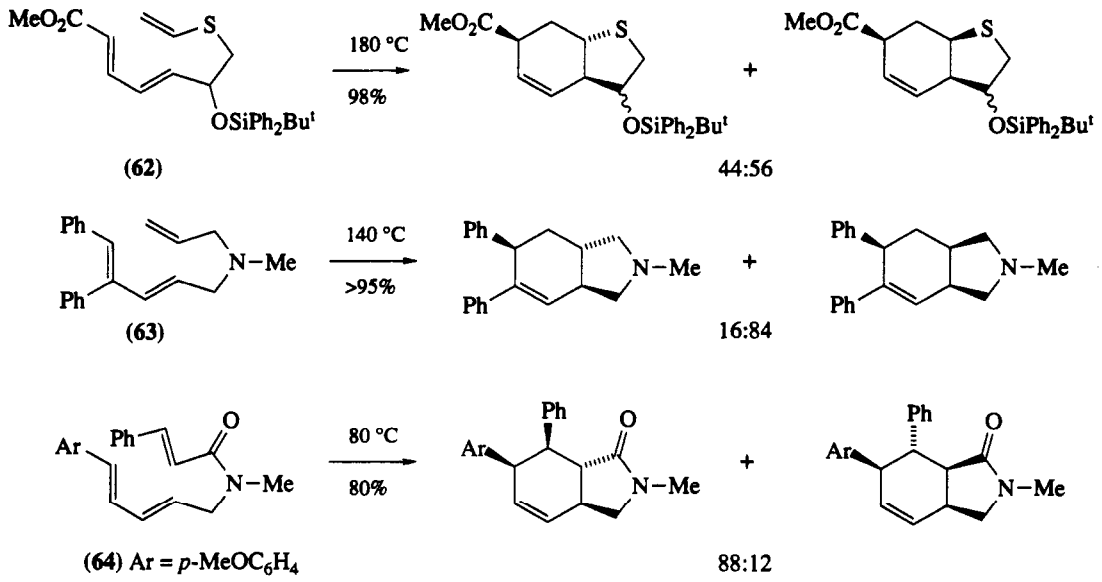


Figure 19

ergies of the *cis* and *trans* transition states if the connecting chain is in a boat conformation (refer to **51**; Figure 15).

Nonatrienes with amide linkages on the connecting chain generally exhibit a preference for the *cis*-fused product as long as a terminal dienophile activating group is not present (Figure 22). The *cis* stereoselectivity of (**73**)[66a] and (**74**)[70] is undoubtedly the result of eclipsing interactions involving H(7) and the nitrogen substituent in the *trans*-fused transition state (*cf.* **71**$_{trans}$) since stereoselectivity in the cyclization of (**74**) increases as the steric bulk of R increases.[70] Other results have been reported that are also consistent with this analysis.[66b,c] *Cis* stereoselectivity also is realized with (**75**), although with (**76**) a mix-

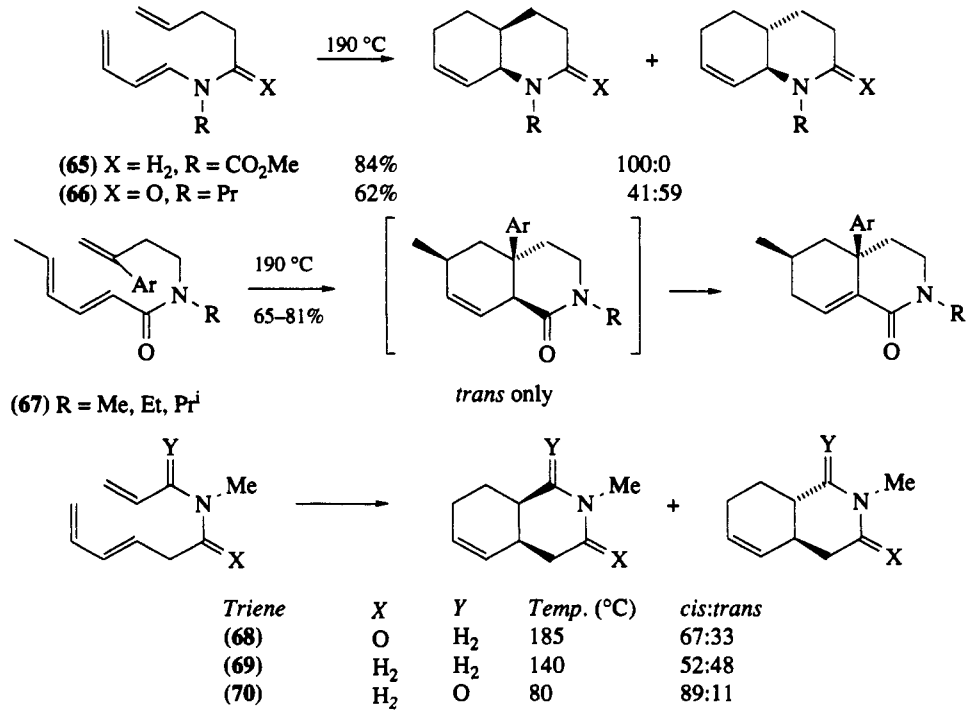
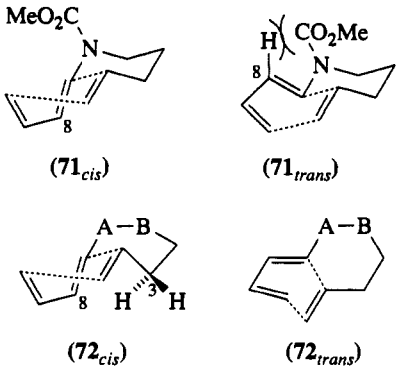


Figure 20

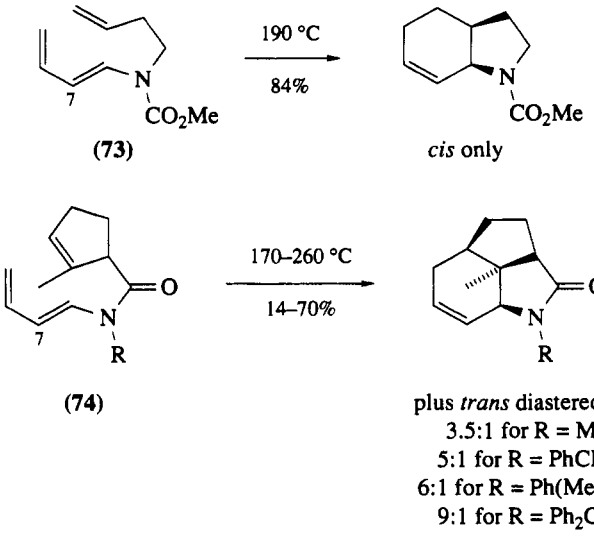


(71_{cis}) (71_{trans}) Transition states for (**65**)

(72_{cis}) (72_{trans}) Transition states for
(**66**) A = NPr, B = CO, and
(**67**) A = CO, B = NR

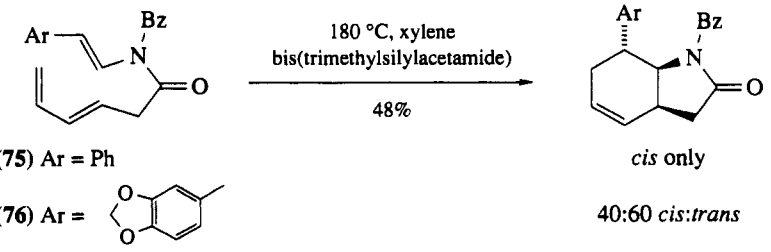
Figure 21

ture of *cis*- and *trans*-fused products is obtained.[71] These results have been rationalized in terms of the nonsynchronous transition state hypothesis. This theory also helps to explain the very high *trans* stereoselectivity exhibited by terminally activated trienes (**78**) and (**79**) compared with (**77**) (see also **64**; Figure 19).[64,65]



(**73**) *cis* only

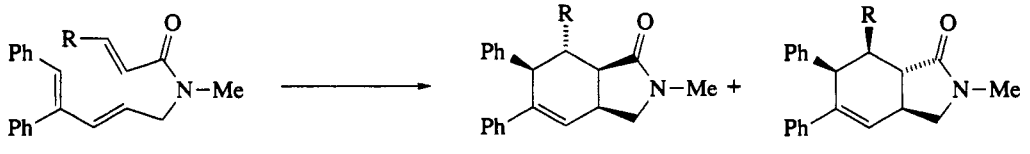
(**74**) plus *trans* diastereomer
3.5:1 for R = Me
5:1 for R = $PhCH_2$
6:1 for R = Ph(Me)CH
9:1 for R = Ph_2CH



(**75**) Ar = Ph
(**76**) Ar =

cis only

40:60 *cis*:*trans*



(**77**) R = H 110 °C, 82% 49:51
(**78**) R = Ph 90 °C, 61% 11:89
(**79**) R = CO_2Me 0 °C, 63% *trans* only

Figure 22

In contrast to carboxamide substitution, the presence of an ester linkage on the bridging chain often introduces problems due to the generally poor reactivity of the resulting trienic system. For example, trienes (**81**) and (**82**) fail to cyclize even when heated at temperatures up to 275 °C.[68] Triene (**80**) similarly fails to cyclize at 200 °C, but when heated at 220–225 °C migration of the diene occurs to give (**83**) that cyclizes to the indicated product mixture (Figure 23).[61] A triene related to (**83**) but lacking the diene methyl and the dienophile MeO_2C substituents required a temperature of 250 °C (120 h) for cyclization to occur.[68] The low reactivity of systems such as these has been attributed to poor overlap of the nonbonding electrons of the ethereal oxygen and the carbonyl group in the transition state,[61] and use of an acetal linkage in place of the reactivity deadening ester unit has been recommended as a solution to this problem.[72]

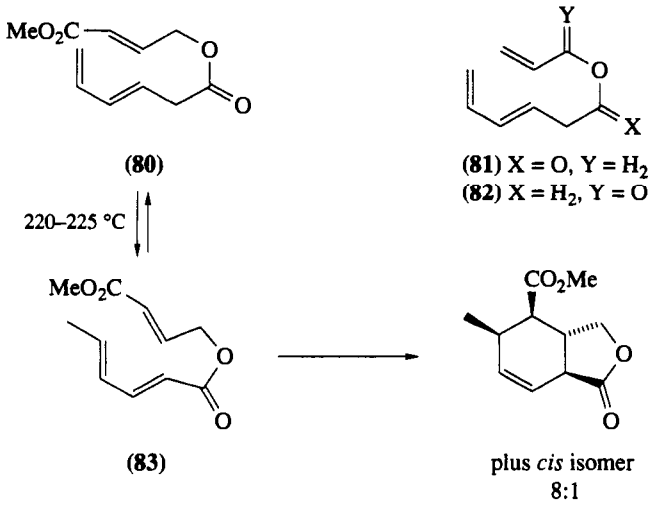


Figure 23

A second means of increasing the reactivity of trienes of general structure (**82**) is to add an additional activating group to the terminus of the diene.[73] The *trans*-fused product is generally favored in these reactions, except when a carboxylic acid is employed as the terminal dienophile activating group (Figure 24).[21,74–76] White has speculated that the aberrant behavior of acid (**87**) relative to ester (**86**) may be due to thermodynamic control.[21] On the other hand, it may be that the carboxylic acid is hydrogen bound to the adjacent ester carbonyl, thereby activating the internal ester such that it dominates the stereoelectronics of a nonsynchronous transition state. Additional examples illustrating the reversal of stereoselectivity by using a terminal carboxylic acid function have appeared, *e.g.* (**88**) *vs.* (**89**).[74]

4.4.2.2.2 Heterodienes and dienophiles

The use of heterodienes and dienophiles, particularly systems containing nitrogen and oxygen substituents, has found increased application in natural products synthesis.[77] Replacement of a carbon atom by a heteroatom on the diene appears to have little effect on the IMDA diastereoselectivity; several representative examples are summarized in Figure 25[78–81] that are in excellent agreement with all carbon diene cases discussed earlier. A particularly interesting case is (**94**) that exhibits a modest preference for the *trans*-fused product when R = H, but which strongly favors the *cis*-fused cycloadduct when R = Me.[81d] This is due to nonbonded interactions between R and the phenyl unit that are more serious in the *trans* transition state; note that in this case the benzo fusion prevents the bridging chain from adopting the usual chair-like conformation that is ordinarily invoked with trienes with all sp^3 hybridized atoms on the connecting chain. The transition state in this case is probably better described as boat-like (see Figure 44 for one representation).

Introduction of heteroatom substituents in the dienophile has a significant effect on diastereoselectivity of the IMDA cyclization owing to electronic effects. For example, trienes (**96**) generated by thermolysis of (**95**) cyclize with excellent stereoselectivity to cycloadduct (**97**) with a *trans* relationship between the two stereocenters on the ring (Figure 26).[82] Assuming that the dienophile has (*E*) geometry as suggested

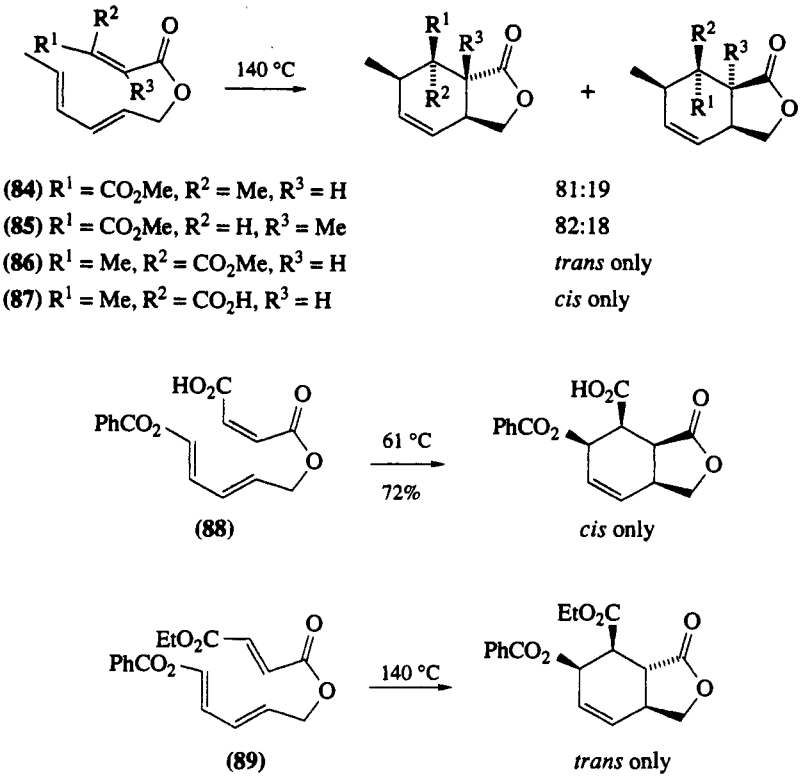


Figure 24

by Weinreb, then it is necessary that (**96**) cyclize *via* transition states in which the internal acyl imine is *endo* and the terminal methoxycarbonyl group is *exo*. This is exactly the opposite of the stereochemistry realized with analogous all carbon dienophiles, *cf.* (**86**) and (**89**) (Figure 24).[74a,c] This difference may be rationalized, however, by invoking a nonsynchronous transition state in which the highly electrophilic acyl imine function dominates the stereoelectronics. Heteroatom substitution at the dienophile terminus also influences IMDA diastereoselectivity, as illustrated by the results summarized in Figure 26 for N, Se and S substituted trienes (**98**)–(**100**).[83–85]

4.4.2.3 Transannular Cycloadditions

Several detailed investigations of transannular IMDA cycloadditions have appeared in recent years.[86,87] This transformation promises to become an important synthetic method owing to the potential for the rapid efficient construction of complex polycyclic ring systems.[88] Other potential strategic benefits include increased reactivity due to diminished entropic requirements ($\Delta S^{\ddagger}$). This is nicely illustrated by the facile cyclization of (**101**) with a tetrasubstituted dienophile, compared with the unsuccessful IMDA reaction of (**102**) (Figure 27).[86c] Although the cyclization of (**101**) proceeds with only moderate diastereoselection, many other examples have been reported that exhibit outstanding selectivity, *e.g.* cyclization of (**103**).[87] It is conceivable that conformational constraints imposed by the macrocyclic system may lead to improved IMDA stereoselectivity relative to conventional acyclic trienes, but this point has not yet been demonstrated in any published examples.

4.4.3 RELATIVE DIASTEREOSELECTION

Relative diastereoselection is an issue that is confronted most frequently in the IMDA reactions of trienes with one or more stereocenters on the chain connecting the diene and dienophile. As a general rule, trienes with saturated connecting chains cyclize *via* transition states with chair-like conformations, while boat-like transition states are frequently encountered with the 1,7,9-decatrienones as well as with

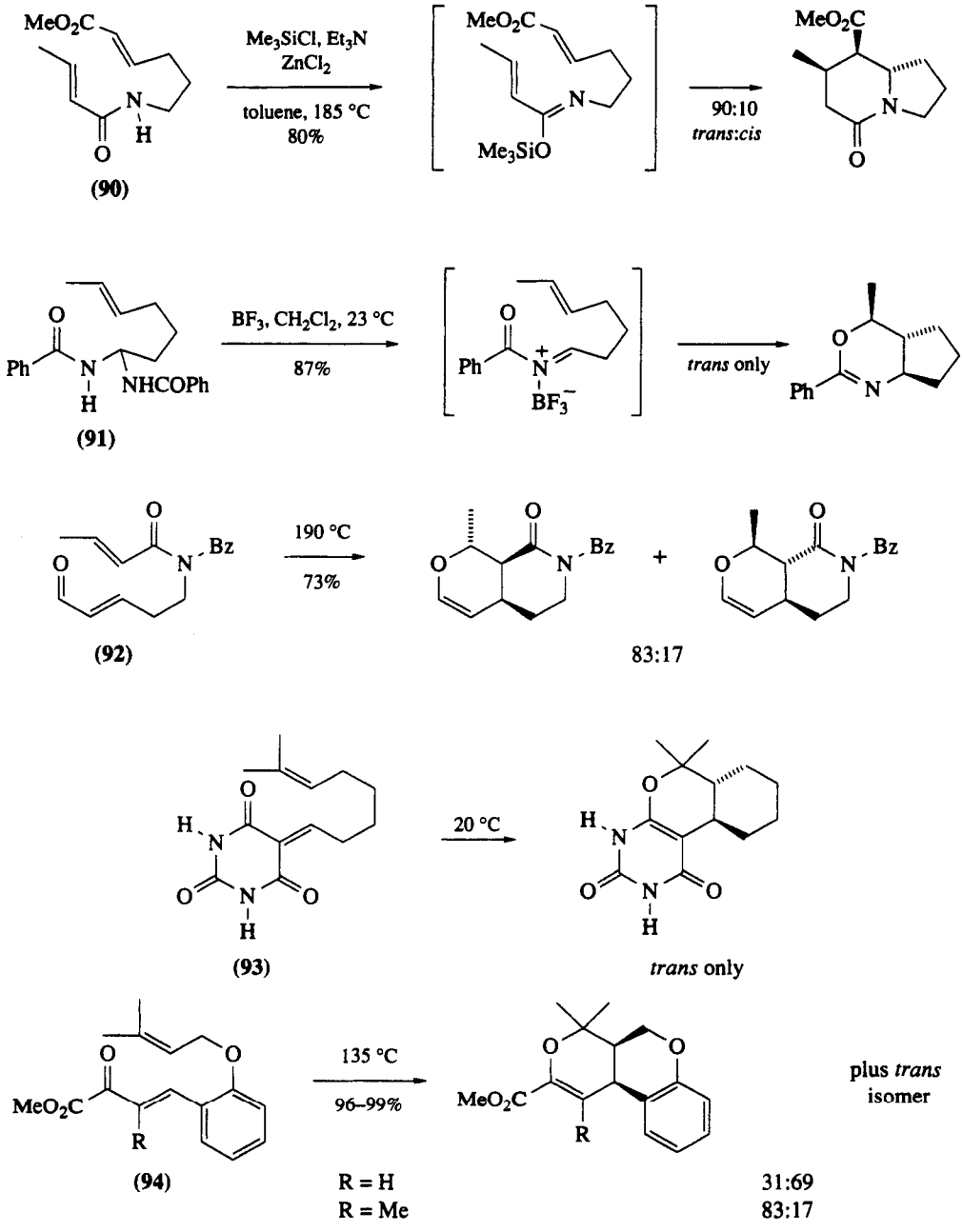


Figure 25

trienes such as (**49**) (Figure 15) that contain one or more sp^2 hybridized atoms on the connecting chain. The stereochemical consequences of these transition states are considered in the following sections.

4.4.3.1 Trienes with Saturated Connecting Chains

Figure 28 defines the sterically preferred orientation of substituents in the *trans*- (**104**) and *cis*-fused (**105**) transition states for conformationally mobile monosubstituted 1,7,9-decatrienes. Substituents at R^1, R^2 and R^3 will preferentially occupy the sterically less demanding equatorial positions in both transition states. Dienylic R^4 substituents generally adopt an equatorial position in the *trans*-fused transition state (**104**), while an axial orientation appears to be sterically favored in the *cis* transition state (**105**) (for example, refer to cyclizations of (**17**) and (**18**), Figure 6). Equatorial placement of R^4 in (**105**) introduces

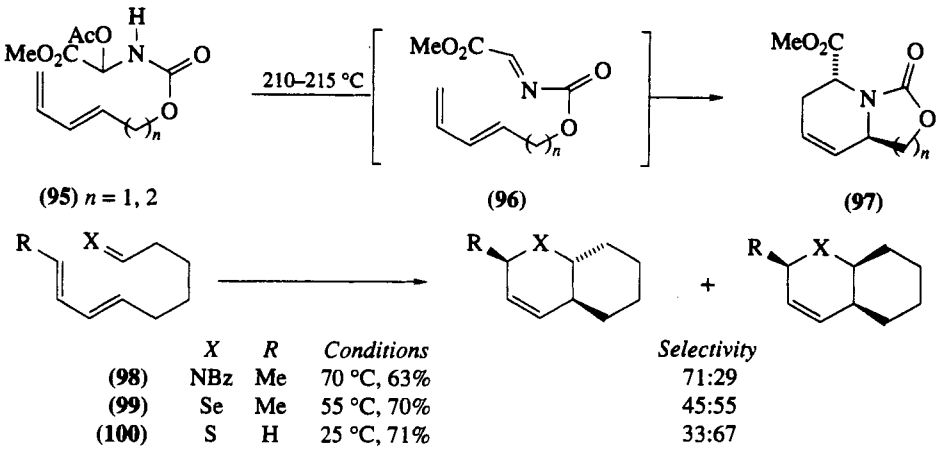


Figure 26

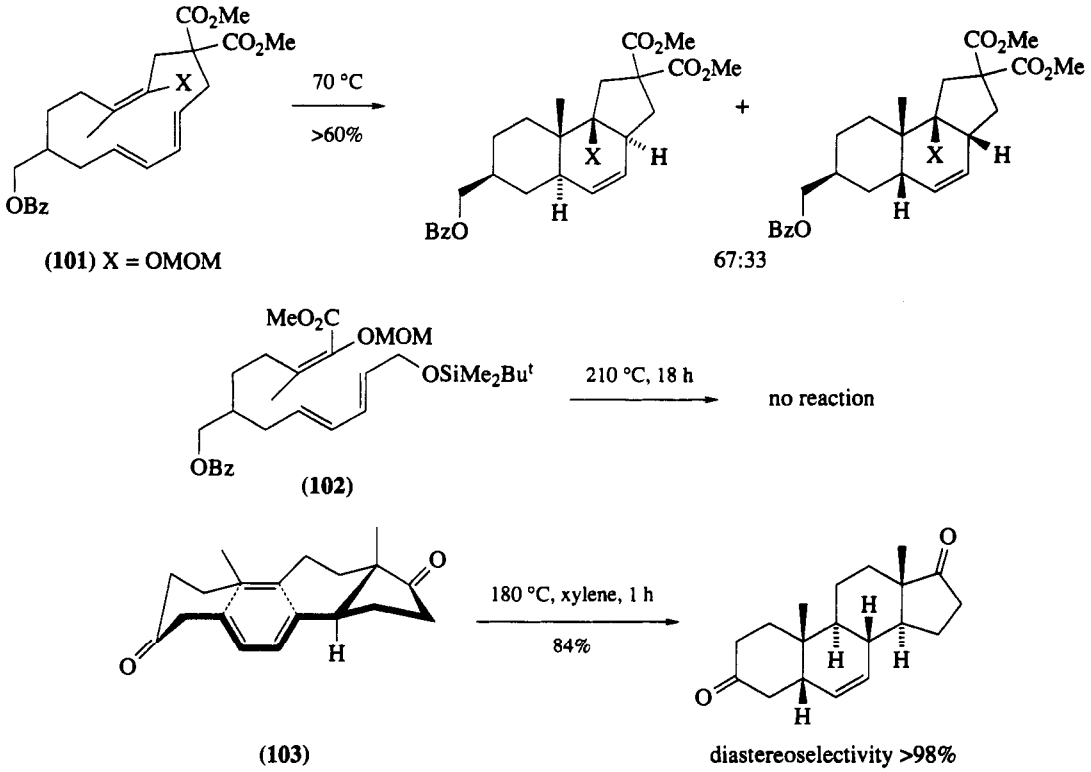


Figure 27

nonbonded allylic interactions with C(8), and thus is often disfavored relative to the axial position.[95h] Similar considerations apply in the nonatriene series, particularly with respect to the two allylic substituents (transition states (**106**) and (**107**), respectively).

The examples presented in Figures 29[29,89,90] and 30,[54,91–94] along with other cases discussed earlier, *e.g.* (**33**), (**47**), (**101**) and (**103**), plus numerous additional ones described in the literature,[29,95] are supportive of this analysis. This discussion of course applies explicitly to trienes with a single substituent on the chain linking the diene and dienophile. When two or more substituents are present, then the observed diastereoselectivity will depend on the relative stereochemistry and the individual preferences for equatorial *vs.* axial placement in the various diastereomeric transition states. In this respect, the very high *cis* ring-fusion selectivity exhibited by (**114**) is noteworthy.[94] The excellent stereoselectivity in this case may be due to the fact that both allylic alkoxy substituents can occupy sterically preferred positions in the *cis*-fused transition state (**107**), even though the preference for each alkoxy group to do so is not large (*vide*

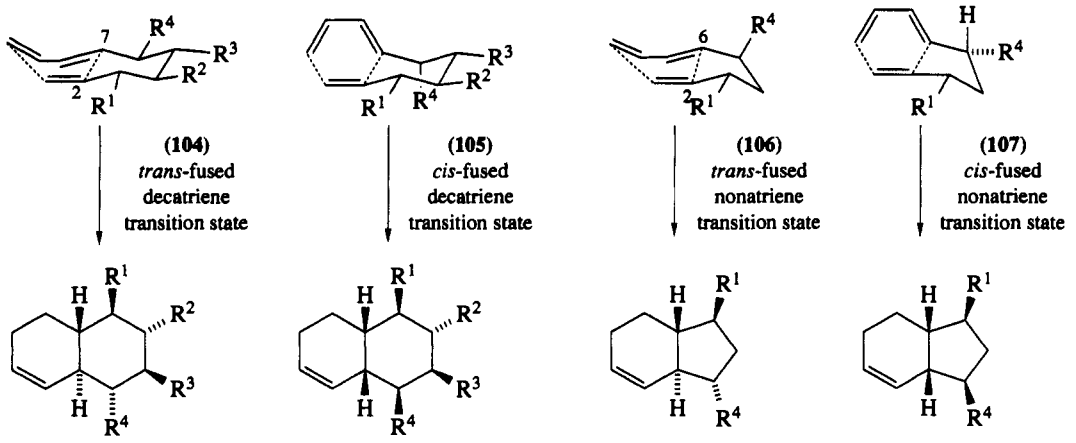
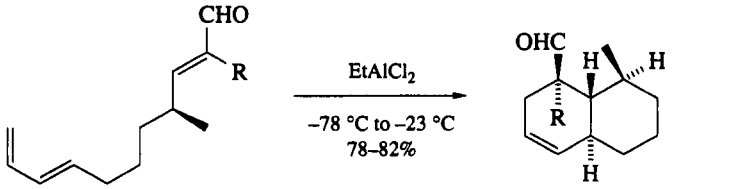


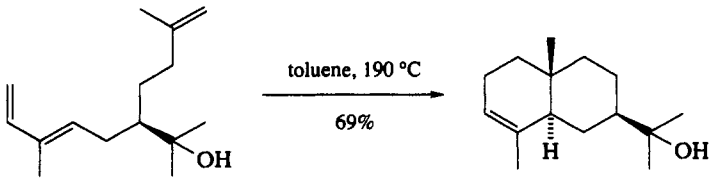
Figure 28 Diastereoselectivity in IMDA reactions of conformationally mobile, monosubstituted 1,7,9-decatrienes and 1,6,8-nonatrienes: sterically favored transition states

infra). This is not possible, however, in the *trans*-fused transition state (**108**). The effect of solvent on stereoselectivity in the cyclizations of (**110**)[90] and (**113**)[54g] is also worthy of note.

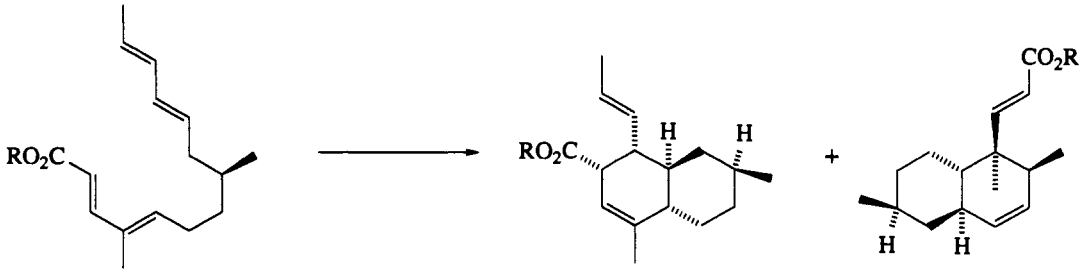
Exceptions to these generalizations occur if the system is constrained to cyclize *via* transition states with substituents in axial positions. Two examples appear in Figure 31. The IMDA cyclization of (**115**)



(**108**) >95% selectivity for R = H, Me

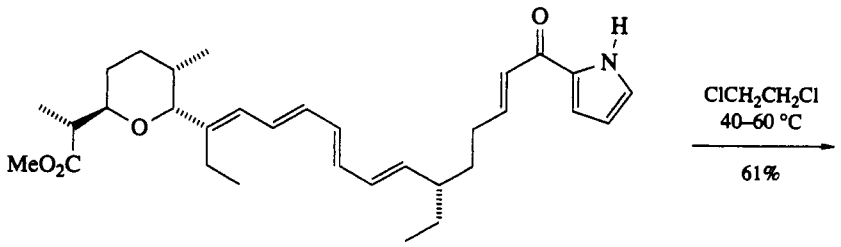


(**109**) major product (82:9:5:4 mixture)

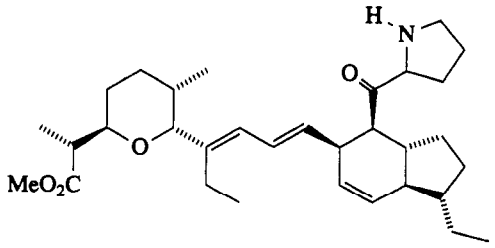


(**110**)	R = Et	toluene, 165°C, 80%	75:25
	R = Et	H_2O, 100 °C, 60%	40:60
	R = Na	H_2O, 100 °C	11:89

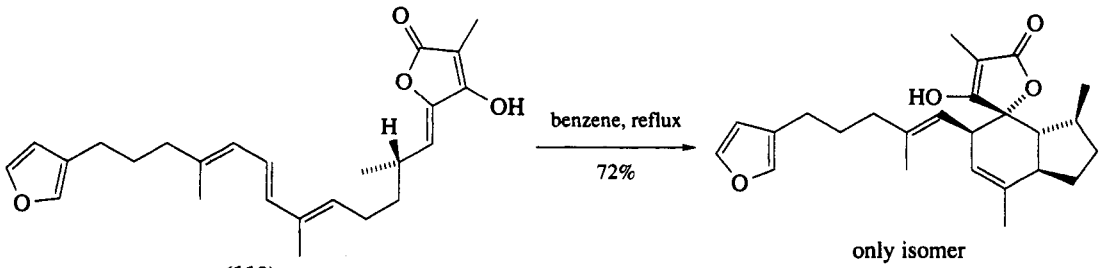
Figure 29



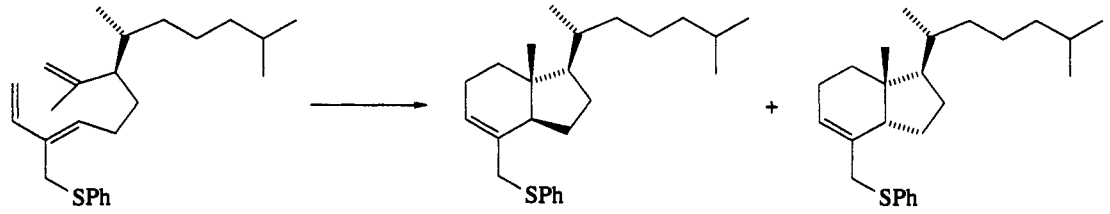
(111)



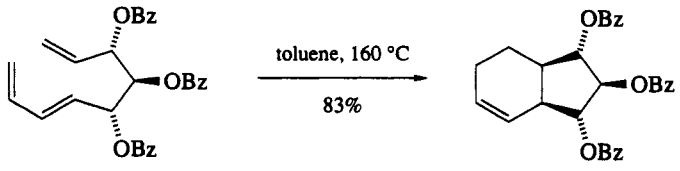
trans- to *cis*-fused = 10:1



(112) only isomer



(113)	dimethylaniline, reflux, 80%	71:29
	toluene, 210 °C	50:50



(114) only isomer

Figure 30

nicely illustrates the strategic consequences of linking two substituents into axial positions in the transition state, in this case as a lactone, since in addition to obtaining products with stereochemical relationships not accessible from trienes lacking the lactone bridge, competition from *cis*-fused transition states was also effectively eliminated, *e.g.* refer to Figure 12.[96] Triene (**116**) cyclizes *via* a chair-like transition state with two substituents, the C(3)-methylene and C(6)-$OSiMe_3$ groups, in axial positions even though the latter interacts strongly with the diene C(8) substituent.[97] The major stereochemical control elements

in this system are the C(3) stereocenter that restricts the diene to approach only one face of the cyclopentenone dienophile, and the substitution pattern of the diene that precludes transition states leading to *cis*-fused products (Figure 12). Consequently, only a single transition state is available to (**116**) and the C(6)-OSiMe$_3$ group has no choice but to occupy an axial position where it eclipses the diene.

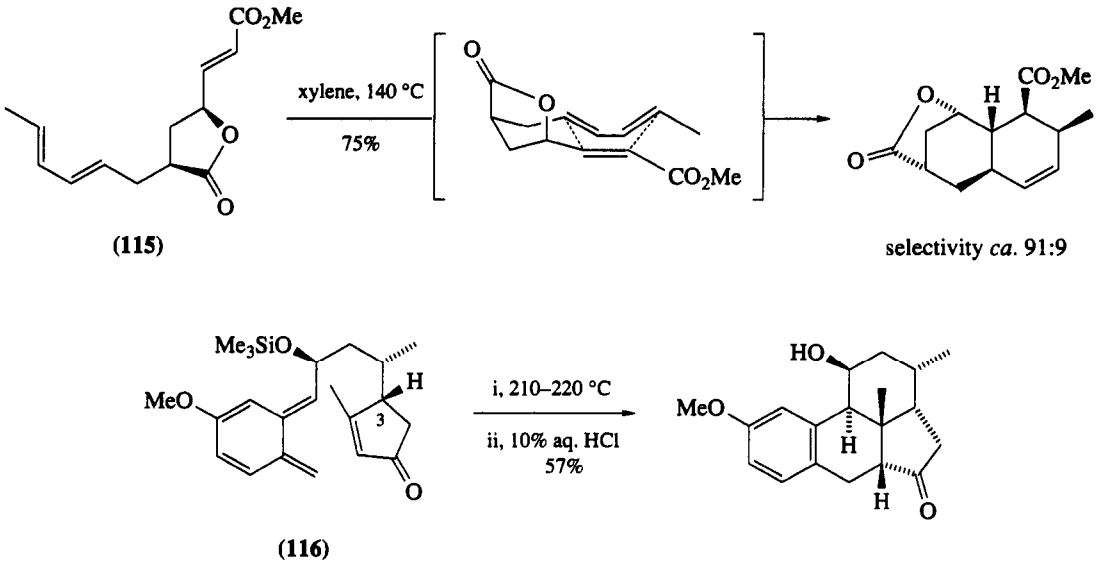


Figure 31

The addition of a ring between the diene and the bridging chain also has an influence on IMDA diastereoselectivity. This structural feature restricts the number of degrees of conformational freedom that are accessible, and in the vast majority of cases the dienophile approaches the diene from the same face as the stereocenter, *e.g.* (**117**) (Figure 32).[98,99] One exception, however, occurs with triene (**118**) that cyclizes preferentially *via* a transition state with the dienophile approaching from the face opposite to the anchor position of the tether.[100] The factors responsible for this unusual result remain to be clarified.

Numerous exceptions to the stereochemical picture presented in Figure 28 occur with trienes possessing allylic heteroatom R^1 and R^4 substituents, particularly allylic alkoxy groups. These substituents are considerably less sterically demanding than methyl or other alkyl groups,[101] and electronic effects may

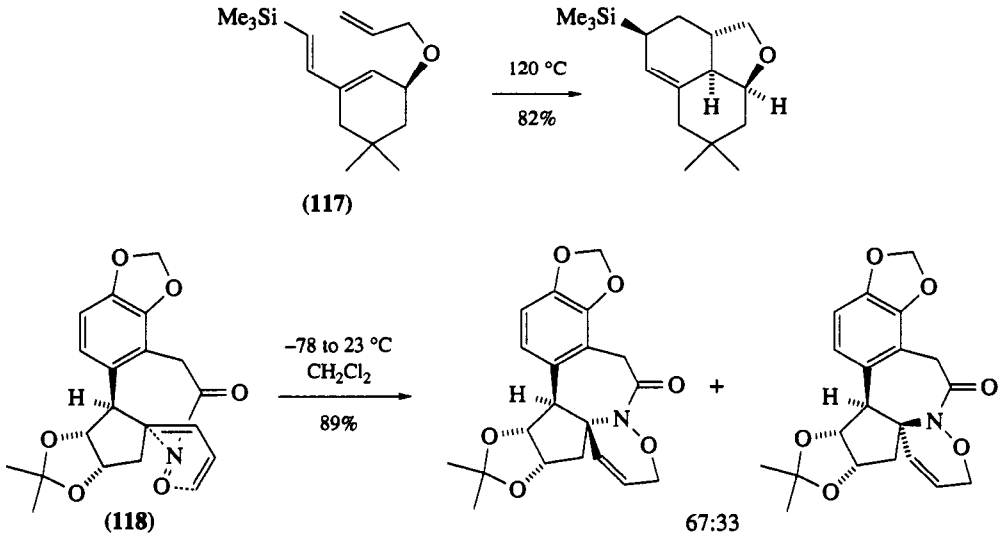
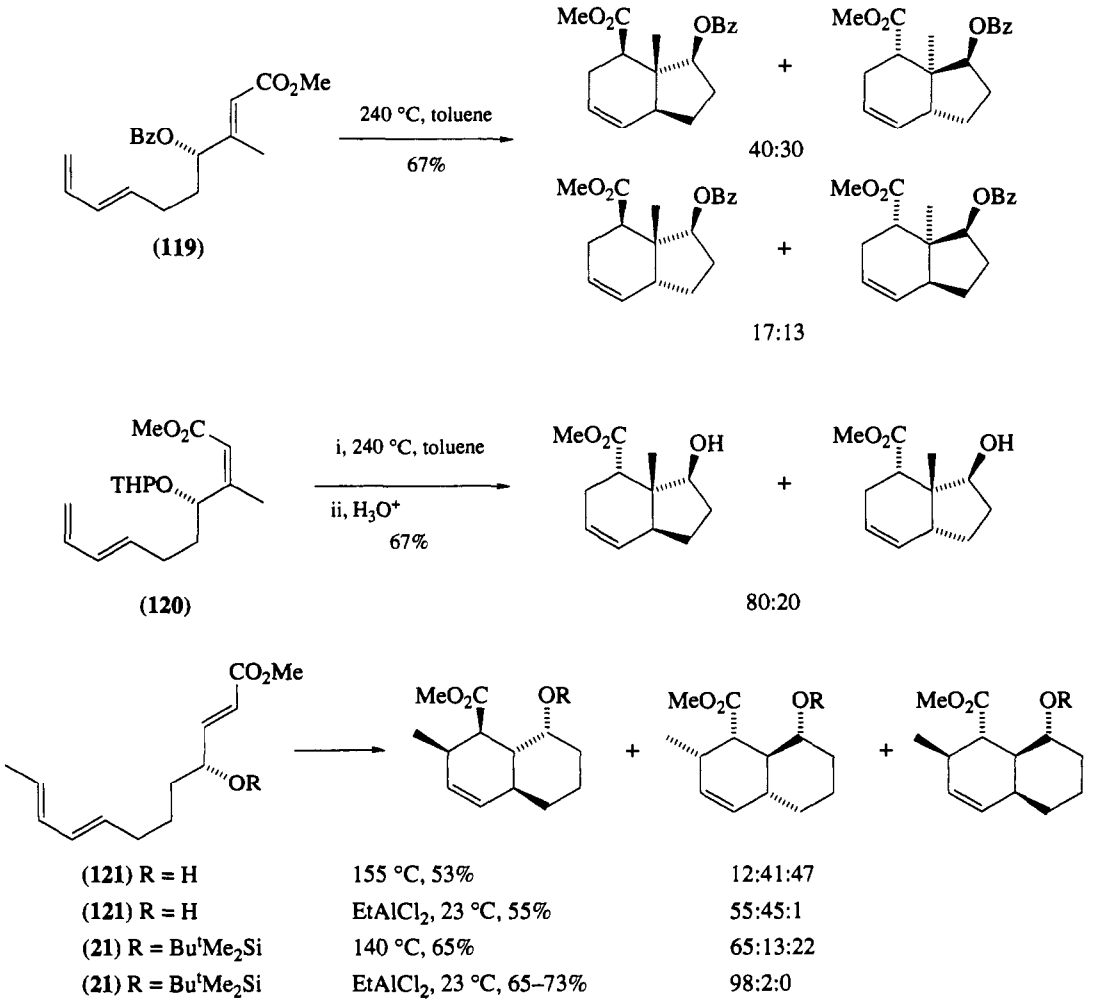


Figure 32

also intervene such that an axial orientation in the transition state is sometimes favored. The examples presented in Figure 33 serve to illustrate these points. The alkoxy group of (**119**) exhibits only a slight preference for orientation in the pseudoequatorial R^1 position in transition states (**106**) and (**107**), and diastereoselectivity is much lower than with alkyl substituted trienes like (**113**) (Figure 30).[12a] With triene (**120**), however, diastereoselectivity is much higher owing to $A_{1,3}$ interactions between the benzyloxy and CO_2Me groups in the transition state, with the former in a pseudoaxial position.[12a] A slightly greater preference for equatorial placement of the hydroxy group occurs in the thermal IMDA reaction of (**121**), but this preference disappears if the cycloaddition is catalyzed with $EtAlCl_2$ or if the hydroxy is protected as a *t*-butyldimethylsilyl (TBDMS) ether; the effects appear to be additive in this case.[102] The preference for pseudoaxial placement of the TBDMSO group in this reaction has been ascribed to a hyperconjugative interaction (σ_{C-O}–$\pi^*_{C=C}$) that lowers the dienophile LUMO and thereby increases the rate of reaction *via* this transition state.



(**121**) R = H	155 °C, 53%	12:41:47
(**121**) R = H	$EtAlCl_2$, 23 °C, 55%	55:45:1
(**21**) R = Bu^tMe_2Si	140 °C, 65%	65:13:22
(**21**) R = Bu^tMe_2Si	$EtAlCl_2$, 23 °C, 65–73%	98:2:0

Figure 33

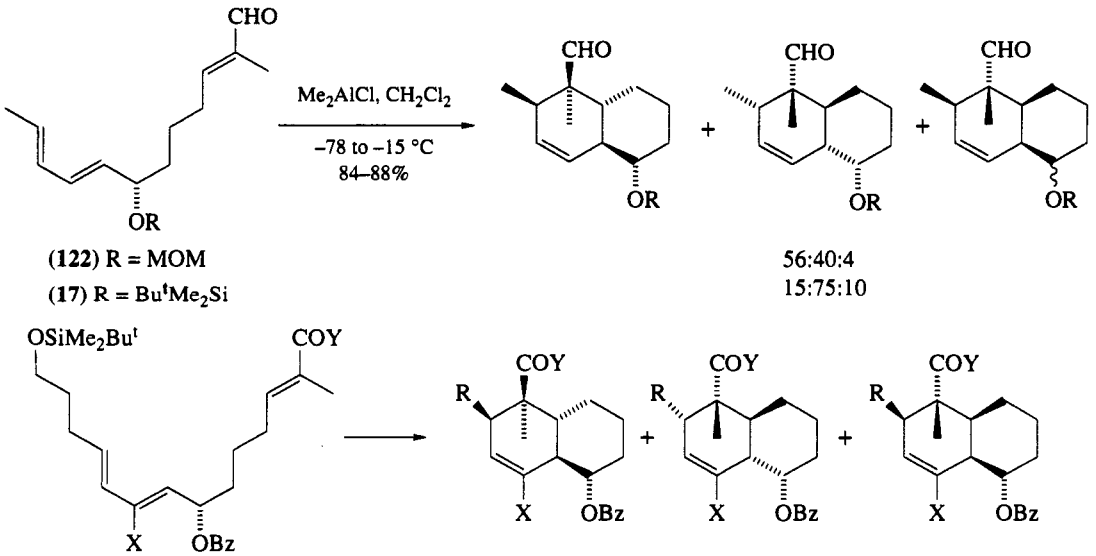
Alkoxy groups at the R^4 position allylic to the diene also generally exhibit a modest preference for either the equatorial or axial placement in the transition state, and the dependence of stereoselectivity on the protecting group has been noted.[29e,103] Larger allylic heteroatom substituents such as a benzenesulfonyl group, however, exhibit a much greater preference for the less sterically demanding pseudoequatorial position.[27] Marshall has made the interesting observation that the axial alkoxy diastereomer is favored in Lewis acid catalyzed cyclizations as long as a silyl ether protecting group is employed; the silyloxy substituent necessarily eclipses the diene in the transition state. Diastereoselectivity is much lower with MOM ether protected substrates, suggesting a stereoelectronic component to these results (compare data

for (**17**) and (**122**), Figure 34).[29e] A similar preference for production of axial silyloxy diastereomers in the IMDA cyclizations of vinylnitrosonium cations has been noted by Denmark, who has provided a detailed discussion of the steric and stereoelectronic factors that presumably contribute to this stereochemical preference.[104] IMDA cycloadducts with equatorial alkoxy groups at the dienylic position can be prepared with good selectivity by application of the steric directing group strategy that also amplifies the selectivity for the *trans*-fused product (for example, trienes (**123**)–(**126**), Figure 34).[50b] The production of significant quantities of *cis*-fused products in these IMDA reactions, especially in the IMDA reactions of (**123**) and (**124**) where X = $SiMe_3$, suggests that the *cis*-fused diastereomers probably arise *via* a boat-like, and not a chair-like, transition state as is usually assumed (Figure 35).[49,50]

4.4.3.2 Decatrienones and Other Trienes with Unsaturated Connecting Chains: Intervention of Boat-like Transition States

While most decatrienes cyclize *via* transition states with chair-like conformations of the connecting chain (*vide supra*), a growing body of evidence indicates that conformationally unrestricted decatrienones preferentially cyclize *via* boat-like transition states.[58] The stereochemical consequences of this are significant, particularly since the cycloadduct obtained *via* the the lowest-energy boat transition state (**127**) is not always the same as the one obtained from the lowest-energy chair conformation (**128**) (Figure 36). Three unambiguous cases that proceed either exclusively, *e.g.* (**129**),[58] or at least preferentially, *e.g.* (**130**)[105] and (**131**),[106] by way of boat transition states are summarized in Figure 37.[107] The IMDA reaction of (**131**) is particularly interesting in that the kinetic product (**132**) derives from a boat transition state, while the thermodynamic product (**133**) is produced *via* the higher-energy chair transition state.[106]

Boat-like transition states have also been implicated in the IMDA cyclizations of heteroatom substituted trienes such as (**134**), (**135**)[108] and (**137**)[109] (Figure 38). Additional support for the involvement of a boat transition state in the cyclization of (**135**) derives from studies of the corresponding immonium ion substituted triene [lacking the carbonyl unit of (**136**)] that presumably cyclizes by way of chair-like transition states and is considerably less diastereoselective.[95g]



(**123**)	X = $SiMe_3$	Y = OMe	160 °C, 85%	78:8:14
(**124**)	X = $SiMe_3$	Y = H	160 °C, 82%	79:9:12
(**124**)	X = $SiMe_3$	Y = H	Et_2AlCl, –15 °C, 77%	89:5:6
(**125**)	X = Br	Y = OMe	160 °C, 80%	62:4:34
(**126**)	X = Br	Y = H	160 °C, 86%	75:3:22
(**126**)	X = Br	Y = H	$EtAlCl_2$, –15 °C, 24%	90:1:9

Figure 34

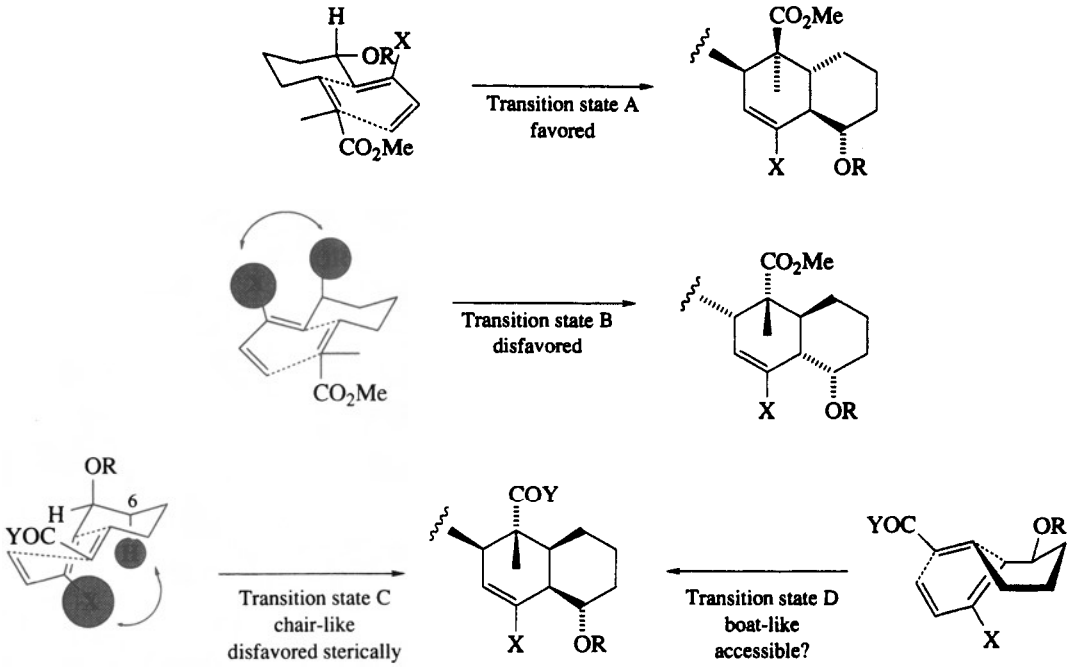


Figure 35 The steric directing group stategy

A rationalization of the preference of boat-like decatrienone transition states has been presented.[58] In the absence of overriding substituent effects, the boat-like transition state is free of destabilizing eclipsing or other unfavorable nonbonded steric interactions, and the C(4)—C(6) segment adopts staggered conformations in both the boat-like (**127**) and chair-like (**128**) arrangements (Figure 36). The principal difference between them is that in (**127**) the C(6)—C(7) unit exists in a favored skew butene conformation and the C(3)—C(4) unit in a favored eclipsed ethanone conformation, while in the chair-like arrangement (**128**) these sp^3–sp^2 rotamers exist in higher-energy *gauche* butene and *gauche* ethanone conformations, respectively. The presence of both stabilizing eclipsing sp^3–sp^2 interactions is unique to the *cis*-fused boat decatrienone transition state; all other decatrienone transition states have no more than one such stabilizing allylic conformation and the available experimental evidence suggests that they are each higher in energy than the *cis*-fused boat transition state.[58]

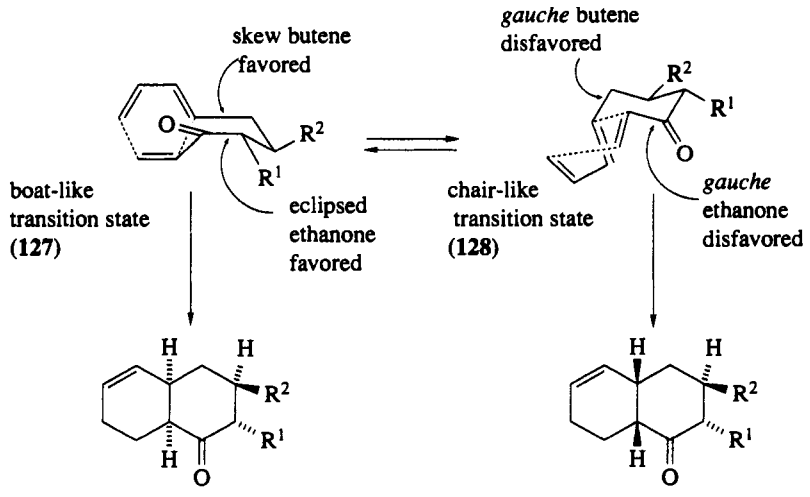


Figure 36

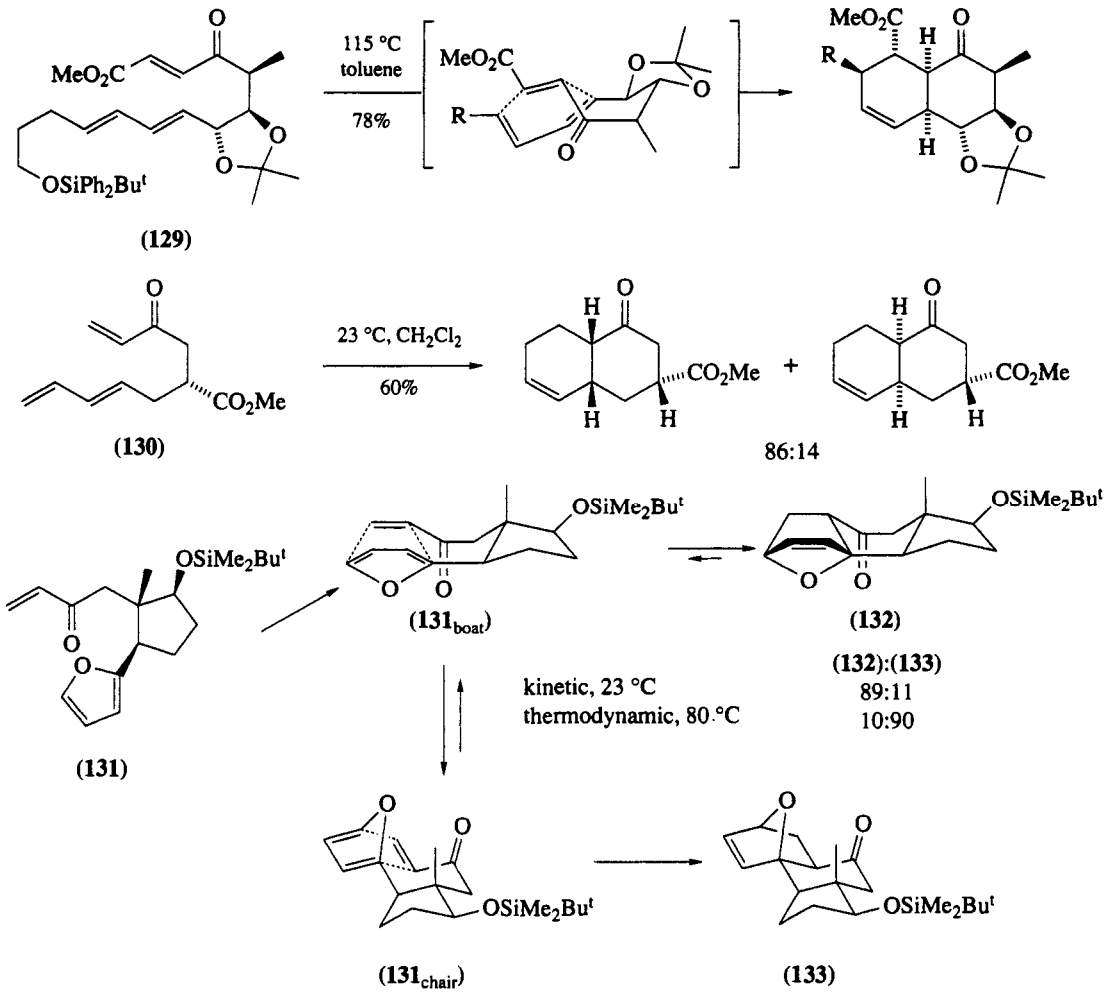


Figure 37

The preference for decatrienones to cyclize by way of boat-like transition states, while significant in the cases cited above, is not so great that competition from chair-like structures is precluded, especially in highly substituted systems. This is nicely illustrated by comparing the diastereoselectivity of the IMDA reactions of (**138**)[110] and (**139**)[111] (Figure 39). Thus triene (**138**) undoubtedly cyclizes by way of boat-like transition state (**140**) since the alternative *cis*-fused chair (**141**) is significantly destabilized by the indicated 1,3-interaction, while *trans*-fused transition state (**142**) is destabilized by the eclipsing interaction between the C(6)-OMe and C(8)-Me units. Examination of models, however, suggests that the two-atom bridge introduces strain into (**140**) relative to the unconstrained boat-like transition structure (**127**) in Figure 36. This is relevant, since replacement of the C(8)-Me with a hydrogen atom in (**139**) causes a reversal of stereoselectivity such that the *trans*-fused product is the only cycloadduct when the IMDA reaction of (**139**) is performed with Lewis acid catalysis. A chair-like transition state resembling (**142**), but lacking the C(8)-Me group, appears to be the most favorable one in this case. Additional examples have been reported that demonstrate that nonbonded interactions may be sufficient to tip the balance such that a chair-like decatrienone transition state is populated in preference to the otherwise favored boat-like arrangement.[58] Thus all possible interactions must be carefully analyzed when attempting to predict the diastereoselectivity of decatrienone (and other) IMDA cyclizations.

While boat-like transition states are frequently observed in decatrienone IMDA reactions, they are only rarely observed in decatriene IMDA reactions. Undoubtedly, this is due to the fact that boat-like conformations of the bridging chain when all atoms are sp^3 hybridized have one eclipsed ethane interaction not present in the chair-like arrangement. Consequently, the boat transition states are intrinsically higher in energy than the chair-like structures.[58] Products deriving from boat decatriene transition states have been observed only in circumstances where the chairs are destabilized by substituent effects or strain, *etc.* One example was presented in Figure 35 concerning the production of *cis*-fused dia-

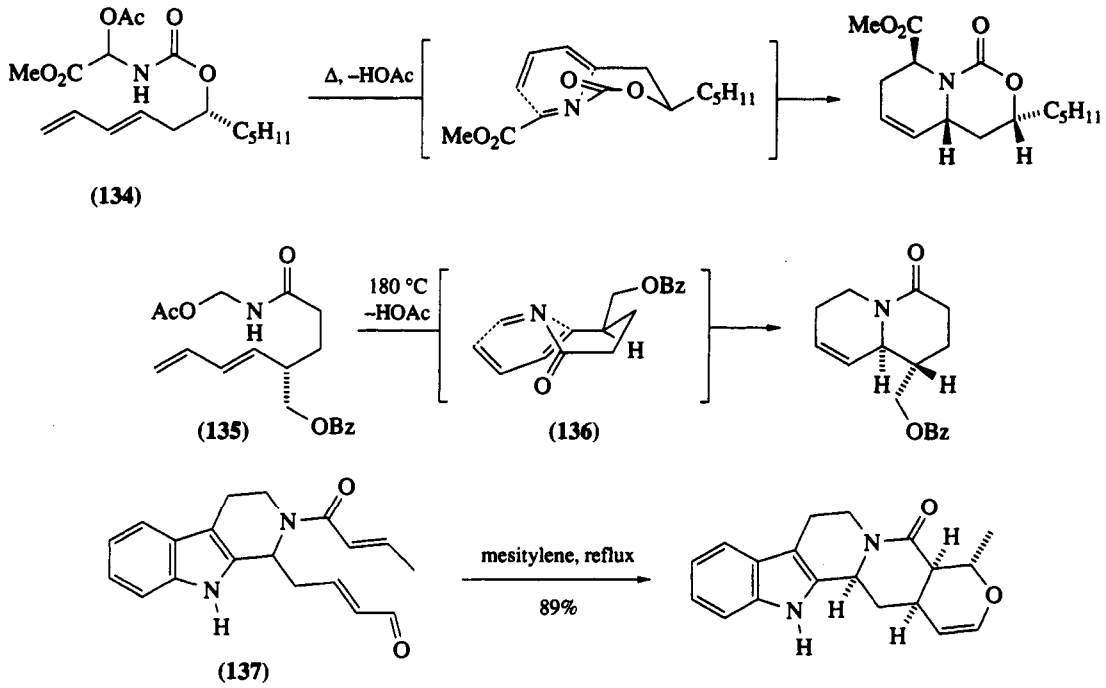


Figure 38

stereomers from the IMDA reactions of (**123**)–(**126**); a second example appears in Figure 40.[112] Koreeda has argued that transition state (**143**$_{chair}$) is strained and therefore higher in energy than (**143**$_{boat}$) since the chair conformation of bicyclo[3.2.1]octane, a model for the developing [3.2.1] bicyclic system in the cycloadducts, is considerably less stable than the boat conformation.[112]

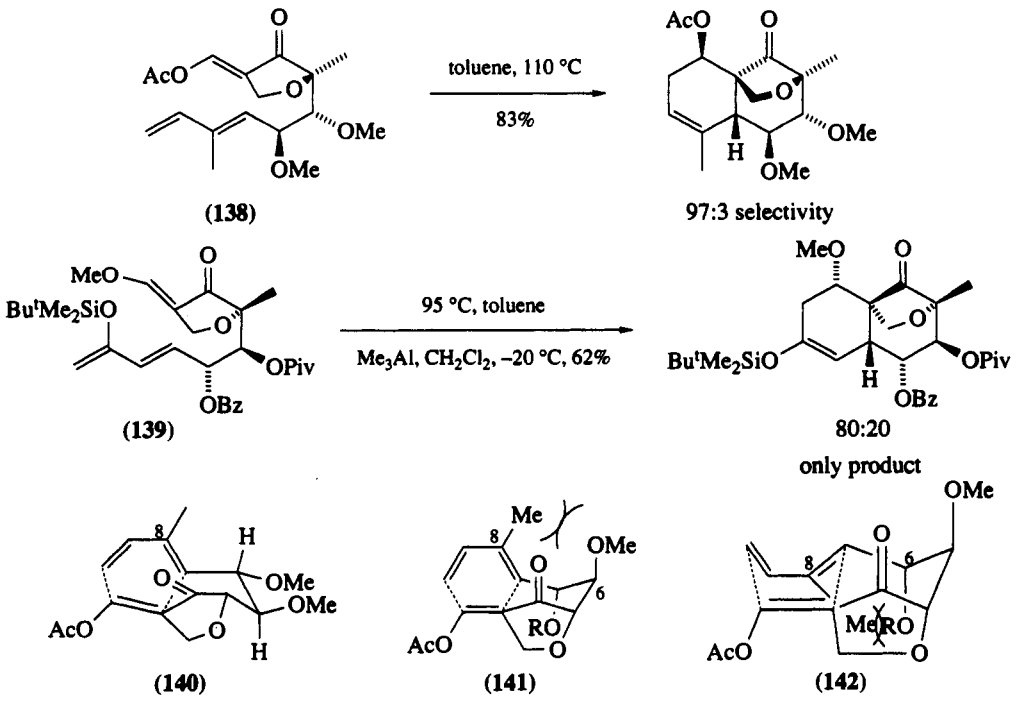


Figure 39

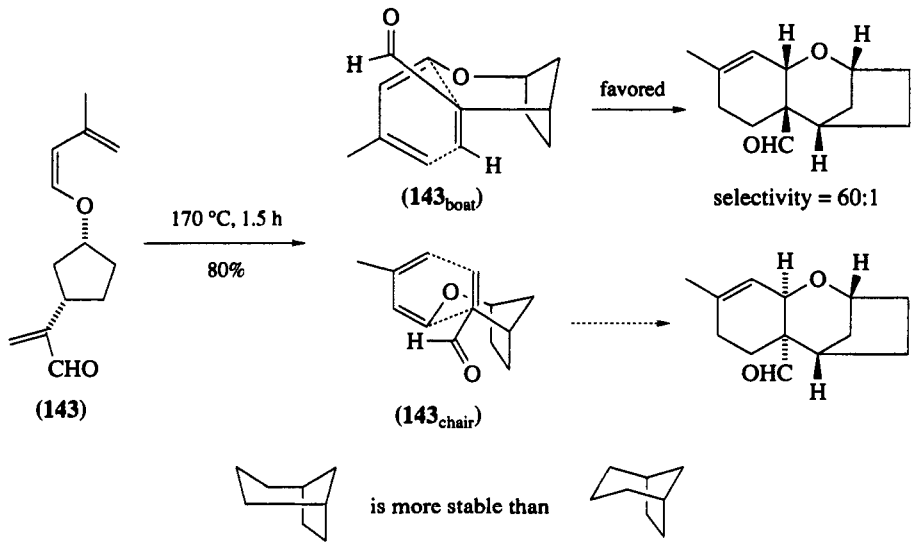
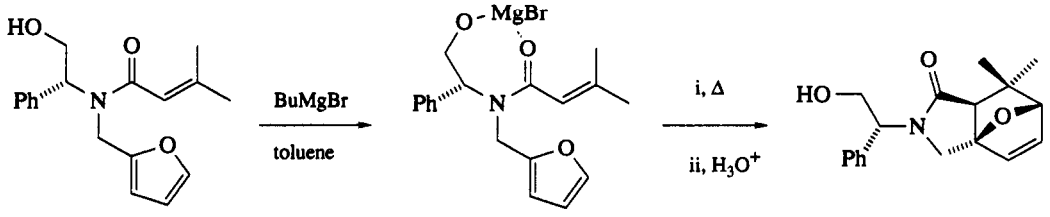


Figure 40

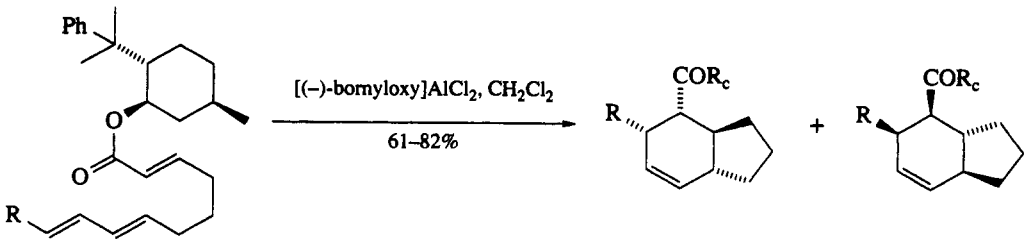
4.4.4 ASYMMETRIC INTRAMOLECULAR DIELS–ALDER REACTIONS

Reactions that involve asymmetric synthesis are traditionally classified separately from other diastereoselective transformations of chiral substrates, even though there is little fundamental difference between them. The degree of success realized in both categories depends on the ability of the chemist to distinguish between competing, diastereomeric transition states; the critical objective is to maximize $\Delta\Delta G^{\ddagger}$. This classification system undoubtedly evolved since the chiral auxiliary used in asymmetric reactions, whether it is introduced as part of a catalyst or is covalently bound to the substrate, is not destined to be an integral structural component of subsequent transformation products, while the reverse situation obviously pertains in the more frequently encountered diastereoselective transformations of chiral substrates. Work that has been reported for asymmetric IMDA reactions is summarized in this section.[113]

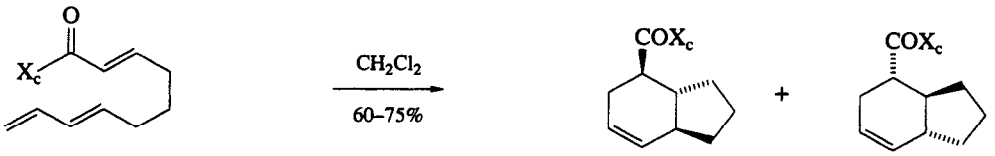
The first example illustrating the use of a removable chiral auxiliary in IMDA reactions was reported by Mukaiyama.[114] The Diels–Alder reaction of (**144**) was slow and showed no diastereofacial selectivity. Conversion of (**144**) to the magnesium alkoxide (**145**), in which the dienophile is activated by chelation to the magnesium ion, however, increased the rate of cyclization and provided the indicated cycloadduct with 76% diastereomeric excess (*de*; 88:12 mixture of diastereomers).



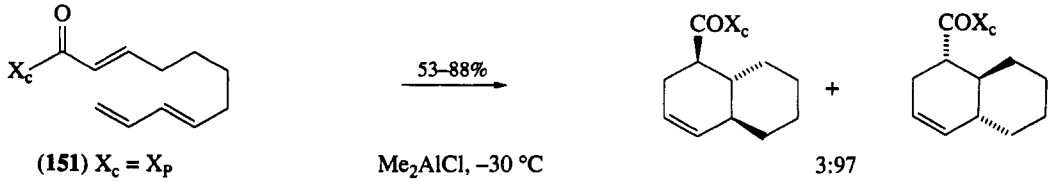
A number of trienes with auxiliaries associated with the dienophile activating group have been studied (Figure 41). The 8-phenylmenthyl auxiliary, that generally affords very good levels of asymmetric induction in bimolecular Diels–Alder reactions,[115] gives relatively poor results with trienes (**146**) and (**147**), probably due to the low reactivity of these trienoates that precludes cycloaddition at temperatures below 0 °C.[11a] Much better results have been achieved with trienes (**148**)–(**155**) incorporating the *N*-acyloxazolidinone, *N*-acyl sultam and α-hydroxy ketone auxiliaries developed by Evans,[116] Oppolzer[117] and Masamune,[118] respectively. Trienes (**148**)–(**153**) are considerably more reactive than (**146**) and (**147**) and their Lewis acid catalyzed cyclizations are complete typically within several hours at –20 °C or –30 °C.[116b,c,117b] *Trans*-fused cycloadducts are obtained with >99:1 selectivity from nonatrienes (**148**)–(**150**),



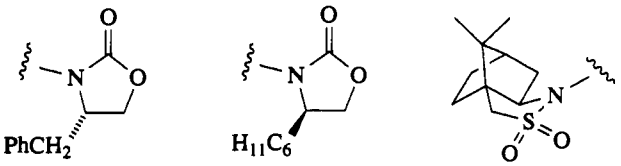
(146) R = Pr^i	23 °C, 92 h	67:33
(147) R = H	23 °C, 36 h	82:18
(147) R = H	8 °C, 330 h	86:14



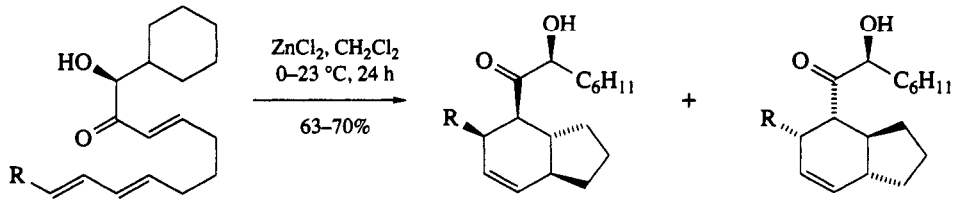
(148) $X_c = X_P$	Me_2AlCl, –30 °C	5:95
(149) $X_c = X_{PPG}$	Me_2AlCl, –30 °C	97:3
(150) $X_c = X_S$	Et_2AlCl, –20 °C	97.5:2.5



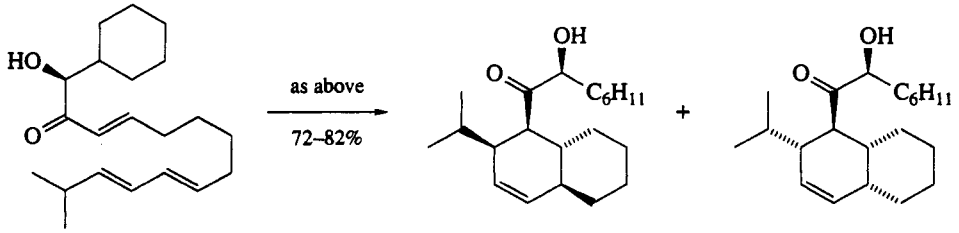
(151) $X_c = X_P$	Me_2AlCl, –30 °C	3:97
(152) $X_c = X_{PPG}$	Me_2AlCl, –30 °C	94:6
(153) $X_c = X_S$	Et_2AlCl, –20 °C	94:2.6:3.4 (*cis*-fused)



X_P X_{PPG} X_S



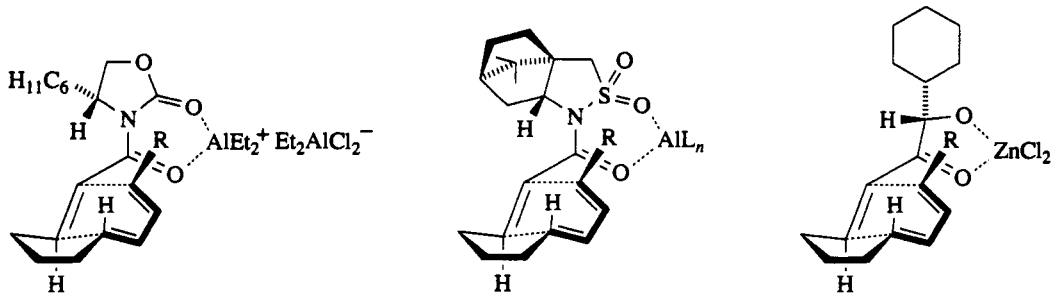
(154) R = H, Pr^i 97:3



(155) 96:4

Figure 41

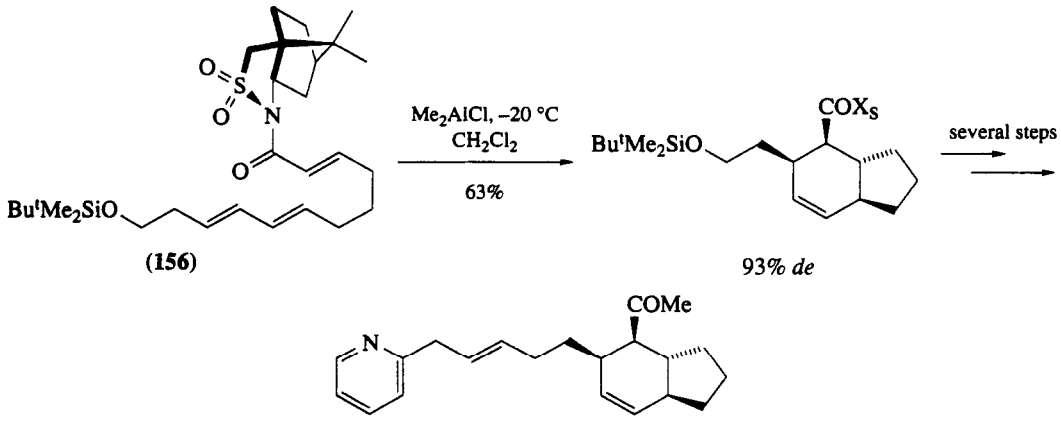
while simple diastereoselection with the decatriene substrates (**151**)–(**153**) is >30:50:1. The major products of these reactions are readily purified by crystallization or chromatography. Comparable levels of diastereoselection have also been realized with trienes (**154**) and (**155**).[119] The sense of relative diastereoselection realized in these cycloadditions can be rationalized by inspection of the transition states depicted in Figure 42 for the IMDA reactions (**149**), (**150**) and (**154**).



(**149**) (**150**) (**154**)

Figure 42

Of these three highly diastereoselective methods for accomplishing asymmetric IMDA reactions, the α-hydroxy ketone protocol[118,119] [trienes (**154**) and (**155**)] is the least convenient owing to the greater difficulty of triene preparation, the moderate reactivity of the trienes, and the destructive removal of the auxiliary. Consequently, the auxiliary systems developed by Evans and Oppolzer are more likely to find application in natural products synthesis. Indeed, Oppolzer has recently applied the *N*-acyl sultam methodology to the asymmetric total synthesis of (–)-pulo'upone (Figure 43).[120]



(**156**) 93% *de*

(–)-Pulo'upone

Figure 43

Two strategies for accomplishing asymmetric hetero-IMDA reactions have been reported (Figure 44). First, Tietze has shown that (**157**), that includes an ephedrine auxiliary as a component of the heterodiene unit, undergoes a highly diastereoselective Lewis acid catalyzed cycloaddition, providing cycloadduct (**158**) with >97% selectivity.[121] Second, Schreiber has shown that (**161**), prepared *in situ* by treatment of (**159**) with the ephedrine-derived aminal (**160**), provides cycloadduct (**162**) with 94% selectivity.[122] In both instances the auxiliaries are readily removed in subsequent transformations.

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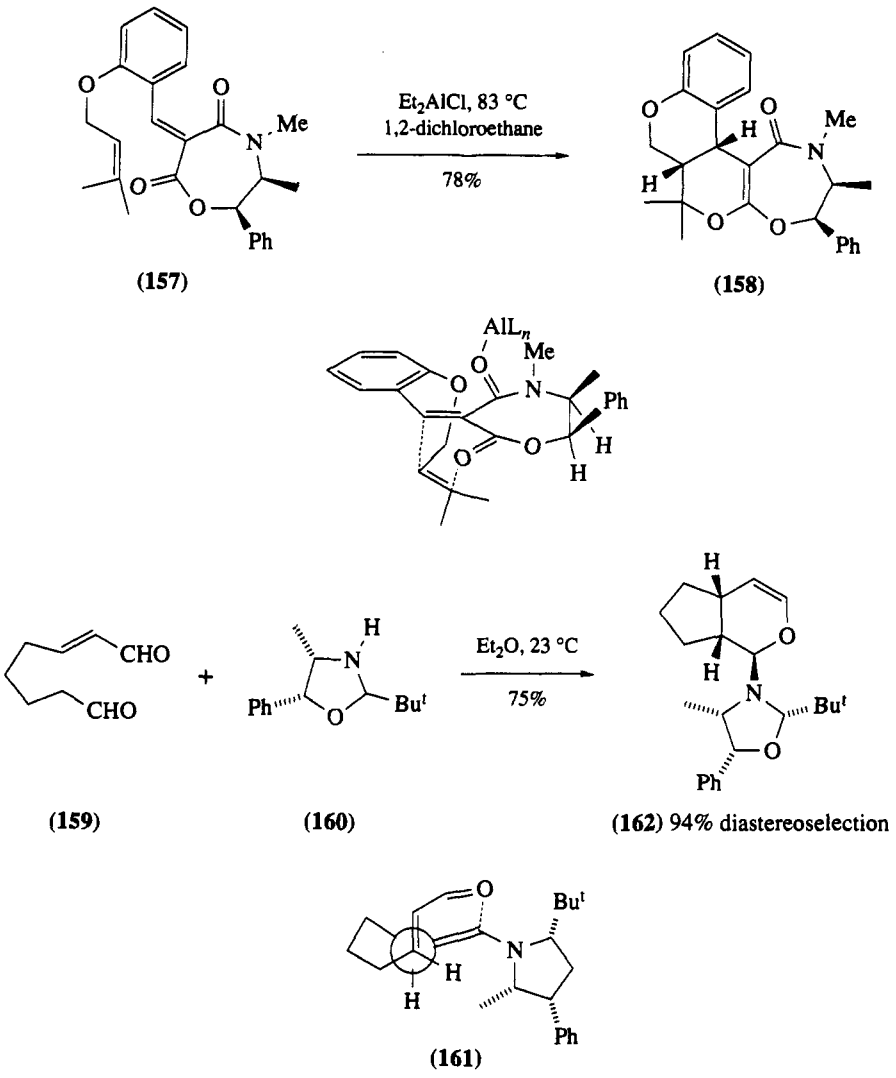

Figure 44

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4.5
Retrograde Diels–Alder Reactions

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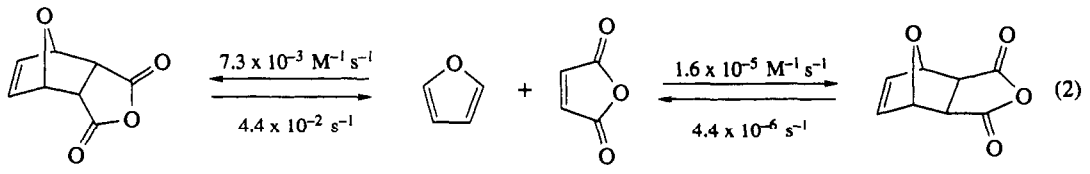
4.5.1 INTRODUCTION

The retro Diels–Alder (rDA) reaction is a $_{\pi}2_s + _{\sigma}2_s + _{\sigma}2_s$ electrocyclic process that, as the name implies, is the reverse of the familiar Diels–Alder cycloaddition reaction. A kinetic study of the prototypical rDA reaction, conversion of cyclohexene to 1,3-butadiene and ethylene (equation 1), has been studied in the temperature range of 541–629 °C.[1] Some early observations of rDA reactions were made in 1906 by Albrecht, who reported that the DA adducts of cyclopentadiene with benzoquinone dissociate at their melting points,[2] and in 1929 by Diels and Alder, who reported the dissociation of a furan–maleic anhydride adduct at its melting point.[3] Alder used the reaction as a test to differentiate between acetylenedicarboxylic ester adducts of cyclopentadiene and of cyclohexadiene;[4] heating the latter adduct eliminates ethylene, while heating the former yields only the starting diene and dienophile (the Alder–Rickert rule). Perhaps the earliest use of the rDA reaction in a synthetic mode was in the preparation of acetylenedicarbonyl chloride,[5] in which an anthracene adduct was used as a removable acetylene protecting group. Use of the rDA reaction in achieving selective synthetic conversions has been reviewed several times to date.[6–9]

(1)

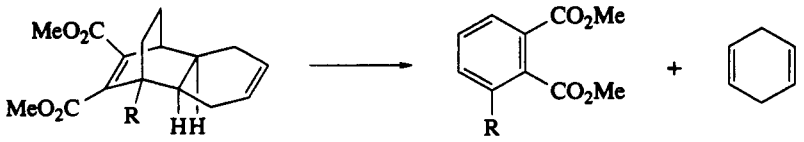
As the focus of this chapter is on the synthetic utility of the rDA reaction, an overview of mechanism is beyond the scope of this review; however, the subject has been reviewed previously.[10–12] Structural and medium effects on the rate of the rDA reaction are of prime importance to their synthetic utility, and therefore warrant discussion here. A study of steric effects on the rate of cycloreversion was the focus of early work by Bachmann[13] and later by Vaughan.[14] The effect of both diene and dienophile substitution on the rate of the rDA reaction in anthracene cycloadducts has been reported in a study employing 45 different adducts.[15] If both cycloaddition and cycloreversion processes are fast on the time scale of a given experiment, reversibility in the DA reaction is observed. Reversible cycloaddition reactions involving anthracenes,[16,17] furans,[18–22] fulvenes[23] and cyclopentadienes[24–26] are known. Herndon has shown that the well-known exception to the '*endo* rule' in the DA reaction of furan with maleic anhydride (equation 2) occurs not because *exo* addition is faster than *endo* addition (it is not), but because cycloreversion of the *endo* adduct is about 10 000 times faster than that of the *exo* adduct.[18]



endo *exo*

(2)

Many rDA reactions are carried out at temperatures of 150 °C or more in solution phase and often at temperatures of 400–600 °C using the flash vapor pyrolysis (FVP) method; individual conditions are referenced throughout the text. However, an accelerating effect by anionic, cationic and radical substitution on either the dienophile or at the termini of the diene fragments has been predicted by Carpenter.[27] Experimentally, this prediction has been substantiated only for anionic substitution. In 1967, Hart reported what is likely the first example of an oxyanion-accelerated rDA reaction.[28] Both oxyanionic[29–35] and carbanionic[36,37] substituents accelerate the cycloreversion reaction such that they proceed rapidly at room temperature (for example, equation 3). In addition, acid-catalyzed rDA reactions have been reported in which protonation effectively makes the dienophile fragment of the adduct more electron deficient.[38,39] Grieco has utilized a room temperature retro aza DA reaction useful for the *N*-methylation of dipeptides and amino acid derivatives (equation 4).[40]

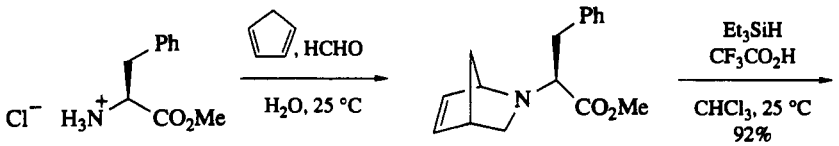


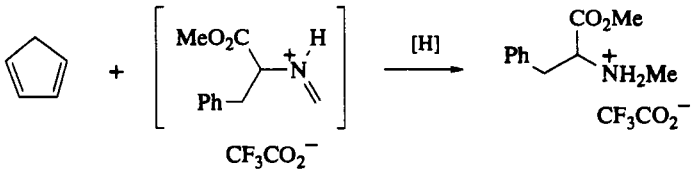
(3)

R = H, $t_{1/2}$ = 176 min at 100 °C

R = $OSiMe_3$, $t_{1/2}$ = 236 min at 60 °C

R = $O^-\ \overset{+}{N}Bu^n_4$, $t_{1/2}$ = <1 min at 25 °C





(4)

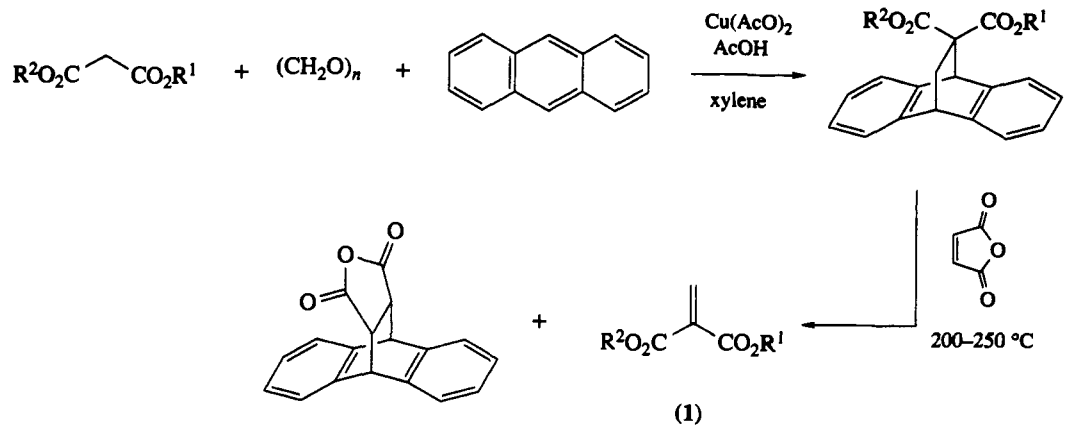
4.5.2 PREPARATION OF SUBSTITUTED ALKENES

4.5.2.1 α,β-Unsaturated Esters

Numerous acyclic ethylenes with oxygen-containing substituents have been obtained *via* the rDA reaction. A series of methylidenemalonic acid diesters (**1a–1s**) was prepared using a synthetic scheme based on the rDA reaction (equation 5).[41] Contamination by anthracene was avoided by performing the thermolytic retrodiene step in the presence of maleic anhydride, which consumes the anthracene produced in a DA reaction. Another series of acrylate esters, methyl 2-alkyl-2-alkenoates (**3**), was prepared by the rDA reaction of adduct (**2**) (equation 6).[42] The thermal cleavage occurs under relatively mild conditions by dissolving (**2**) in diphenyl ether and distilling the products directly from the solution at 170–190 °C. This simple preparation is preferable to various multistep methods for the synthesis of methyl 2-alkyl-2-alkenoates.[43,44]

4.5.2.2 α,β-Unsaturated Aldehydes and Ketones

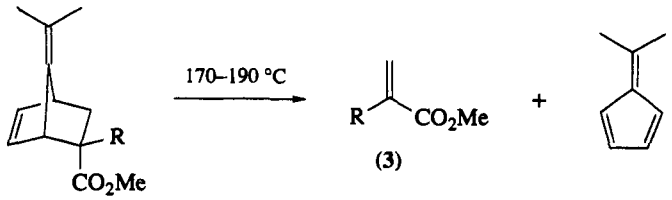
The preparation of acyclic alkenic ketones and aldehydes has been shown to be operable *via* methods based on the rDA elimination. A DA–rDA scheme was used to convert methyl vinyl ketone (**4**) into various alkenic ketones (**5**) as shown in equation (7).[45] Yields for the cycloreversion step are reported to be >90%. A similar DA–rDA path has been applied to terpenoid synthesis using cyclopentadiene to protect the double bond. The synthesis of (–)-turmenone (**7**) was accomplished by distilling ketone (**6**) as given in equation (8).[46] Ethylenic hydroxy ketones, which are useful synthetic intermediates for polyhydroxylated natural products, are obtained by rDA reactions. Adduct (**8a**) was flash thermolyzed at 500 °C to give ethylenic ketone (**9a**) (equation 9);[47] however, a competing retro aldol complicated this reaction. Protection of the alcohol with trimethylsilyl chloride followed by thermolysis of protected aldol (**8b**) gave siloxy ketone (**9b**) in 80% yield. The preparation of *cis*-crotonaldehyde (**12**) has been described *via* a three-step synthesis as outlined in equation (10);[48] protection of the double bond is accomplished by DA addition in the initial step giving adduct (**10**), followed by nitrile transformation to aldehyde (**11**). The sequence is completed by regeneration of the double bond by a rDA thermolysis to give *cis*-crotonaldehyde (**12**).



(5)

(1)

Compound	R^1	R^2	*Yield (%)*
(1a)	Me	Me	54
(1b)	Et	Et	67
(1c)	Pr^n	Pr^n	81
(1d)	Bu^n	Bu^n	68
(1e)	Pr^i	Pr^i	64
(1f)	Bu^i	Bu^i	61
(1g)	n-C_5H_{11}	n-C_5H_{11}	46
(1h)	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	48
(1i)	Me	Bu^n	75
(1j)	Me	n-C_6H_{13}	77
(1k)	Et	Pr^n	63
(1l)	Et	Bu^n	71
(1m)	Et	$CH_2CH{=}CH_2$	48
(1n)	Et	$CH_2C{\equiv}CH$	20
(1o)	Et	CH_2CH_2OEt	43
(1p)	Et	CH_2CO_2Et	62
(1q)	Et	$(CH_2)_3CO_2Et$	32
(1r)	Pr^n	Bu^n	53
(1s)	Bu^n	n-C_5H_{11}	78



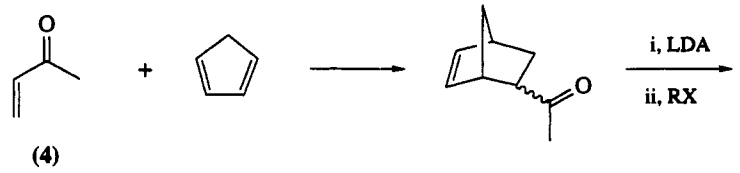
(6)

(3)

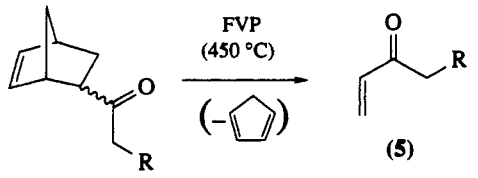
(2) R = Me, Et, $CH_2CH{=}CH_2$, $CH_2CH{=}CHMe$, CH_2Ph, CH_2CO_2Et

4.5.2.3 Acyclic Allylic Alcohols

The preparation of alkenic alcohols based on rDA processes has found application in the synthesis of natural products. Matsutake alcohol (**14a**; (–)-(*R*)-1-octen-3-ol), an important flavor component of mushrooms, can be prepared in high enantiomeric purity by a method that includes rDA cleavage as a key step. Asymmetric DA addition gave enantiomerically pure adducts that were modified dia-

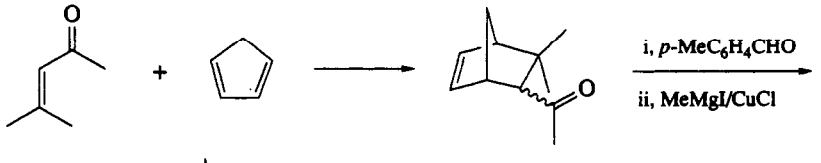


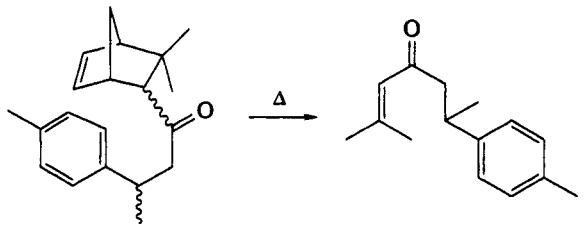
(4)



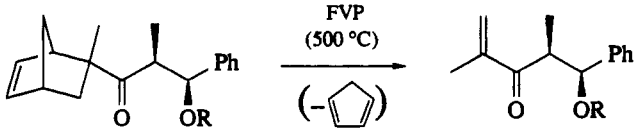
(5) (7)

R = Me, Et, n-C_5H_{11}, $CH_2CH{=}CH_2$, $CH_2CH{=}CMe_2$



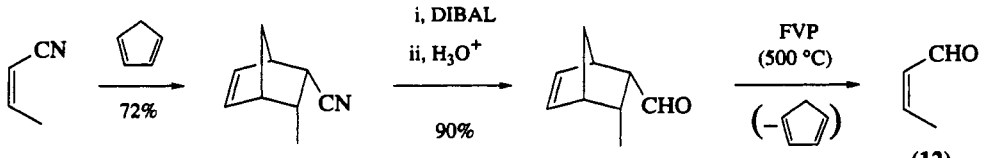


(6) (7) (8)



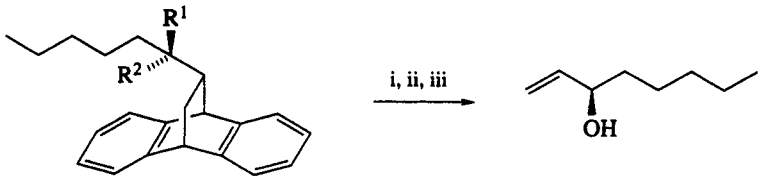
(8a) R = H
(8b) R = $SiMe_3$

(9) (9)



(10) (10) (+ *exo*) (11) (+ *exo*) (12)

stereoselectively to give isomeric adducts (**13a**) and (**13b**).[49] The isomers were individually *O*-silylated, subjected to FVP and desilylated to give (–)-(*R*)-1-octen-3-ol (**14a**) and (*S*)-1-octen-3-ol (**14b**). The rDA reaction yielding these sensitive allylic alcohol derivatives was not accompanied by racemization. A DA–rDA scheme has been applied to the high yield syntheses of linalool and nerolidol.[45] A similar scheme involving DA protection of a double bond with final rDA regeneration of an alkenic alcohol was used to prepare (±)-ipsenol (**16**). The final step of the synthesis was rDA thermolysis of adduct (**15**) at 450 °C to give (±)-ipsenol in quantitative yield (equation 12).[50]

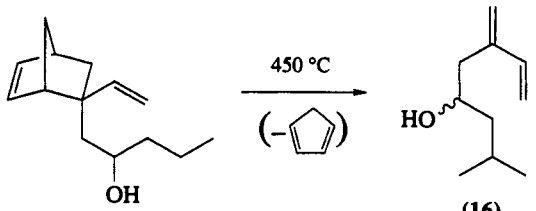


(13a) $R^1 = H$, $R^2 = OH$ (14a)

(13b) $R^1 = OH$, $R^2 = H$ i, ii, iii (14b)

(11)

i, $MeCON(Me)SiMe_3$, CH_2Cl_2; ii, FVP, 660 °C/0.005 Torr; iii, AcOH, $MeOH/H_2O$

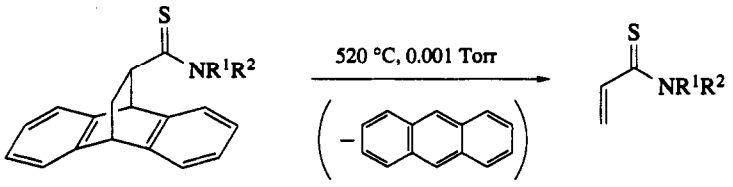


(15) (16)

(12)

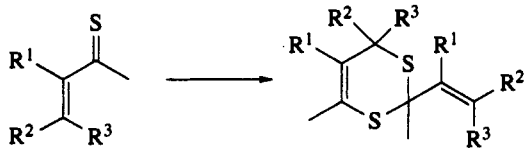
4.5.2.4 α,β-Unsaturated Thio Compounds

Acyclic alkenic sulfur compounds have also been obtained *via* pyrolytic rDA reactions. A general route to thioacrylamides utilizing rDA reactions under FVP conditions has been developed. The rDA reaction of the appropriate adducts yields thioacrylamide, *N*-methylthioacrylamide and *N,N*-dimethylthioacrylamide in approximately quantitative yield (equation 13).[51] The high reactivity of these α,β-unsaturated thioamides had previously limited their availability. α,β-Unsaturated acyclic thioketones such as (**17**) were prepared *via* a rDA reaction using a FVP technique. These highly reactive species dimerize to 4*H*-1,3-dithiins (**18**) on warming to –60 °C (equation 14).[52]



(13)

R^1, R^2 = H or Me



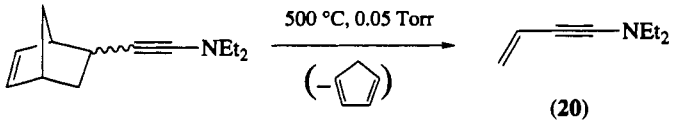
(17) (18)

(14)

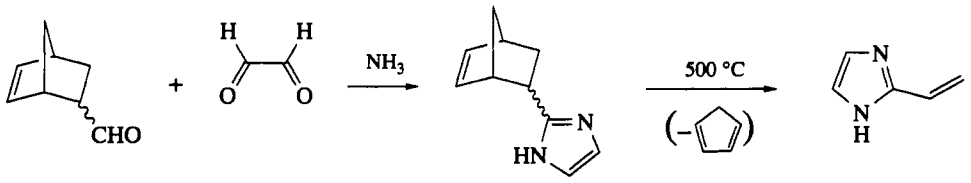
R^1, R^2 = H or Me

4.5.2.5 Alkenic Nitrogen Species

A few syntheses of alkenic nitrogen compounds based on the rDA reaction are known. For example, ynamine (**19**), *via* rDA decomposition under FVP conditions, gives 1-*N*,*N*-diethylamino-3-buten-1-yl (**20**).[53] 2-Vinylimidazoles had previously been obtained by lengthy reaction schemes with low yields;[54,55] however, a practical laboratory synthesis of 2-vinylimidazoles based on a DA–rDA scheme has been developed. The DA adduct of acrolein and cyclopentadiene was converted to 2-(5-norbornen-2-yl)imidazole (**21**), which was readily transformed into 2-vinylimidazole (**22**) as depicted in equation (16).[56] Glyoxal gave the best result, but other α-dicarbonyl compounds could be substituted to obtain various 2-vinylimidazoles.



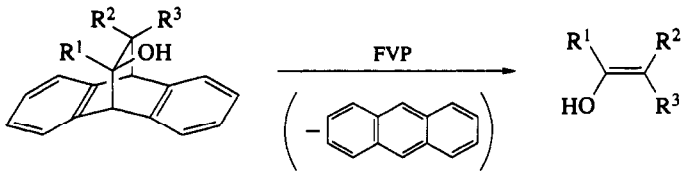
(19) (20) (15)



(21) (22) (16)

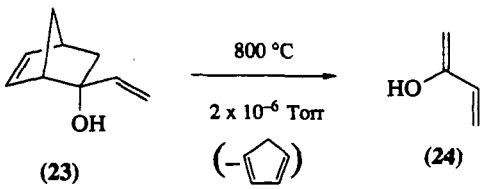
4.5.2.6 Vinyl Alcohols, Ethers and Esters

The preparation of enols of simple aldehydes and ketones has been achieved by rDA reactions under FVP conditions. Equation (17) illustrates the formation of enols by this method.[57] The percentage of enol reported shows that the enols of aldehydes appear to be isolated more readily than those of the ketones. The last two entries are preparations of the simplest enediols, (*E*)- and (*Z*)-ethylene-1,2-diols. A very similar process was used to unmask the 'protected' ethylene cycloadduct (**23**) and produce 2-hydroxybutadiene (**24**), an elusive enol form of the more stable unsaturated ketone, as given by equation (18).[58]



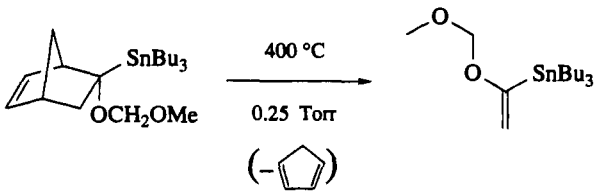
(17)

R^1	R^2	R^3	*FVP conditions*	*Enol (%)*
H	H	H	550 °C, 10^{-4} Torr	55
H	H	Me	550 °C, 10^{-4} Torr	80
H	Me	H	550 °C, 10^{-4} Torr	75
H	Me	Me	550 °C, 10^{-4} Torr	100
Me	H	H	550 °C, 10^{-4} Torr	–
Me	H	Me	550 °C, 10^{-4} Torr	5
Me	Me	H	550 °C, 10^{-4} Torr	–
Me	Me	Me	550 °C, 10^{-4} Torr	–
H	H	OH	600 °C, 10^{-5} Torr	–
H	OH	H	600 °C, 10^{-5} Torr	–



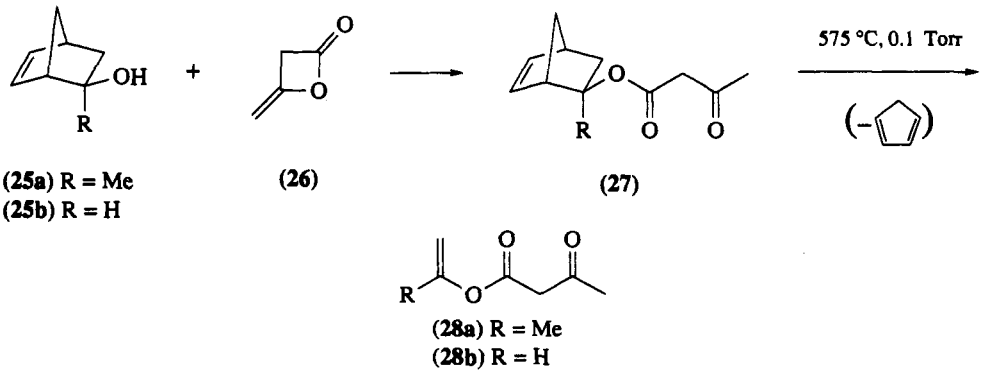
(23) (24) (18)

A series of metalated alkoxymethyl vinyl ethers has been prepared by the thermolysis of substituted bicyclo[2.2.1]hept-5-enes, one example of which is shown in equation (19).[59]



98% (19)

The rDA route to isopropenyl acetoacetate and to vinyl acetoacetate was apparently the first synthesis of acetoacetate esters of enols. The reaction between diketene (**26**) and norbornenols (**25a**) and (**25b**) generated the 'protected' ethylene cycloadducts (**27**), which upon FVP gave the desired isopropenyl acetoacetate (**28a**) in 48% yield and vinyl acetoacetate (**28b**) in 61% yield (equation 20).[60]



(**25a**) R = Me
(**25b**) R = H

(**26**) (**27**)

(**28a**) R = Me
(**28b**) R = H

(20)

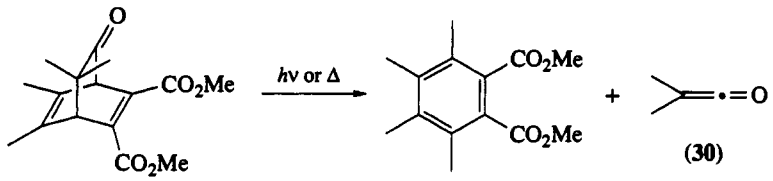
4.5.2.7 Ketenes

Ketenes are generated by rDA pathways; however, most examples are not hetero retrodiene processes. Instead, ketenes are most often produced by the rDA reaction of a 'masked' ethylene cycloadduct generating the carbon–carbon double bond of the ketene. One of the simplest ketenes, dimethylketene (**30**), can be produced by thermal or photochemical elimination of bicyclo[2.2.1]octadienone (**29**) as given in equation (21).[61] The ease with which the ketene is formed by the photolytic retrodiene extrusion process stands in contrast to the high temperature, 450–550 °C, required for the corresponding thermolytic cleavage. Ketenes have also been generated by intramolecular rDA reactions. Upon photolysis of ketone (**31**), intermediate ketene (**32**) formed that reacted with methanol to give cyclooctadiene diester (**33**) (equation 22).[62] In an enantioselective process, the photochemically generated ketene (**34**) reacted with (+)-ephedrine with induction of optical activity (equation 23).[63]

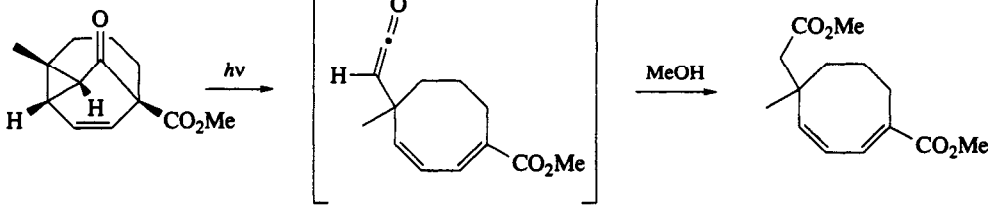
4.5.2.8 Enamines

Generation of the double bond of enamines is possible *via* a rDA reaction. Ethylenamine and its methyl derivatives have been prepared by FVP of the corresponding anthracene adducts (equation 24).[62] Identification of the primary enamines in a pure state has been accomplished at –80 °C, while the less

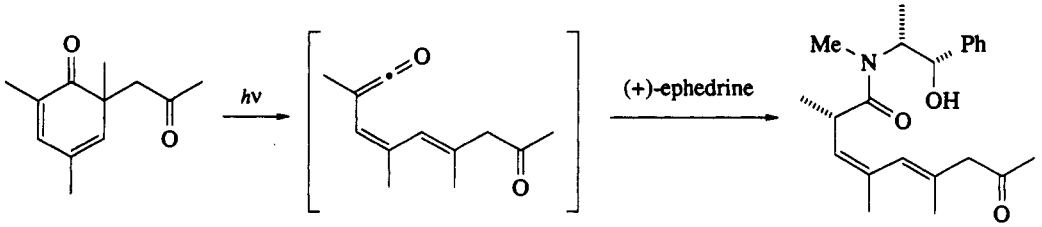
stable secondary enamines are accompanied by the corresponding tautomeric imines. The preparation of 2-aza-1,3-dienes has been achieved by rDA reaction on imine adducts as outlined in equation (25).[64] 2-Aza-1,3-dienes are compounds with utility in the synthesis of six-membered N-heterocycles.



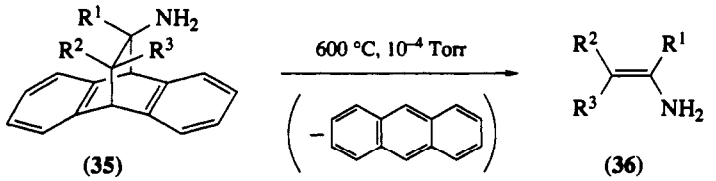
(29) (21)



(31) (32) (33) (22)

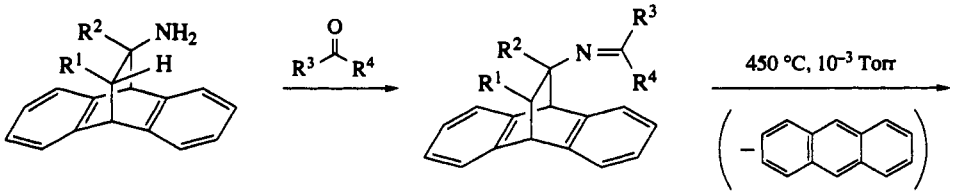


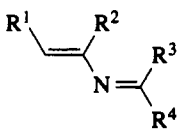
(34) (23)



(35) (36) (24)

R^1, R^2, R^3 = H or Me





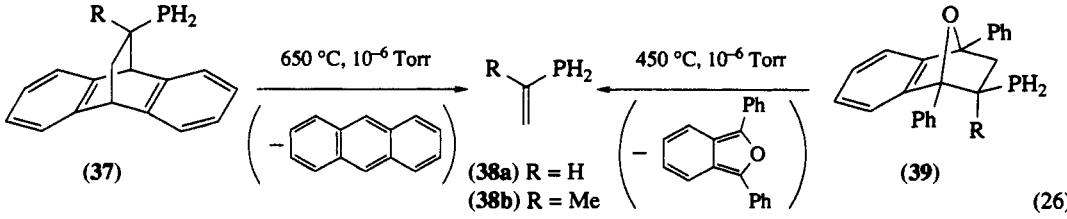
R^1, R^2, R^3 = H or Me

R^4 = Me, Et or Ph

(25)

4.5.2.9 Vinylphosphines

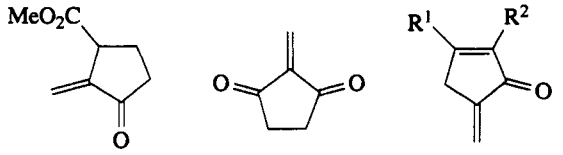
The synthesis of primary alkenylphosphines has been accomplished utilizing the same rDA method that was used to synthesize primary enamines.[62] The synthesis of primary alkenylphosphines had been an unsolved problem owing to the high reactivity of the phosphine group under acidic, basic and neutral conditions.[65] The preparation of vinylphosphine (**38a**) and isopropenylphosphine (**38b**) by FVP of the appropriate anthracene (**37**) or 1,3-diphenylbenzofuran (**39**) adduct has been accomplished as shown in equation (26).[66] (*E*)-Prop-1-enylphosphine was synthesized by a similar rDA route.[66] These phosphines were found to be surprisingly stable, with a half-life of approximately 8 d for (**38a**).



(37) (38a) R = H (38b) R = Me (39) (26)

4.5.2.10 Exocyclic Alkenes

Exocyclic alkenes have been generated *via* rDA processes. The antibiotic sarcomycin, an antitumor agent, and its methyl ester (**40**) have been the goals of many synthetic efforts. Generation of the exocyclic carbon–carbon double bond by a rDA reaction was the final step to the preparation of ester (**40**).[67] An acid-catalyzed rDA reaction has been used to generate the exocyclic double bond of dione (**41**).[68] The rDA reaction has found further use in the synthesis of α-methylenecyclopentenone antibiotics. FVP of spirocyclopentenone precursors yields the corresponding α-methylenecyclopentenones (**42**) in quantitative or nearly quantitative yield.[69]

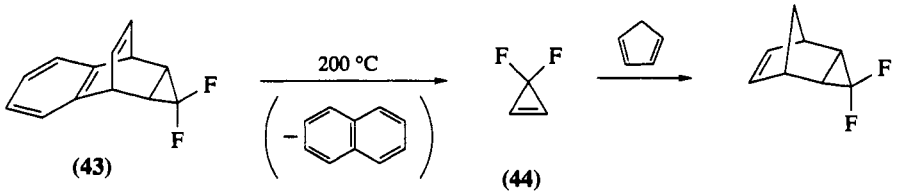


(40) (41) (42)

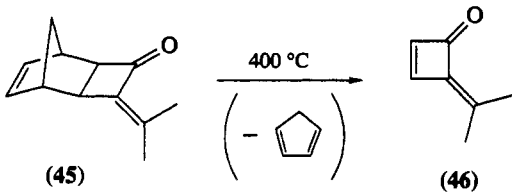
4.5.2.11 Endocyclic Alkenes

The rDA reaction has been applied as well to the synthesis of a wide range of compounds containing endocyclic carbon–carbon double bonds. For example, adduct (**43**) as a mixture of *syn* and *anti* isomers yields 3,3-difluorocyclopropene (**44**) and naphthalene upon heating at 200 °C (equation 27).[70] One of the first syntheses of the methylenecyclobutenone moiety was accomplished by a rDA process. The pyrolysis of (**45**) gave approximately 25% conversion to isopropylidenecyclobutenone (**46**) as shown in equation (28).[71] Similarly, the pyrolysis of adduct (**47**) at 425 °C produced the endocyclic double bond of dimethylenecyclobutene (**48**) as shown in equation (29).[69]

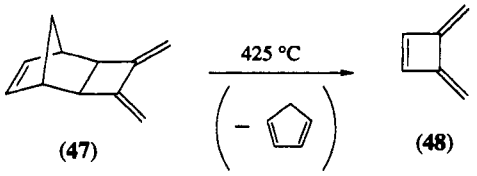
rDA processes have been used extensively to generate the endocyclic carbon–carbon double bond of cyclopentene derivatives. Functionalized cyclopentenones are important synthetic intermediates in the synthesis of many quinane natural products.[72–77] The synthesis of optically active cyclopentenones with a predetermined absolute configuration has been achieved. Conjugate addition to enone (**49**) gives adducts (**50a–f**) stereospecifically, which upon FVP yield cyclopentenones (**51a–f**) (equation 30).[78] The development of a general method to prepare 4,5-disubstituted 2-cyclopentenones (**52**) is of value owing to the



(43) *syn* + *anti* (44) (27)

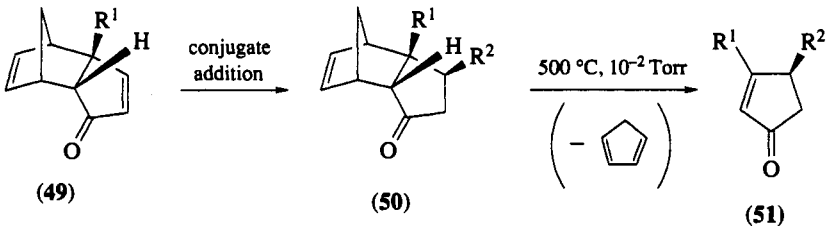


(28)



(29)

occurrence of this system in a variety of natural products. Such systems have been synthesized with a rDA reaction as the key step; the method is outlined in equation (31).[79]

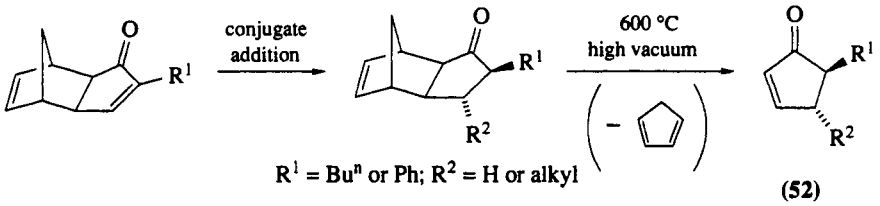


(30)

a: $R^1 = H$, $R^2 = Me$ **d**: $R^1 = CO_2Et$, $R^2 = Me$

b: $R^1 = H$, $R^2 = C_7H_{15}$ **e**: $R^1 = CO_2Et$, $R^2 = C_7H_{15}$

c: $R^1 = H$, $R^2 = CH(CO_2Me)_2$ **f**: $R^1 = CO_2Et$, $R^2 = CH(CO_2Me)_2$

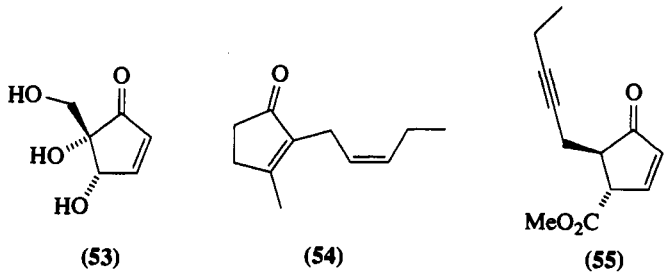


(31)

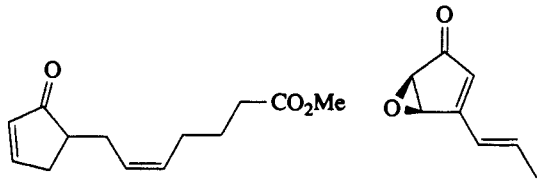
Generation of the endocyclic double bond of cyclopentanoids has been accomplished frequently by rDA reaction of the appropriate cyclopentadiene. FVP has been used as the last step of the synthesis of the antibiotic (±)-pentenomycin (**53**) in 50% yield.[80] Other cyclopentanoid natural products that are synthesized by procedures based upon a nearly quantitative rDA reaction are jasmone (**54**)[81] and alkyne (**55**), a precursor to methyl jasmonate.[82] This same procedure has been applied to the synthesis of intermediates of prostaglandins such as (**56**).[83]

A facile synthesis of cyclopentadienone epoxides *via* thermal rDA cycloreversion of a tricyclodecenone epoxide and its acetal derivatives has been applied to the preparation of cyclopentanoid antibiotics.[84,85] This procedure has been used in an efficient synthesis of terrein, a mould metabolite from *Aspergillus terreus*, by rDA synthesis of cyclopentadiene epoxide intermediate (**57**).[85] FVP conditions for these reactions typically involve temperatures of 420–600 °C. Furan-derived DA adducts have also been used to generate cyclopentadienone epoxides. The thermal rDA reaction of the furan-derived DA adduct (**58**) proceeds at temperatures as low as 330 °C with complete cycloreversion and generation of epoxide (**59**) in nearly quantitative yield (equation 32).[84] Subsequent elaboration led to epipentenomycin derivatives such as (**60**).

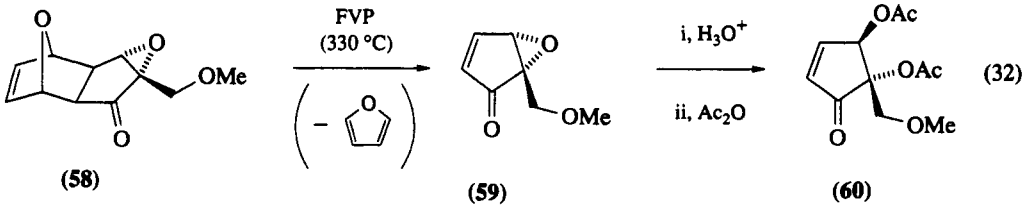
A facile synthesis of enol lactones was achieved by a process dependent upon successful rDA decomposition. The tricyclic (*E*)-enol lactones (**61**) thermally decomposed to the corresponding (*E*)-enol lactones (**62**) in excellent yield as shown in equation (33).[86] Tricyclic (*E*)-enol lactones (**61**) could be photoisomerized to the corresponding (*Z*)-enol lactones, which were also thermally cleaved to the (*Z*)-enol lactones (**62**).



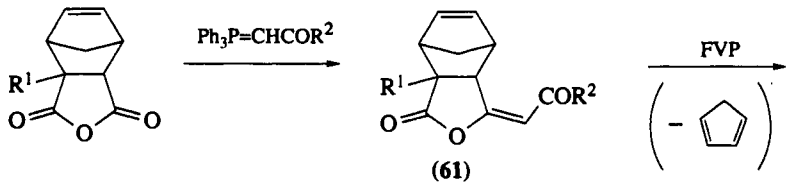
(53) (54) (55)



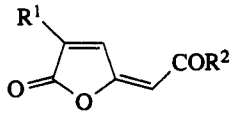
(56) (57)



(58) (59) (60) (32)



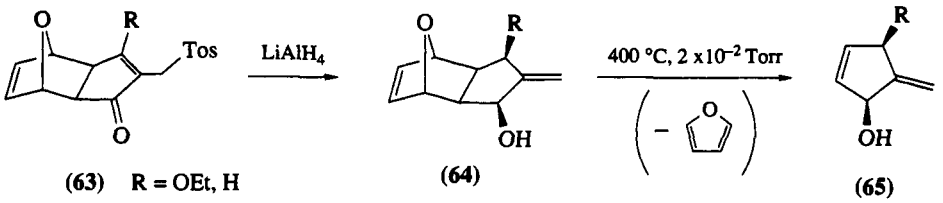
(61)



(62) (33)

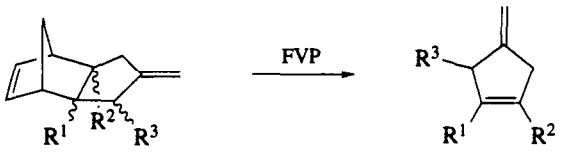
Compound	R^1	R^2	FVP conditions	Yield of (62) (%)
(61a)	H	OEt	450 °C, 0.3 Torr	95
(61b)	Me	OEt	310 °C, 0.3 Torr	93
(61c)	H	OBu^t	490 °C, 0.3 Torr	88
(61d)	H	Me	310 °C, 0.3 Torr	92
(61e)	Me	Me	300 °C, 0.3 Torr	89

Many rDA processes exist for the generation of cyclopentene units not possessing a carbonyl in the cyclic framework. The previously unknown alkylidenecyclopentenols have been accessed by a procedure dependent upon a rDA cycloreversion. Reaction of lithium aluminum hydride with 4-*p*-tolylsulfonylmethyloxatricyclo[5.2.1.0]decadienone (**63**) gave the *exo*-methylene tricyclodecenols (**64**) regioselectively and stereospecifically, which upon FVP yielded the *exo*-methylene cyclopentenols (**65**) (equation 34).[87] These cyclopentenols in turn serve as precursors for prostanoid natural products such as clavulones and punaglandins.[88]



(63) R = OEt, H (64) (65) (34)

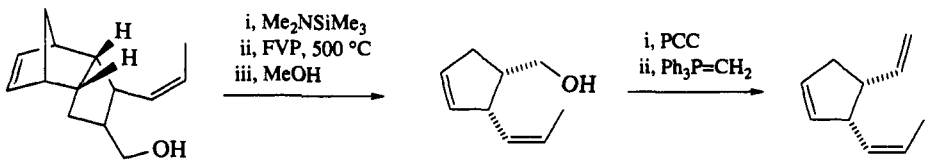
The development of syntheses for highly functionalized cyclopentanes has been enhanced by the isolation of numerous cyclopentanoid natural products. 4-Methylene-1-cyclopentenes (**67**) are interesting and versatile building blocks for such species. The preparation of these cyclopentenes has been accomplished by a three-step synthesis, the last of which is rDA cycloreversion under FVP conditions (equation 35).[89] This final rDA step simply involves distillation of the adducts (**66a–h**), which yields cyclopentenes (**67a–h**) in a virtually pure state.



(66) (67) (35)

Compound	R^1	R^2	R^3	*rDA conditions*	*Yield of (67) (%)*
(**66a**)	CO_2Me	CO_2Me	H	550 °C, 2 Torr	100
(**66b**)	CO_2Me	CO_2Me	Me	530 °C, 0.1 Torr	94
(**66c**)	H	CO_2Me	H	600 °C, 2 Torr	89
(**66d**)	H	CO_2Et	H	755 °C, 0.03 Torr	58
(**66e**)	H	COPh	H	560 °C, 0.03 Torr	52
(**66f**)	H	SO_2Ph	H	560 °C, 0.03 Torr	72
(**66g**)	$-CH_2OCO-$		H	580 °C, 0.03 Torr	95
(**66h**)	CH_2OH	CH_2OH	H	575 °C, 0.03 Torr	100

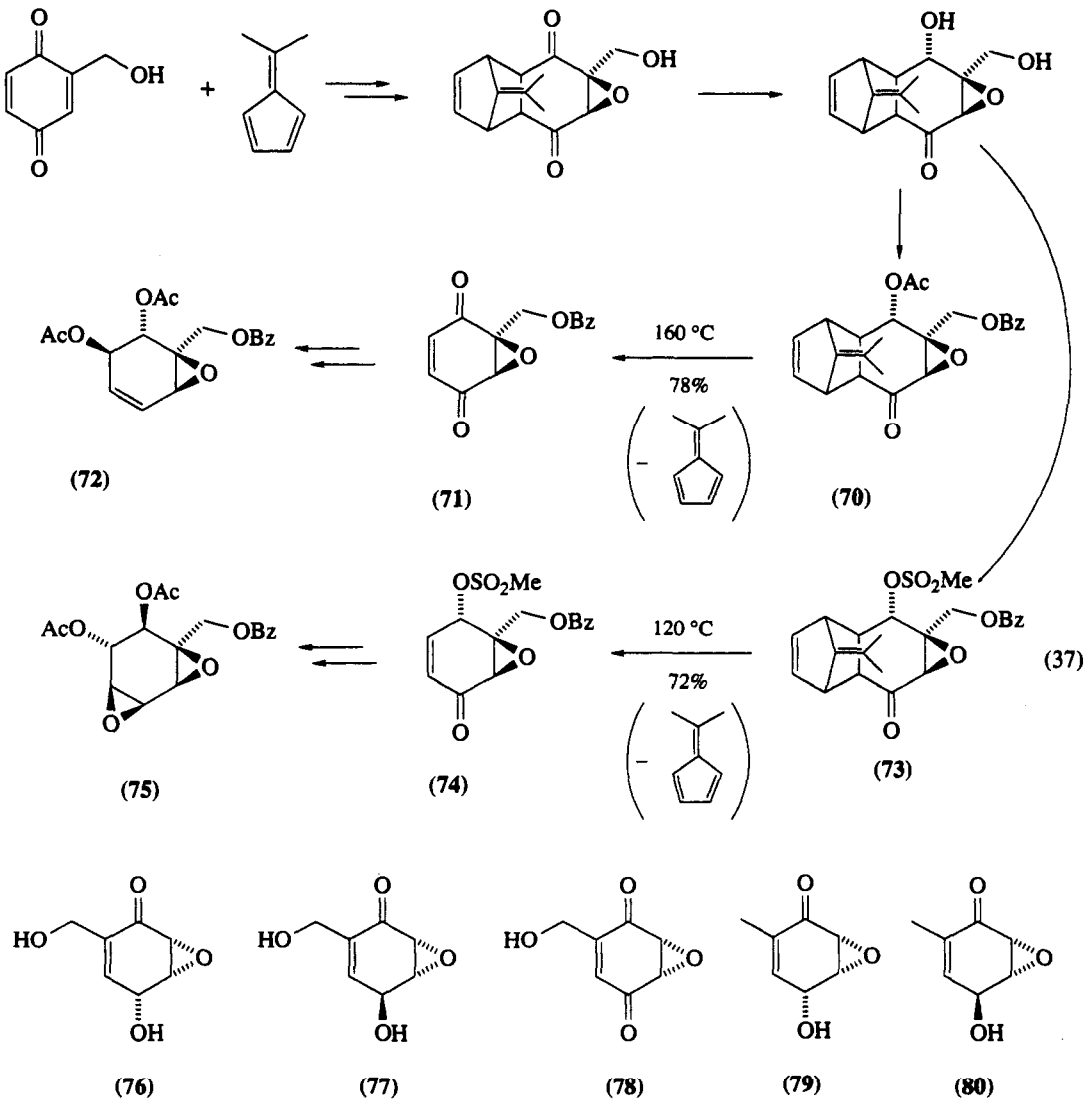
Multifidene (**69**), a major constituent of the essential oil of *Cutleria multifida*,[90] has been prepared by a method based upon rDA cleavage of adduct (**68**) (equation 36).[91] The synthesis of (**69**) combines a high degree of stereoselectivity with broad variability, giving easy access to analogs of multifidene.



(68) (69) (36)

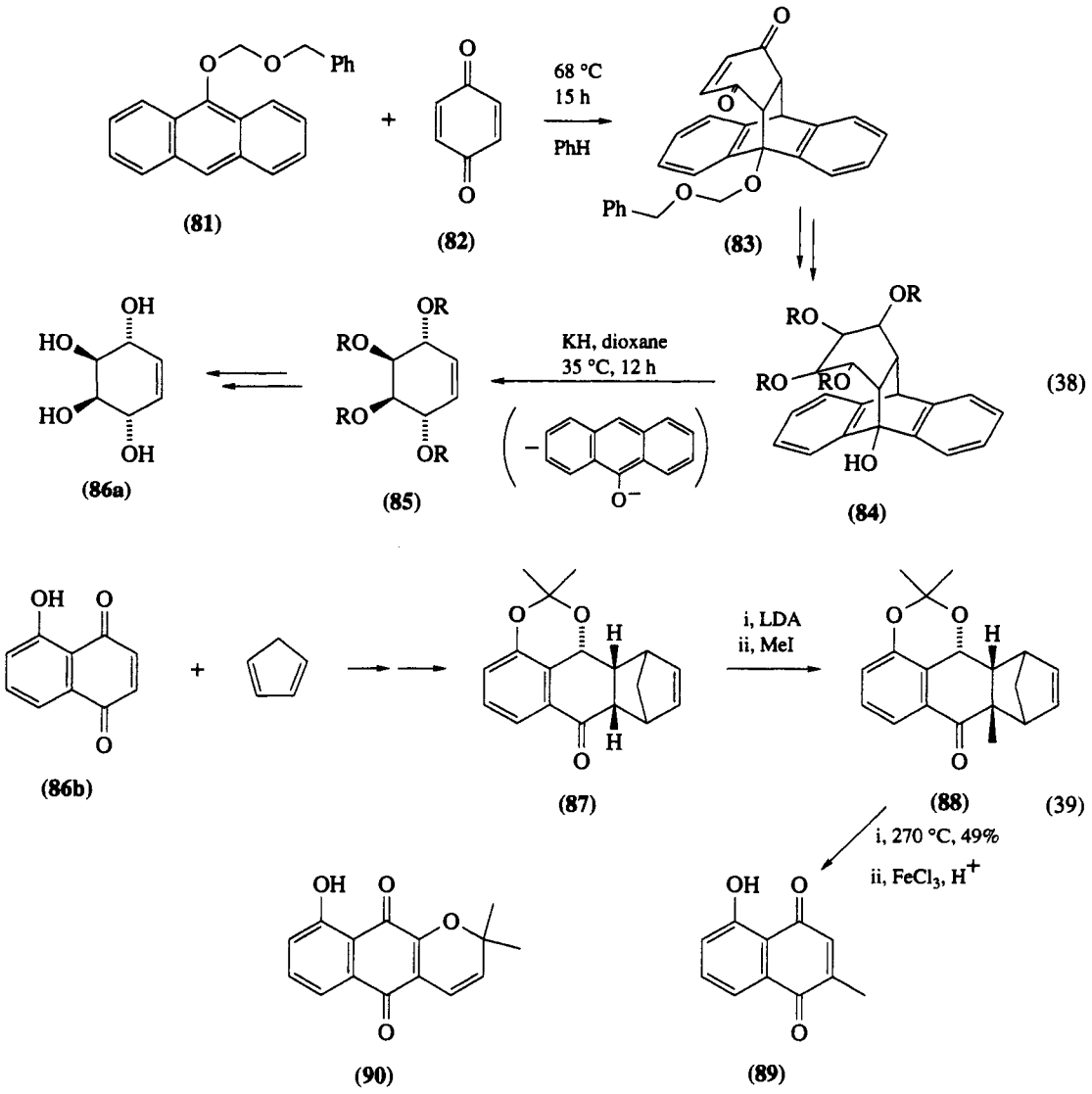
The rDA reaction has been applied to the synthesis of quinone epoxides and α-epoxycyclohexenones. Dimethylfulvene was used as the diene since the rDA cycloreversion of these adducts proceeds at much lower temperatures than do the corresponding cyclopentadiene adducts. The rDA reaction of these epoxide adducts was performed by two procedures involving heating at 150–190 °C in (a) high-boiling solvents such as diphenyl ether, xylene or diglyme, or (b) low-boiling solvents such as benzene, THF or toluene in a sealed tube.[92] This process is illustrated by the two similar synthetic schemes (equation 37) used to generate (±)-senepoxyde (**72**), isolated from the fruits of *Uvaria catocarpa*, and (±)-crotepoxide (**75**), a tumor inhibitor isolated from the fruits of *Croton macrostachys*.[93] The rDA reaction of adducts (**70**) and (**73**) gave the epoxycyclohexenones (**71**) and (**74**), respectively, and each was subsequently transformed into the natural product. This process has been used for the preparation of many bioactive

natural products, including epoxydon (**76**), epiepoxydon (**77**), phyllostine (**78**), epoformine (**79**) and epi-epoformine (**80**).[94]



Knapp has used the oxyanion-accelerated rDA reaction to advantage in the synthesis of conduritol A. The masked dienol used was 9-[(benzyloxy)methoxy]anthracene (**81**), which upon reaction with benzoquinone (**82**) gave the protected adduct (**83**) (equation 38).[31] Further transformations yielded (**84**), which upon treatment with potassium hydride caused rDA fragmentation to occur at 35 °C. Two subsequent steps produced conduritol A (**86a**), a naturally occurring cyclitol, in 39% overall yield from (**82**). The room-temperature DA activity of anthranol reported by Rickborn,[95] coupled with the observed low-temperature rDA reactivity of its adducts, makes anthranol a highly useful alkene protecting group *via* a DA/rDA sequence.

Alkylated naphthoquinones can be generated by the rDA strategy that has been used in natural products synthesis. Plumbagin (**89**), an alkylated naphthoquinone that has antimicrobial and antineoplastic activities, has been obtained by an alkylation of juglone (**86b**) based on a DA/rDA reaction sequence (equation 39).[96] This method enabled alkylation of C-2 in juglone by alkylation of cycloadduct (**87**) with methyl iodide. The subsequent rDA reaction of (**88**) followed by oxidation gave plumbagin (**89**). A similar alkylation scheme based on the rDA reaction has been applied to the synthesis of α-caryopterone (**90**), a red pyranojuglone from *Caryopteis clandonensis*.[97]



(81) (82) (83) (84) (85) (86a) (38)

(86b) (87) (88) (39)

(90) (89)

4.5.2.12 Alkynes

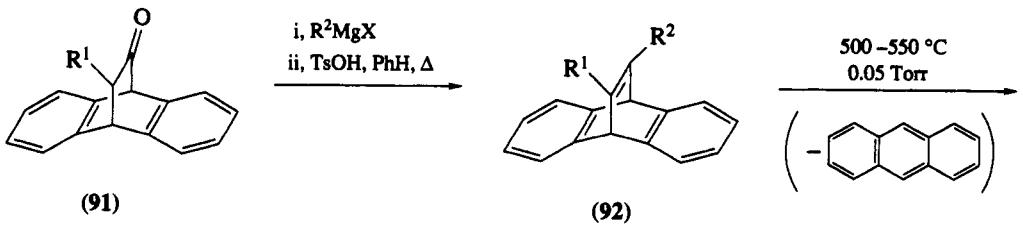
Functionalized alkynes are made *via* rDA cycloreversion of cycloadducts that act as 'protected' alkynes. Substituted alkynes (**93a–h**) are obtained from adducts (**92a–h**) *via* FVP-induced rDA cycloreversion as shown in equation (40).[98] This method, based on the rDA reaction, provides an alternative route to the alkynic bond, which is more commonly formed *via* elimination reactions.

Substituted alkynic compounds result when two cycloreversions are carried out on the same carbon–carbon bond of a bis-DA adduct. Thermolysis of bis-adduct (**94**) produced alkyne (**95**) and anthracene *via* two rDA cycloreversions as shown in equation (41).[99]

4.5.3 PREPARATION OF POLYUNSATURATED HYDROCARBONS

4.5.3.1 Substituted Acyclic Butadienes

The generation of variously substituted butadienes has been accomplished *via* the thermal rDA reaction of substituted cyclohexene derivatives. Derivatives of 1,3-butadiene-2,3-dicarboxylic acid, which are otherwise difficult to prepare, have been obtained by the vapor-phase pyrolysis of cyclohexene-1,2-

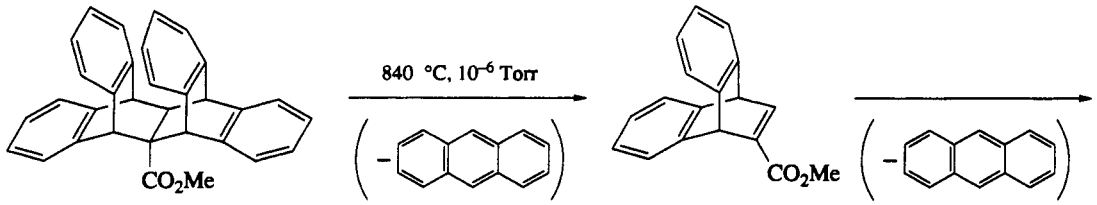


(91) (92)

$R^1—\equiv—R^2$ (40)

(93)

Compound	R^1	R^2	*% of* (93) *from* (92)
(91a)	H	Ph	~100
(91b)	Me	Ph	~100
(91c)	Et	Ph	~100
(91d)	CH_2Ph	Et	~100
(91e)	Me	Et	82
(91f)	Et	Et	80
(91g)	CH_2Ph	Me	60
(91h)	CH_2Ph	Et	72

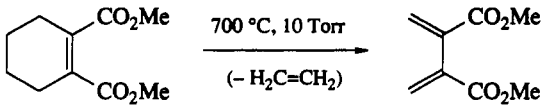


(94)

$H—\equiv—CO_2Me$ (41)

(95)

dicarboxylic acid analogs. Thus cyclohexene-1,2-dicarboxylate yielded dimethyl 1,3-butadiene-2,3-dicarboxylate as shown in equation (42), and cyclohexene-1,2-dicarbonitrile produced 1,3-butadiene-2,3-dicarbonitrile as given in equation (43).[100] The synthesis of 4-alkyl-2-amino-4-(substituted amino)-1,1,3-tricyano-1,3-butadienes has been accomplished *via* selective thermal decomposition of the corresponding amino adducts as shown in equation (44).[101] An interesting aspect of the synthesis of these dienes is the mild rDA conditions used, simple refluxing in xylene or decalin.



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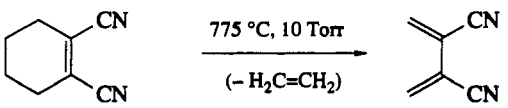

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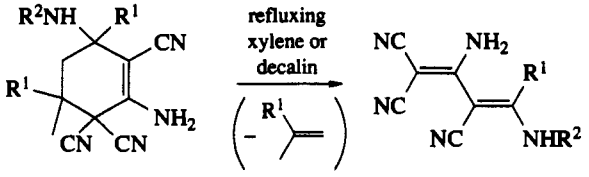


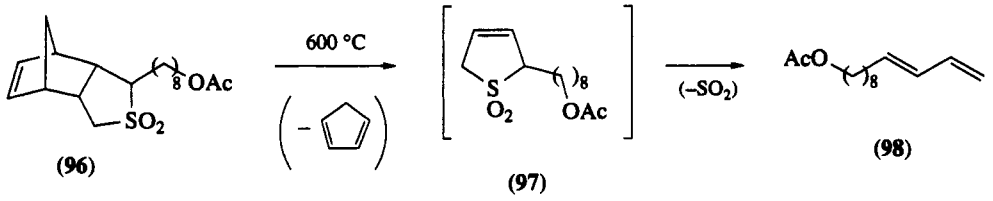
(44)

4.5.3.2 Extrusion of Sulfur Dioxide

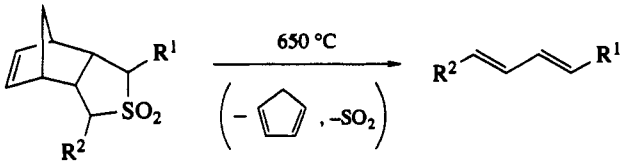
The thermolysis of 2-substituted 2,5-dihydrothiophene 1,1-dioxides leads to (*E*) conjugated dienes *via* cycloreversion followed by the concerted cheletropic extrusion of sulfur dioxide. The thermolysis of the α,β-alkylated sulfone (**96**) gives the intermediate, which loses SO_2 to give (*E*)-9,11-dodecadien-1-yl acetate (**98**), a component of the sex pheromone of the red bollworm moth.[102] This procedure has been extended to the thermolysis of α,β-dialkylated sulfones in order to obtain (*E,E*)-1,4-disubstituted-1,3-dienes (equation 46).[103] Similar processes have been used for the syntheses of alkaloids. The synthesis of an Elaeocarpus alkaloid, elaeokanine A (**100**), makes use of the retrodiene extrusion of sulfur dioxide to give the 1,3-diene intermediate (**99**) that is subsequently consumed by an intramolecular imino DA reaction (equation 47).[104] *o*-Xylylene (**102**) has been generated by rDA expulsion of SO_2 from benzo-fused 3,6-dihydro-1,2-oxathiin 2-oxide (**101**).[105]

4.5.3.3 Extrusion of Molecular Nitrogen

Model studies of rDA reactions exhibit a high degree of stereoselectivity. This fact is evidenced by the oxidation of the *cis* hydrazo compound (**103**), which gives nearly a quantitative yield of nitrogen *via* the



(96) (97) (98) (45)



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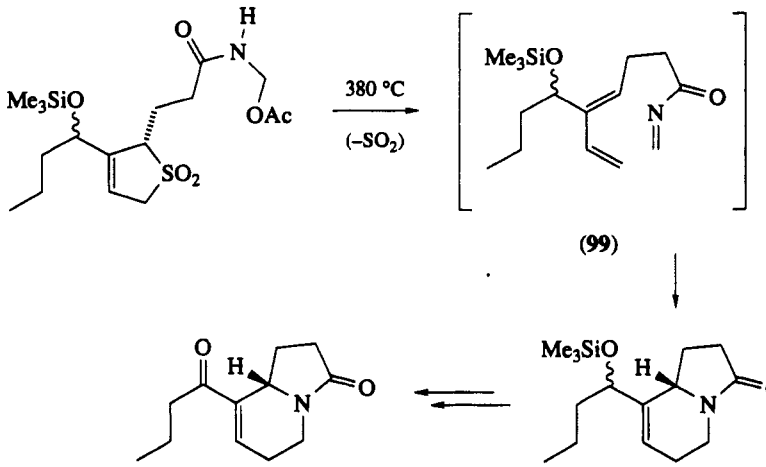
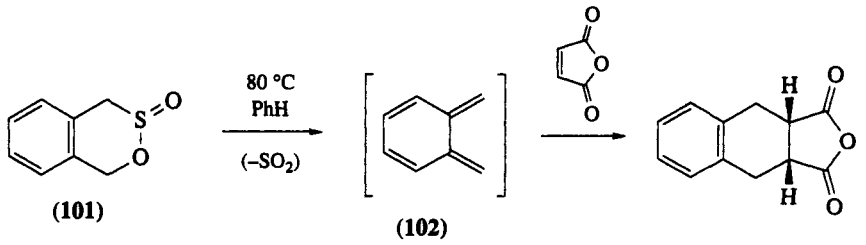


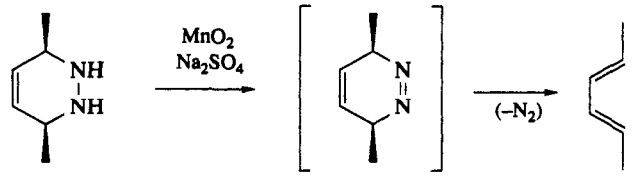
(99)

(100) (47)

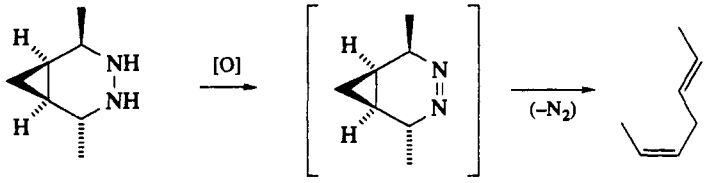


(101) (102) (48)

unstable azo compound (**104**) (equation 49).[106] The process has been extended to cyclopropane (**105**), which upon oxidation gives the azo intermediate (**106**) that extrudes nitrogen at room temperature producing *cis,trans*-2,5-heptadiene (**107**).[106]



(103) (104) (49)

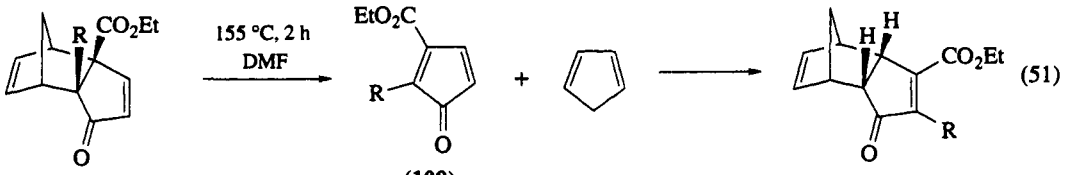


(105) (106) (107) (50)

4.5.3.4 Cyclobutadiene and Cyclopentadienes

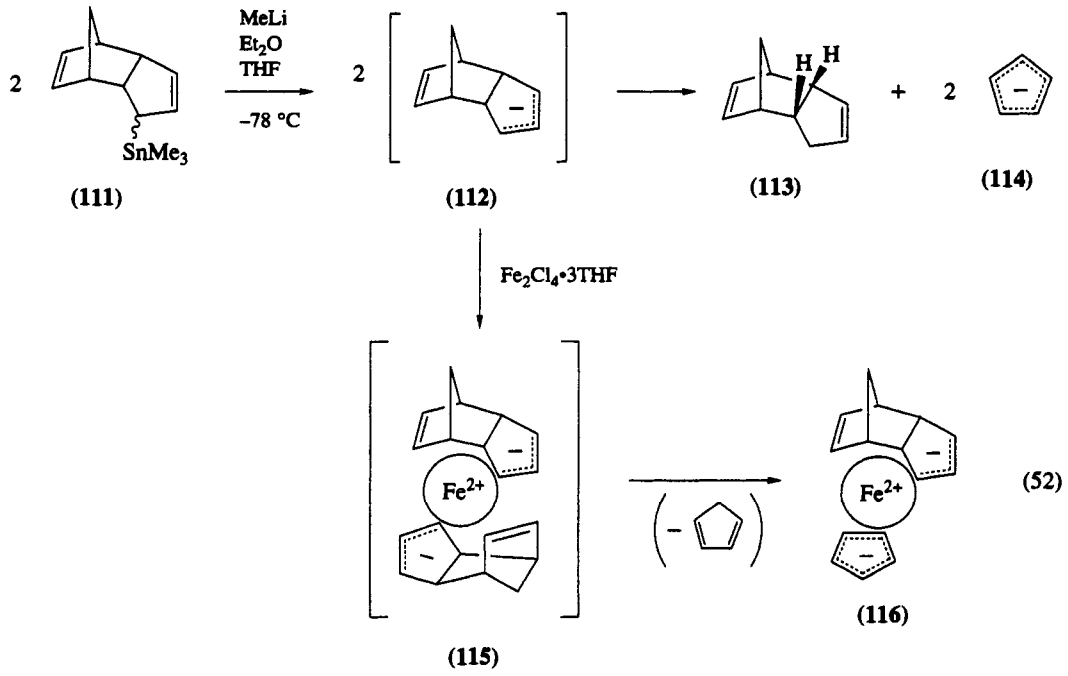
The formation of 1,3-dienes within a cyclic framework has been accomplished *via* extrusion of molecular nitrogen. Cyclobutadiene has been obtained by nitrogen extrusion from 2,3-diazo-Dewar benzene, which is generated by mild oxidation of 2,3-dioxybicyclo[2.2.0]hex-5-ene. Other cyclic dienes that have been similarly obtained are cyclopentadiene and cyclohexa-1,3-diene from the corresponding diazo compounds.[107,108]

Substituted cyclopentadienones have been generated *via* rDA thermolyses. Thermolysis of adduct (**108**) unmasks dienone (**109**) as shown in equation (51).[109] The generation of (**109**) was followed by trapping with cyclopentadiene to produce the tricyclic enones (**110**), which are used as synthons for sarkomycin derivatives.[109] The presence of the alkyl group at the 6-position in ester (**108**) enhances fragmentation *via* a rDA process, while in its absence (R = H) fragmentation occurs by decarbonylation.



(108) (109) (110) (51)

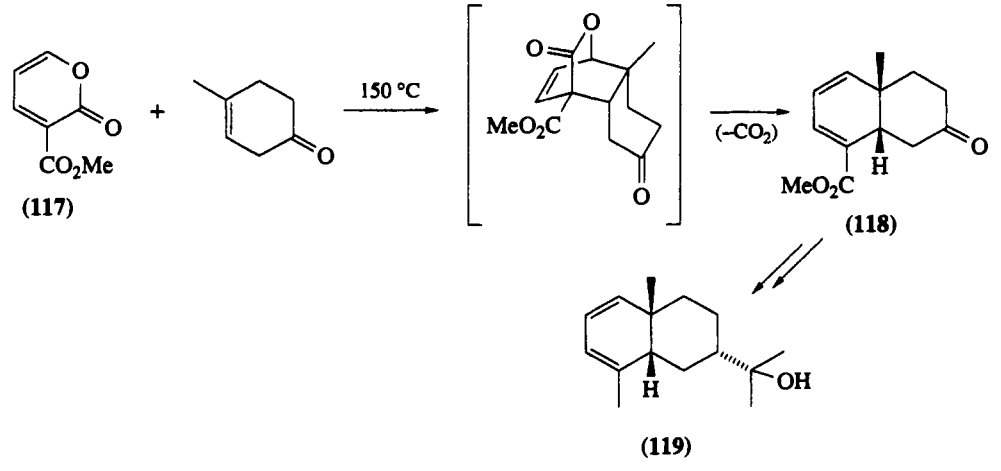
The reaction of stannylated dicyclopentadiene (**111**) with methyllithium gave dicyclopentadiene (**113**) and cyclopentadienyllithium (**114**) even at –78 °C.[110] The intermediate can be trapped by addition of iron(II) chloride to give intermediate (**115**), which then cleaves off cyclopentadiene from one of the two dicyclopentadiene ligands in a rDA process to give (**116**) as the isolated product. It therefore appears that the rDA decomposition is only partially blocked by trapping with iron(II) chloride.



(52)

4.5.3.5 Cyclohexadiene Derivatives

Cyclohexadiene generation by the rDA reaction has been used in the synthesis of natural products. The reaction of pyrone (**117**) with 4-methyl-3-cyclohexenone provides keto ester (**118**) regio- and stereoselectively (equation 53).[111] Fixation of both the correct ring fusion and the *cis*-diene functionality in a single step makes the keto ester a useful intermediate for the synthesis of natural products such as occidentalol (**119**).[111] The unmasking of DA adducts of steroidal ring-B dienes that are protected by cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (**121**) has been accomplished by a rDA process. In the synthesis of 22,23-epoxyvitamin D_2 (**123**) the protected steroidal adduct (**120**) was heated with base in dimethyl sulfoxide to give the corresponding steroidal 5,7-diene (**122**) as shown in equation (54).[112] This rDA method is useful because it can be applied to compounds having groups that are sensitive to lithium aluminum hydride, which had been previously used for regenerating the protected steroidal ring-B diene system. The rDA reaction of the neolignan asatone (**124**) produces dienone intermediate (**125**), which reacts with 1-allyl-3,4,5-trimethoxybenzene (**126**) to give the two novel neolignans heterotropanone (**127**) and isoheterotropanone (**128**) as shown in equation (55).[113]



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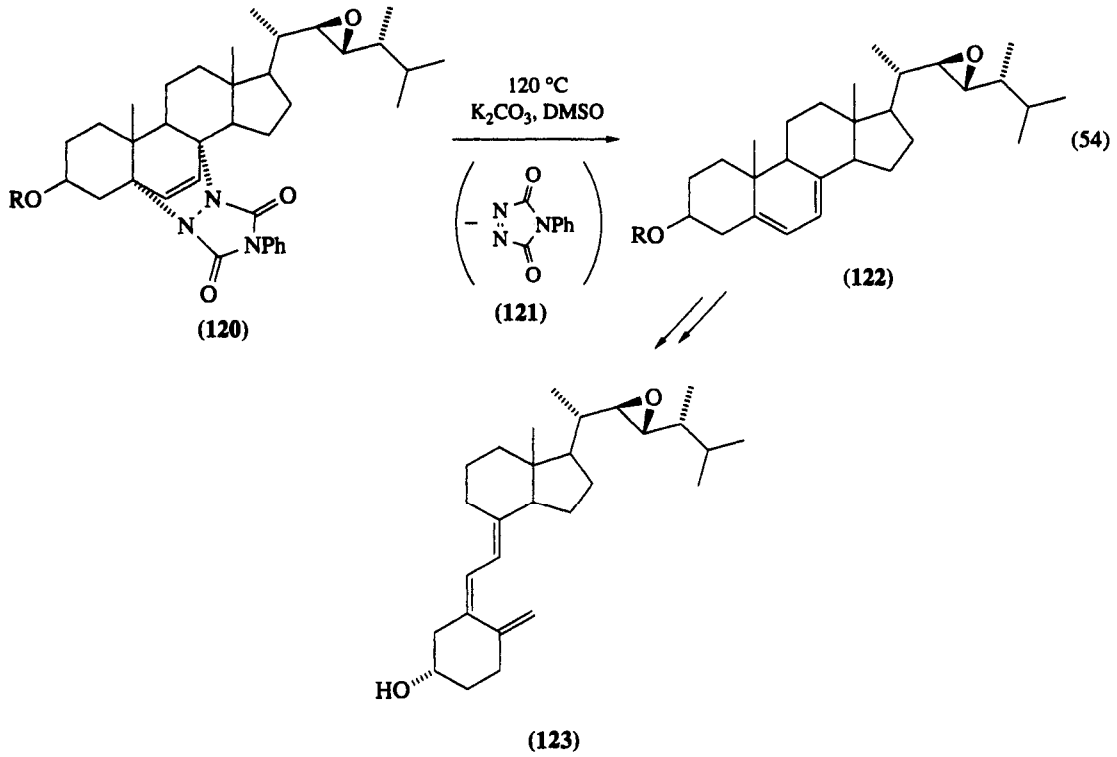
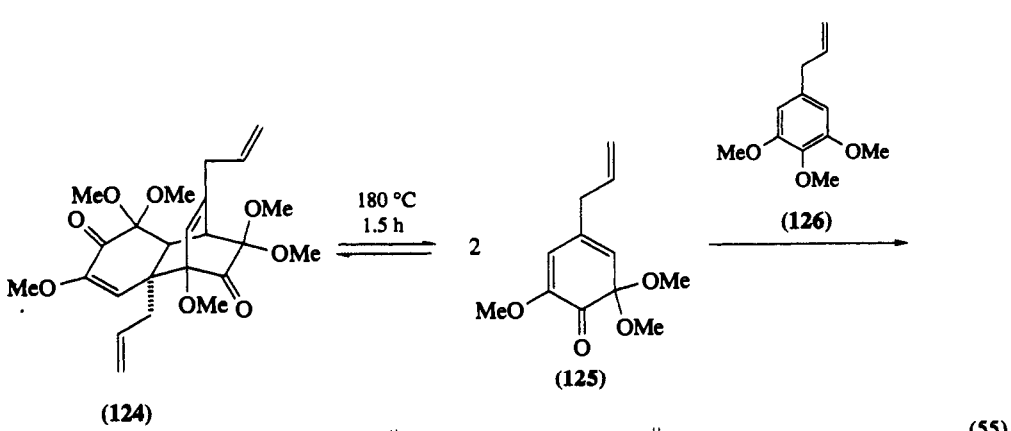


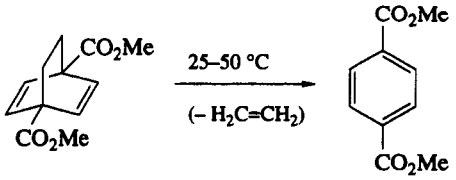
(120) (121) (122) (123) (54)



(55)

4.5.3.6 Benzene and Benzene Derivatives

Many cycloadducts produce aromatic rings *via* rDA processes. The generation of benzene has been obtained by the FVP of bicyclo[2.2.2]octa-2,5-diene[114] and of barrelene[115] in the gas phase. Dimethyl terephthalate was generated by the thermolysis of 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene as depicted in equation (56).[116] This cycloreversion has been shown to proceed even at room temperature, and readily occurs at temperatures as low as 50 °C. Sulfene extrusion *via* the rDA reaction also yields benzene derivatives: dimethyl phthalate was obtained by the thermolysis of the bicyclo adduct shown in equation (57).[117] Sulfene extrusion *via* a rDA route competes with the predominant process of sulfur dioxide extrusion. The presence of a phenyl group at C-4 can suppress the alternate route to norcaradiene formation by sulfur dioxide elimination and force the reaction to proceed exclusively *via* the rDA sulfene extrusion path.[118] *N*-Aminopyrroles are used in a versatile DA–rDA sequence to produce substituted benzenes in high yields. Diels–Alder reaction of *N*-aminopyrrole (**129a**) with DMAD produces benzene derivative (**131**) *via* rDA nitrene extrusion from adduct (**130**) (equation 58).[119] It is of interest that the rate of DA addition increases in the order (**129a**) > (**129b**) > (**129c**), whereas adduct rDA decomposition to (**131**) increases in the order (**130c**) > (**130b**) > (**130a**). A series of phthalate esters was prepared by the rDA reaction of the adduct between substituted pyridones and DMAD (equation 59).[120]



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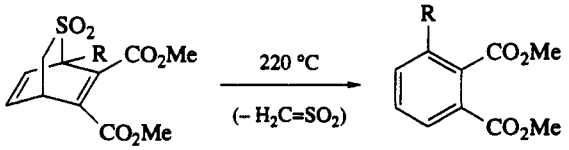
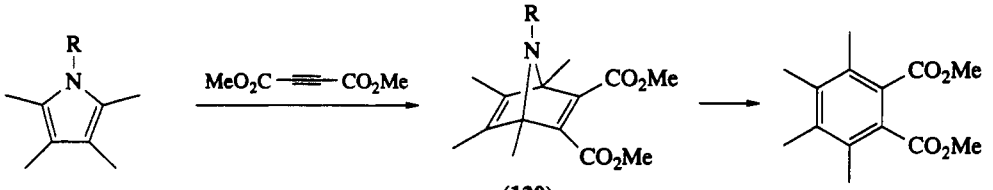


R = H, Ph

(57)



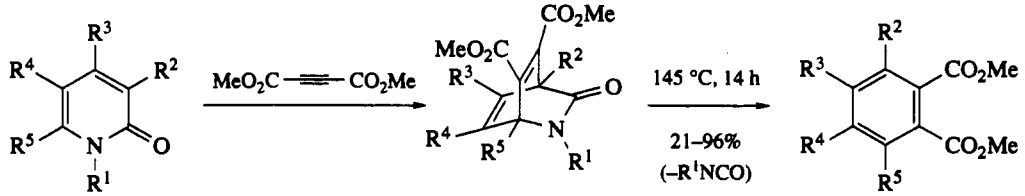
(**129a**) R = NH_2
(**129b**) R = NHMe
(**129c**) R = NMe_2

(**130**)

(**131**)

+ R–N:

(58)

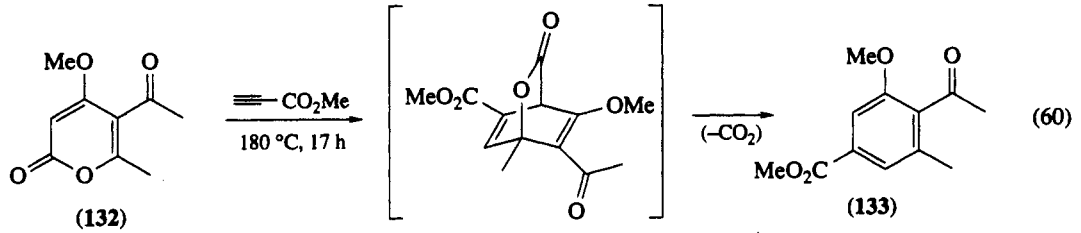


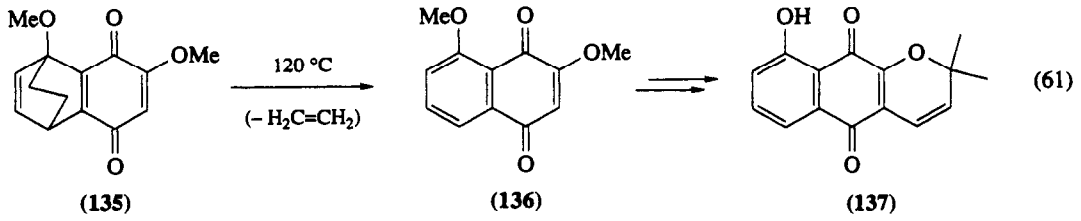
(59)

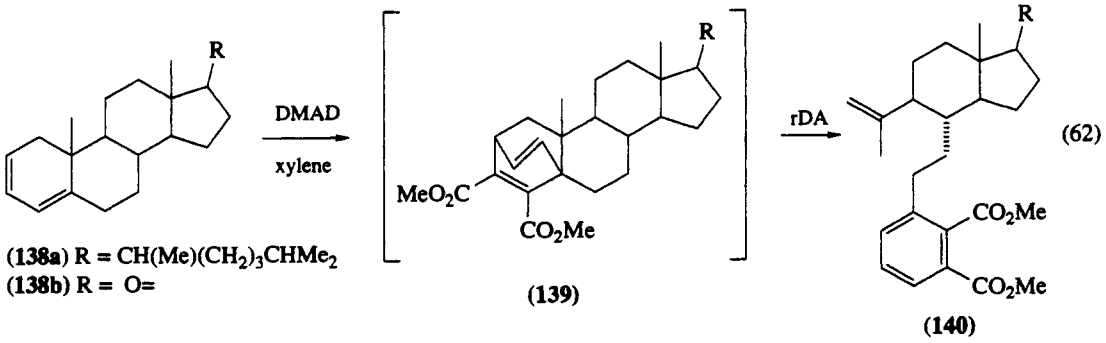
R^n = H, Me or Ph

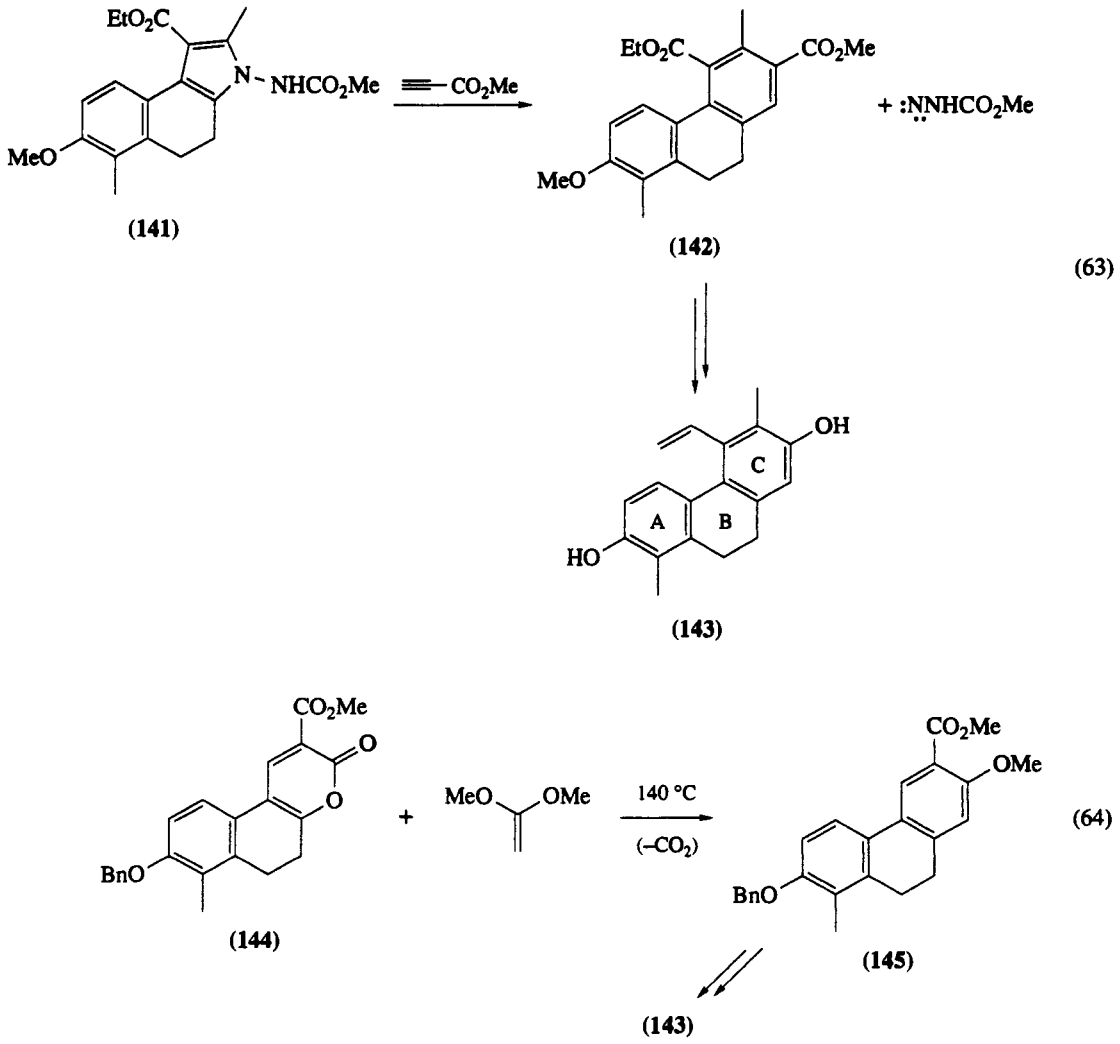
The formation of aromatic rings *via* rDA processes has found application in the synthesis of many natural products; only a representative set can be presented here. Pyrenochaetic acid A (**134**), a phytotoxic metabolite, was synthesized by a process involving a rDA reaction as a key step. The DA reaction of pyrone (**132**) with ethyl propiolate gave, after isolation, benzoate (**133**) *via* a rDA reaction evolving carbon dioxide (equation 60).[121] A synthesis of α-cartopterone (**137**) has been achieved that involves the rDA elimination of ethylene. The key step is rDA decomposition of adduct (**135**) to naphthoquinone

(**136**) as in equation (61).[122] Hydrindane derivatives (**140a**) and (**140b**) are formed by the reaction of 2,4-cholestadiene (**138a**) and 2,4-androstadien-17-one (**138b**), respectively, with DMAD in boiling xylene (equation 62).[123] The products, (**140a**) and (**140b**), are formed *via* DA addition of the steroid diene followed by subsequent rDA decomposition of adduct (**139**). The rDA reaction of these adducts provides a simple method for the simultaneous cleavage of rings A and B in steroids.[123] The synthesis of the cytotoxic phytoalexin juncusol (**143**) has been accomplished *via* two pathways based upon different rDA processes. One pathway involves the previously described reaction of *N*-aminopyrroles. The reaction of *N*-aminopyrrole (**141**) with methyl propiolate gave dihydrophenanthrene (**142**), after HPLC isolation. Formation of (**142**) occurred by a DA addition–rDA extrusion of *N*-aminonitrene pathway (equation 63),[124] and the product was subsequently transformed into juncusol. The second pathway to juncusol based on a rDA step involved the use of 3-methoxycarbonyl-2-pyrones. The formation of the aromatic ring C is obtained by DA addition of 1,1-dimethoxyethylene to the 3-methoxycarbonyl-2-pyrone (**144**) followed by subsequent rDA extrusion of carbon dioxide to give the 9,10-dihydrophenanthrene (**145**) (equation 64),[125,126] which is also a precursor of juncusol.









4.5.3.7 Cyclic Trienes in Non-aromatic Systems

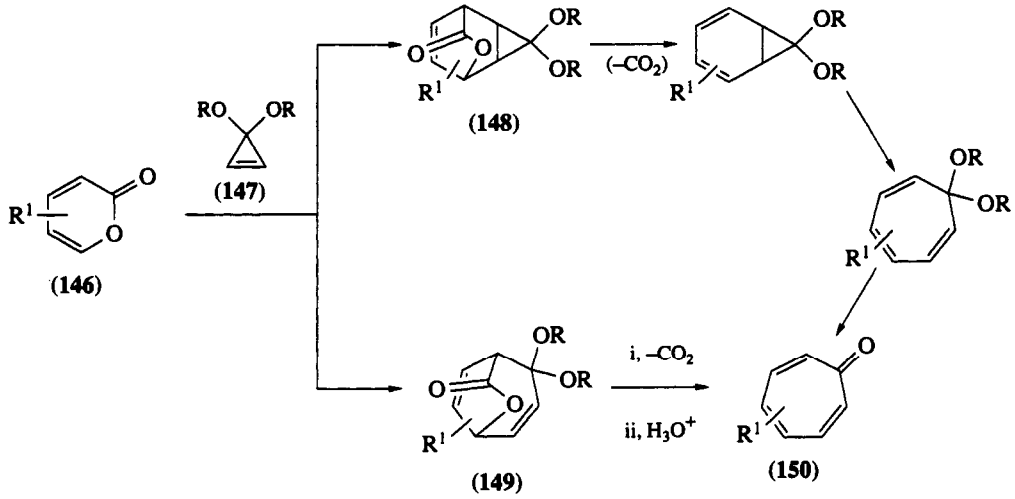
A final example of a rDA cycloreversion of a cycloadduct that acts as a 'protected' butadiene illustrates the generation of extended conjugation in a non-aromatic cyclic system. Equation (65) shows that the addition of cyclopropene (**147**) to (146) can yield either (**148**) or (**149**), and both adducts undergo rDA extrusion of carbon dioxide to produce a triene.[127] Hydrolysis of the triene ketals gives access to substituted tropones (**150**).

4.5.4 FORMATION OF DOUBLY BONDED HETEROATOMS

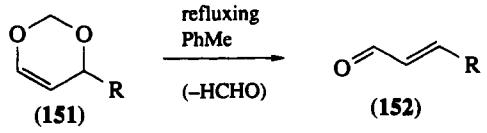
4.5.4.1 Acyclic Aldehydes, Ketones and Carboxylic Esters

Formation of a double bond between carbon and a heteroatom or between two heteroatoms can be accomplished by a hetero retro-Diels–Alder reaction. Aldehydes, ketones and carboxylic esters can be obtained by this retrodiene process. A series of α,β-unsaturated aldehydes (**152**) was prepared by Funk using the facile bis-hetero retro-Diels–Alder reaction of 4-alkyl-4*H*-1,3-dioxins (**151**) as shown in equation (66).[128] This retrodiene process involves exceptionally mild conditions, refluxing in toluene, in order to unmask the α,β-unsaturated aldehyde. The diversity of this process is illustrated by the partial list of reactions shown.[128] The same mild conditions can be used to prepare α,β-unsaturated ketones by reflux-

ing the appropriate 4,6-dialkyl-1,3-dioxins in toluene.[129] During the synthesis of the 'right-wing' equivalent (**156**) of the ionophore antibiotic indanomycin, an unexpected hetero retro-Diels–Alder reaction preempted the planned Claisen 3,3-shift. However, a subsequent intramolecular Diels–Alder reaction of intermediate (**154**) gave the desired product (**155**) of the planned Claisen 3,3-shift (equation 67).[130]

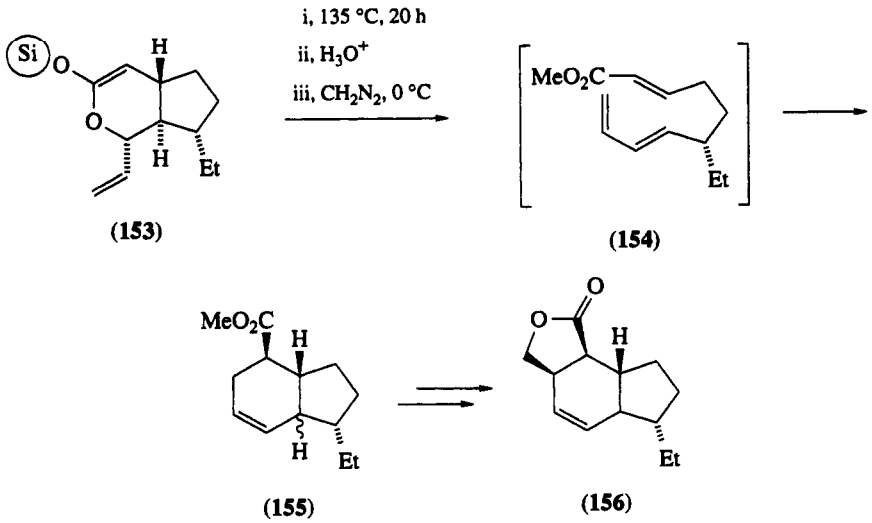


(65)



(66)

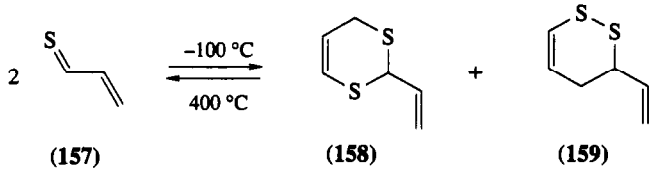
Compound	*R*	*Yield (%)*
(151a)	$(CH_2)_7Me$	74
(151b)	$CH(Me)(CH_2)_2CH{=}CMe_2$	73
(151c)	CH_2Ph	83
(151d)	$CH_2C(O)Me$	45
(151e)	CH(OH)CH=CHMe	70



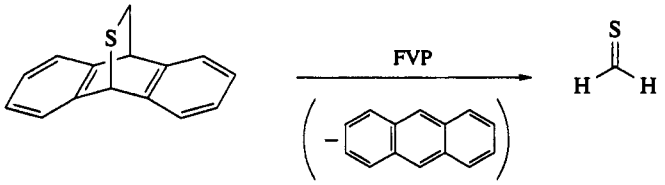
(67)

4.5.4.2 Thio Analogs

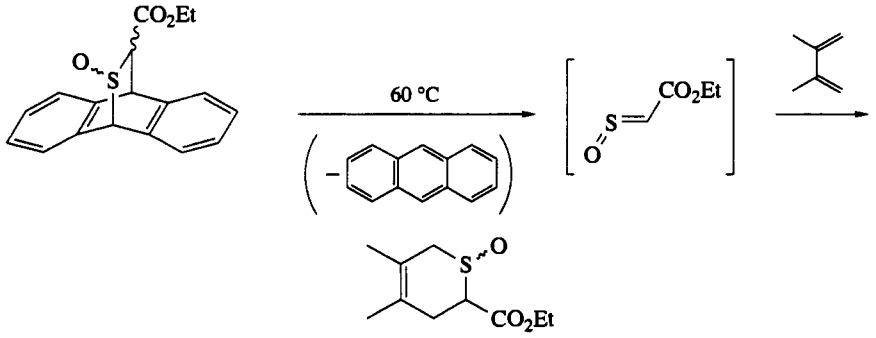
The types of compounds containing carbon–sulfur double bonds that can be generated *via* a retro-Diels–Alder reaction are quite varied. Thioacrolein (**157**), a vinyl thioaldehyde, once generated forms a Diels–Alder dimer mixture of (**158**) and (**159**). By thermal retrodiene splitting of the dimer mixture at 400 °C, thioacrolein has become available for preparative use (equation 68).[131] The simplest thioaldehyde, thioformaldehyde, can be obtained by the FVP of the anthracene adduct as shown in equation (69).[132] The most reactive and labile class of sulfines, the thioaldehyde *S*-oxides, are generated by heating the cycloadduct of the sulfine with anthracene or cyclopentadiene. The liberated sulfine can be trapped *in situ* by cycloaddition to a conjugated diene, for example 2,3-dimethylbuta-1,3-diene as illustrated in equation (70).[133] The thioamide vinylog (**161**) has been obtained by the thermally induced cycloreversion of 4*H*-1,3-thiazine (**160**) as given in equation (71).[134] By prolonged heating in the presence of dimethyl acetylenedicarboxylate the 4*H*-thiopyran (**162**) was formed. Thioketenes, when devoid of bulky substituents, are very reactive species with few available methods for synthesis. Propadienethione has been produced by the FVP of a ketene dithioacetal as shown in equation (72).[135]



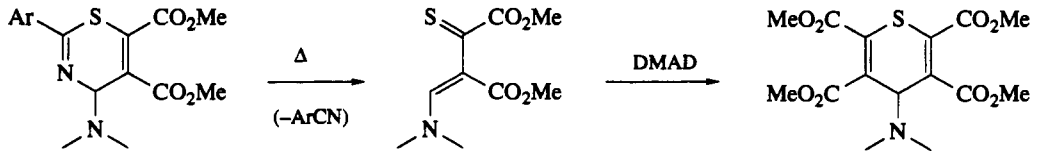
(157) (158) (159) (68)



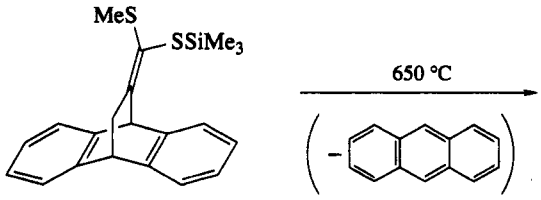
(69)



(70)



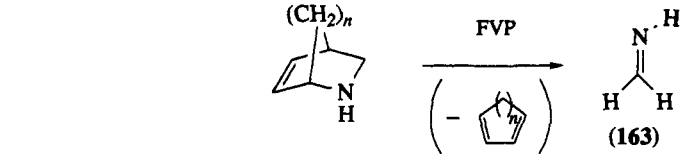
(160) (161) (162) (71)



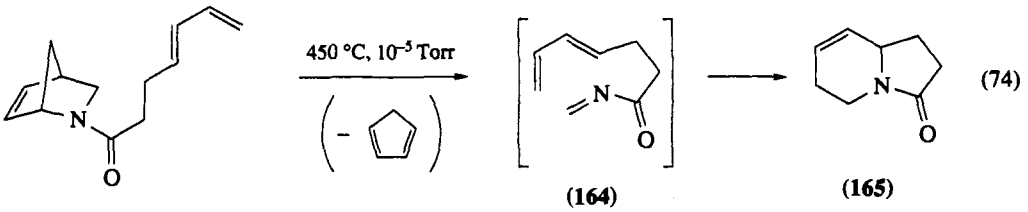
(72)

4.5.4.3 Nitrogen Analogs

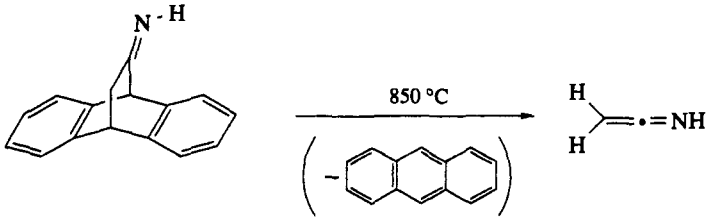
Use of the rDA reaction has been applied to the preparation of numerous compounds containing nitrogen double bonded to carbon or another heteroatom. The simplest compound possessing a carbon–nitrogen double bond is methanimine (**163**), which has been generated by the FVP of 2-azabicyclo[2.2.*n*]alkenes in almost quantitative yields (equation 73).[136] Application of the method for the synthesis of methanimine has led to the preparation of several *N*-acylmethanimines and *N*-methylenemethanesulfonamide.[137] The high reactivity of *N*-acylimino groups towards 1,3-dienes was evidenced by the production of lactam (**165**) *via* intramolecular cycloaddition of the intermediate acylimine (**164**) (equation 74).[137] Vinylideneamine was obtained *via* a rDA reaction of the anthracene adduct as shown in equation (75).[214]



(73)



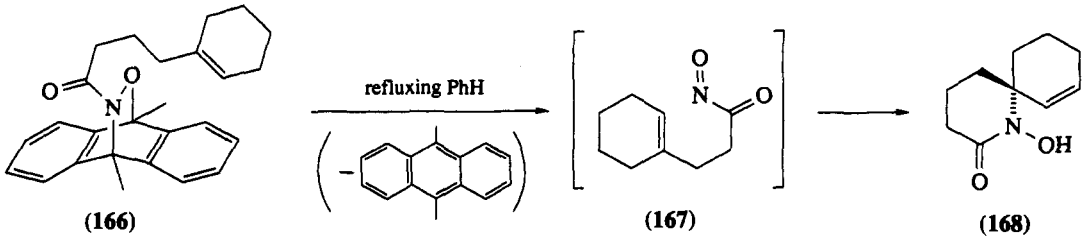
(74)

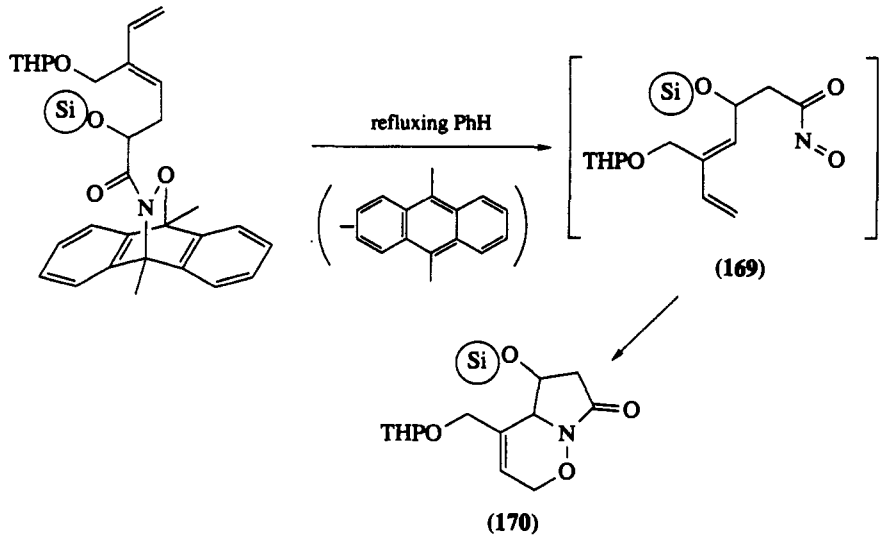


(75)

Acylnitroso alkenes produced *via* rDA reactions are key intermediates in the synthesis of alkaloids.[138–144] The acylnitroso alkene intermediate (**167**) that is generated from anthracene adduct (**166**) can react by an intramolecular ene reaction, resulting in the formation of hydroxamic acid (**168**).[138] If the acylnitroso alkene is produced in the presence of a diene, an intramolecular Diels–Alder reaction can occur to give a 1,2-oxazine derivative such as (**170**) as shown in equation (76).[143]

The preparation of compounds containing nitrogen double bonded to another heteroatom has been accomplished by a rDA pathway. *Cis*- and *trans*-azomethane have been synthesized from tetrahydropyridazine (**171**) by thermal retrodiene extrusion (equation 77).[145] The *anti* conformation of (**171**) is presumed to give *trans*-azomethane and the *syn* conformations yields the *cis*-isomer. Preparation of nitrosyl hydride (**173**) has been accomplished under mild nonphotochemical conditions, unlike conditions used in previous preparations. The extrusion of nitrosyl hydride from anthracene adduct (**172**) as shown in equation (78),[146] which occurs at a very mild temperature, was followed by microwave detection of (**173**).





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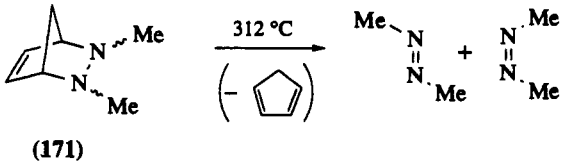

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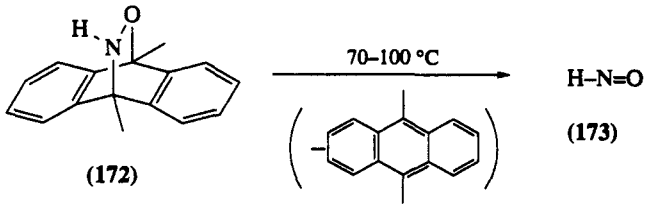
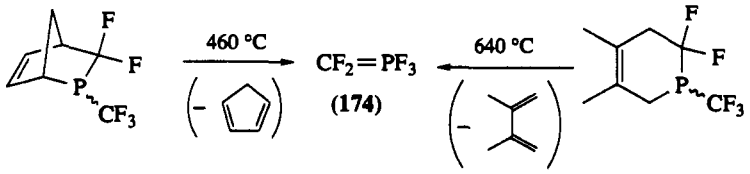


(78)

4.5.4.4 Phosphaalkene

Phosphaalkene (**174**) has been generated from two different adducts (equation 79).[147]



(79)

4.5.5 PREPARATION OF UNSATURATED HETEROCYCLES

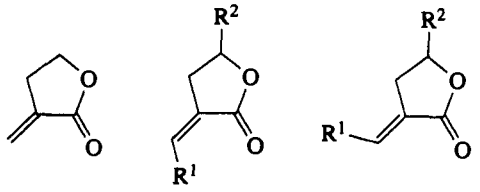
4.5.5.1 Oxygen Heterocyclics Generated by Ethylene Formation

The preparation of many unsaturated heterocyclic compounds can be achieved *via* rDA processes. The vast majority of these compounds are either oxygen or nitrogen containing heterocyclics, preparation of which is most often accomplished by the expulsion of an ethylene or a butadiene moiety. α-Methyleneoxetane (**175a**) and β-methyleneoxetane (**175b**) are obtained by a rDA process from the anthracene cycloadducts.[148]

The generation of exocyclic double bonds by rDA cycloreversion is useful for the synthesis of unsaturated lactones, which are an important part of many natural products. The α-methylenebutyrolactone tuli-

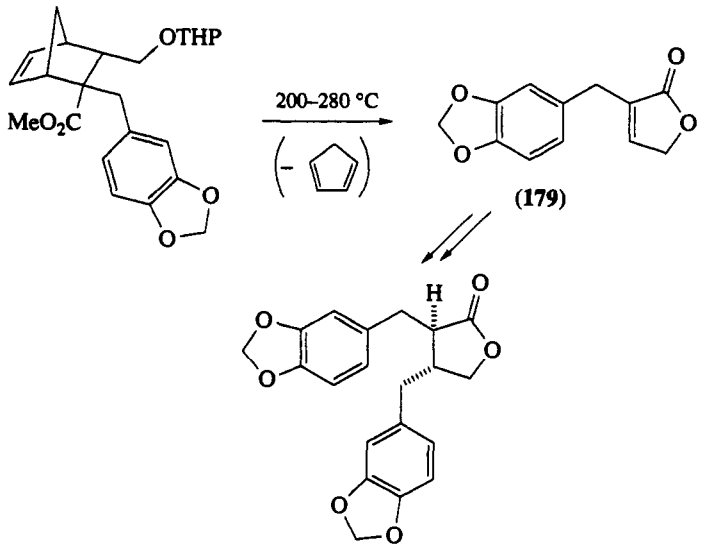
(175a) (175b)

palin A (**176**), an antifungal phytotoxic compound isolated from tulip bulbs, has been prepared by two independent syntheses *via* rDA reactions.[149,150] The syntheses of α-methylene-γ-butyrolactones (**177**) and (**178**) were achieved in good yield by rDA cycloreversion of the corresponding anthracene adducts.[151]



(176) (177) (178)

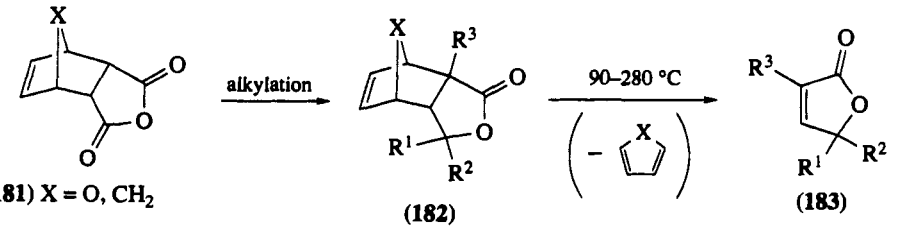
The formation of the endocyclic double bonds of unsaturated lactones has been accomplished *via* the rDA reaction. The preparation of 2-alkyl-2-butenolactones, such as (**179**), by a method that incorporates the rDA reaction as a key step has been applied to the synthesis of butyrolactone lignans such as (±)-hinokinin (**180**) as shown in equation (80).[152] An extensive study of the preparation of substituted 2-butenolides (**183**) has been reported. The mono-, di- and tri-alkyl bicyclobutenolides are prepared by reacting adducts (**181**) with Grignard reagents or with LDA followed by alkyl halides. Alkylated adducts (**182**) were then either directly distilled under vacuum or heated in a sealed tube to give the alkylated 2-butenolides (**183**) (equation 81).[153–157]



(179)

(180)

(80)

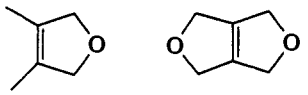


(181) X = O, CH_2 (182) (183)

(81)

R^1 = H, alkyl, aryl, benzyl; R^2 = H, alkyl, aryl, benzyl; R^3 = H, alkyl, allyl, aryl, benzyl

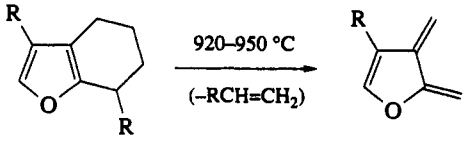
The generation of a carbon–carbon double bond from a protected ethylene cycloadduct by rDA cycloreversion has been used for the preparation of 2,5-dihydrofurans. The syntheses of 3,4-dimethyl-2,5-dihydrofuran (**184**) and 3,7-dioxabicyclo[3.3.0]oct-1(5)-ene (**185**) were accomplished in high yield using FVP conditions to effect cycloreversion of the anthracene adducts at 550 and 800 °C, respectively.[158,159]



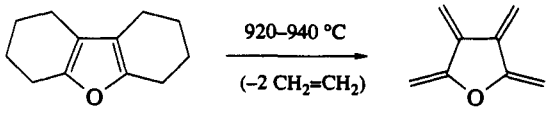
(**184**) (**185**)

4.5.5.2 Oxygen Heterocyclics Generated by Butadiene Formation

The rDA cycloreversion of a 'protected' butadiene adduct has been applied to the synthesis of unsaturated oxygen heterocycles. The very unstable 2,3-dihydro-2,3-bis(methylene)furan and its 4-methyl derivative have been generated by rDA reaction of 4,5,6,7-tetrahydrobenzofuran and its dimethylated derivative (equation 82).[160] Characterization of these dienes was accomplished by trapping with various dienophiles. This method was extended to a two-step rDA synthesis of tetramethylenetetrahydrofuran as shown in equation (83).[161]

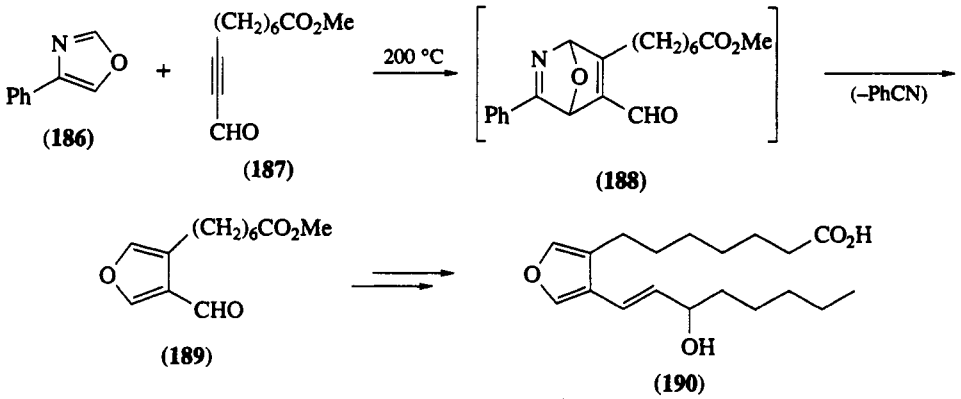


(82)

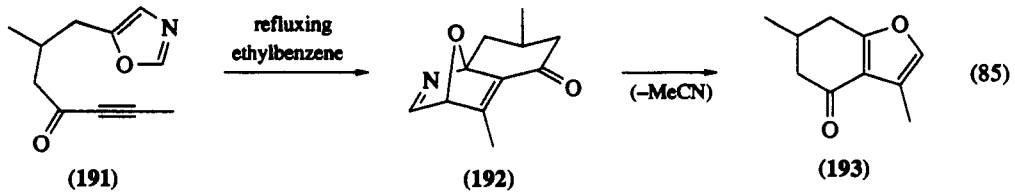


(83)

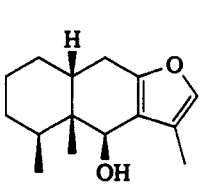
Another 3,4-disubstituted furan, compound (**189**), was prepared by an interesting one-pot DA–rDA process. The reaction of methyl 10-oxodec-8-ynoate (**187**) with 4-phenyloxazole (**186**) produced disubstituted furan (**189**), which was subsequently converted into the 3,4-disubstituted furan prostanoid (**190**). The method of furan formation based upon the intramolecular DA addition between oxazoles and alkynes, followed by subsequent rDA reaction extruding an alkyl nitrile, has been extended to the synthesis of several natural products. Upon refluxing in ethylbenzene, oxazole (**191**) gave evodone (**193**), the simplest member of the naturally occurring furanoterpenes.[162] This method has been used similarly to prepare the furanoeremophilanes (±)-petasalbine (**194**), (±)-ligularone (**195**)[163] and (±)-paniculide A (**196**),[164] and the furanosesquiterpenes gnididione (**197a**) and isognididione (**197b**).[165]



(84)



(191) (192) (193) (85)



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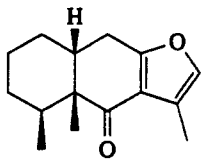

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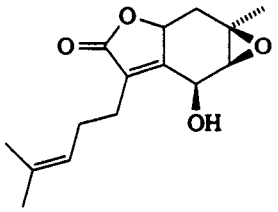

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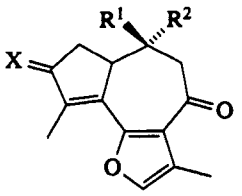
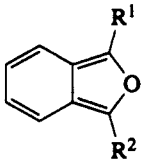


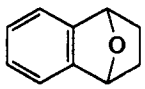
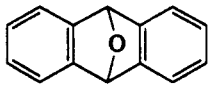
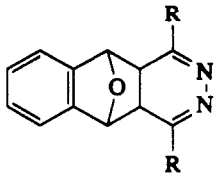
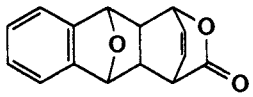
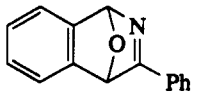
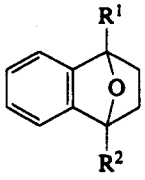
(197a) X = , R^1 = Me, R^2 = H

(197b) X = O, R^1 = H, R^2 = Me

Isobenzofuran (**198**; $R^1 = R^2 = H$) and substituted isobenzofurans have been formed *via* rDA cycloreversions from many adducts. Depicted are some of the various adducts that have been used for this purpose.[166–170]

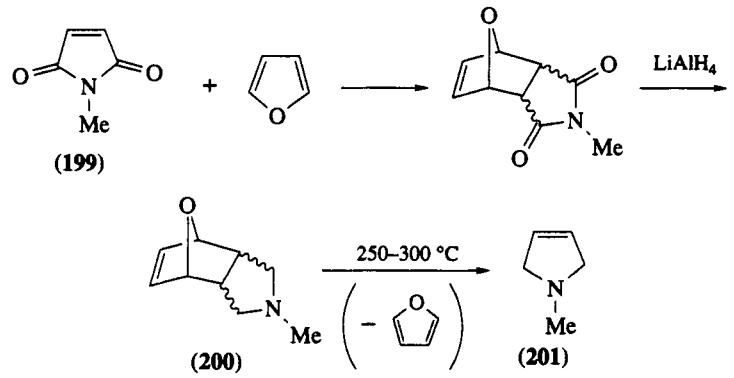


(198)

Adduct	*rDA temp.* (°C)	*Yield of isobenzofuran (%)*
	650	100
	170	100
	120	–
	130	30
	80	78
	600	100

4.5.5.3 Nitrogen Heterocyclics Generated by Ethylene Formation

The generation of the carbon–carbon double bond of unsaturated nitrogen heterocycles by the rDA reaction of cycloadducts that act as 'protected' ethylenes has been accomplished. Azetines have been prepared by this method.[171] Another example is the synthesis of 1-methyl-3-pyrroline (**201**). By protecting the ethylene of *N*-methylmaleimide (**199**) with furan and then reducing with lithium aluminum hydride, adduct (**200**) was obtained (equation 86).[172] Pyrolysis of adduct (**200**) at 250–300 °C gave 1-methyl-3-pyrroline (**201**) in 60% isolated yield. The ethylene moiety of *N*-substituted maleimides can also be generated *via* rDA reactions. Examples include the generation of *N*-phenylmaleimide (equation 87)[173] and of *N*-acetoxymaleimide (equation 88).[174]



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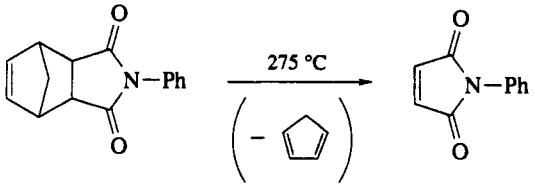

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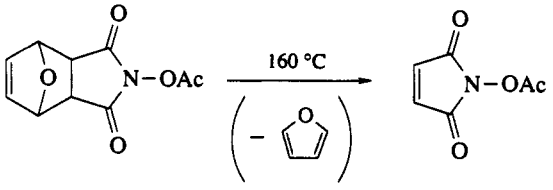


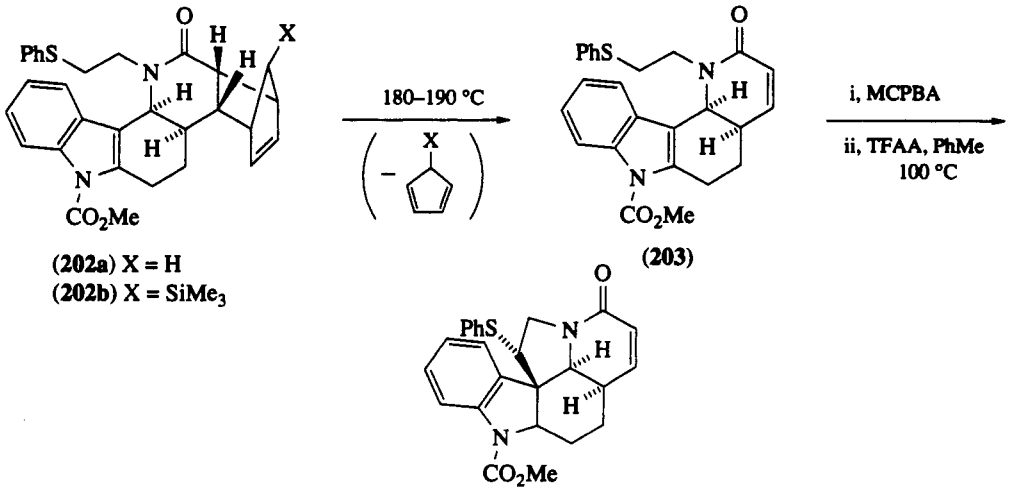
(88)

Generation of an ethylene unit from a 'protected' cycloadduct has found application in the synthesis of the α,β-unsaturated lactam moiety of indole alkaloids. The formation of lactam (**203**) occurs by pyrolysis at 180–190 °C *via* rDA extrusion from (**202a**) in 120 hours (67% yield) or from (**202b**) in seven hours (100% yield) as shown in equation (89).[175] Acceleration of the rDA process in (**202b**) is due to the trimethylsilyl group, which lowers the activation energy of the extrusion process by charge, radical or double bond stabilization β to the trimethylsilyl group. This 7-trimethylsilyl accelerated rDA process is useful for regeneration of the ethylene moiety under mild conditions. Lactam (**203**) was subsequently converted to the pentacyclic deethylaspidosperma-type alkaloid (**204**).[175]

4.5.5.4 Nitrogen Heterocyclics Generated by Butadiene Formation

Substituted pyrroles such as verrucarine E (**208**), an antimitotic agent, have been synthesized by methods that incorporate a rDA reaction as a key step. In order to prepare 3,4-disubstituted pyrroles in reasonable yields, an electron-withdrawing *N*-substituent must be present. Therefore, as shown in equation (90), *N*-benzoylpyrrole (**205**) was subjected to a DA–rDA sequence with acetylene elimination to produce diester (**207**), which was transformed into verrucarine E (**208**).[176]

The photochemical generation of pyrroles has been accomplished *via* intramolecular rDA reactions. Irradiation of azatricyclodecenone (**209**) in methanol resulted in a photoinitiated retrograde reaction that

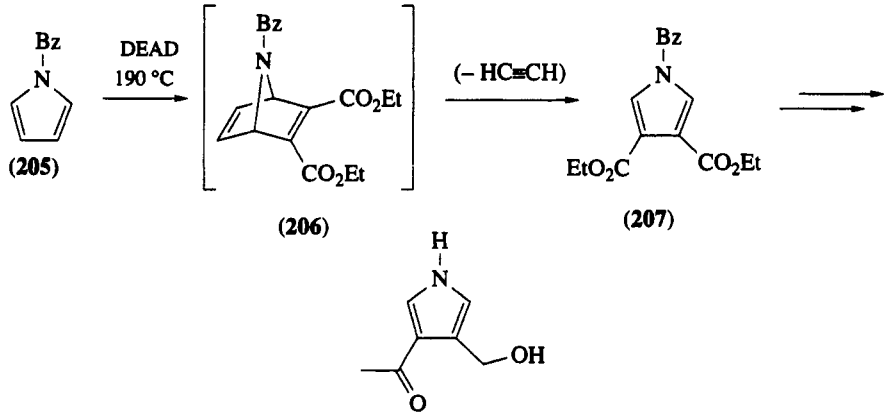


(202a) X = H
(202b) X = $SiMe_3$

(203)

(89)

(204)



(205)

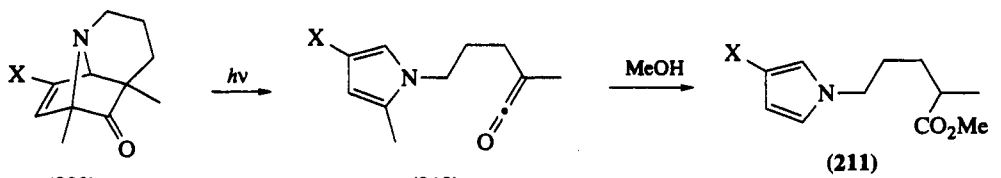
(206)

(207)

(90)

(208)

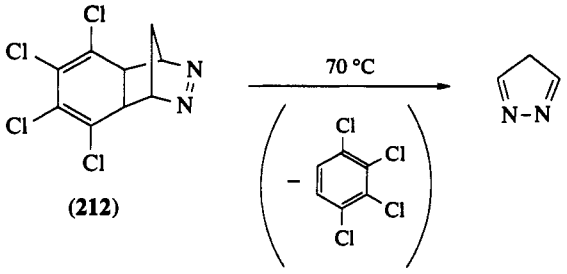
yielded pyrrole ketene (**210**). The final product, pyrrole methyl ester (**211**), was obtained by reaction of (**210**) with methanol (equation 91).[177]



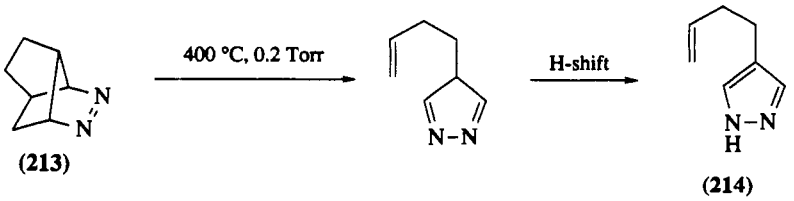
(209) (210) (211) (91)

The generation of pyrazole has been effected by thermal rDA decomposition of diazatricycle (**212**) (equation 92), while photolysis resulted in nitrogen elimination.[178] The formation of 4-(3-butenyl)-1,2-pyrazole (**214**) occurred *via* rDA reaction of adduct (**213**) (equation 93).[179] Apparently the rigidity of the tricyclic azoalkane (**213**) prevented nitrogen extrusion under the usual thermolysis conditions. Again, photolysis resulted in nitrogen elimination rather than cycloreversion.

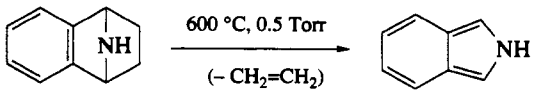
Isoindole was formed in essentially quantitative yield by rDA reaction of its ethylene adduct under FVP conditions (equation 94).[180] Substituted isoindoles (**215**)[181] and (**216**)[182] have been obtained by a similar rDA extrusion process.



(212) (92)



(213) (214) (93)



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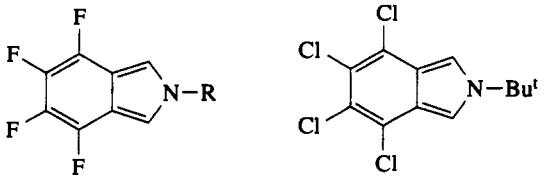
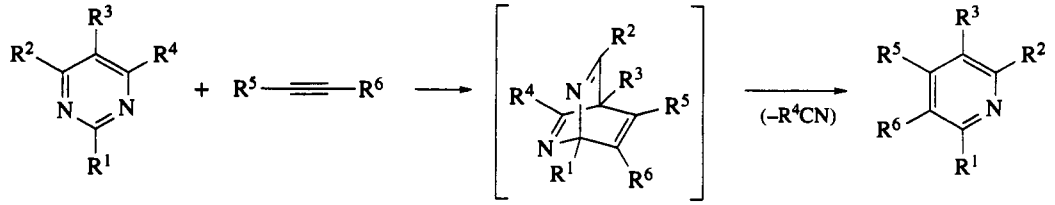


(215a) R = H
(215b) R = CH_2Ph (216)

4.5.5.5 Six-membered Nitrogen Heterocyclics

A vast array of six-membered nitrogen heterocyclics has been synthesized by rDA methods. Pyridine,[183] 1,4-dihydropyridine,[184] 5,6-dihydropyridine[185] and pyrimidinone[186] syntheses have all been reported.

Boger has devised numerous synthetic schemes for the synthesis of six-membered nitrogen heterocycles based upon DA addition with subsequent rDA extrusion, and has reviewed the subject.[187,188] Representative examples are shown for the synthesis of substituted pyridines (equation 95),[189] substituted pyrimidines (equation 96)[190] and substituted 1,2-diazines (equation 97).[191]



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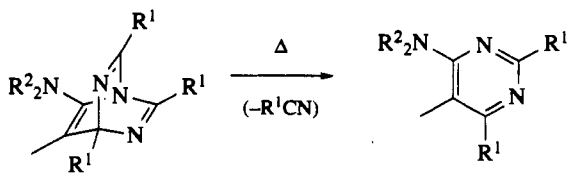

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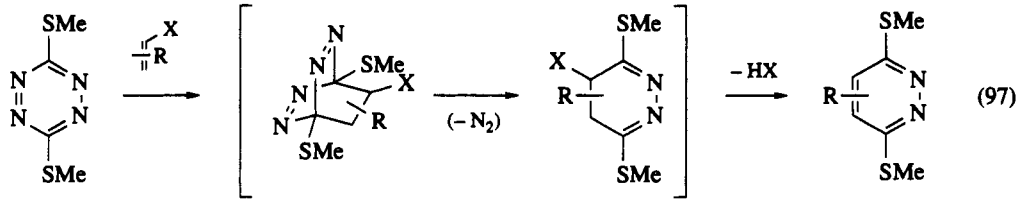
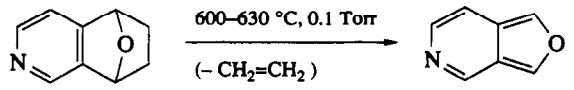


(97)

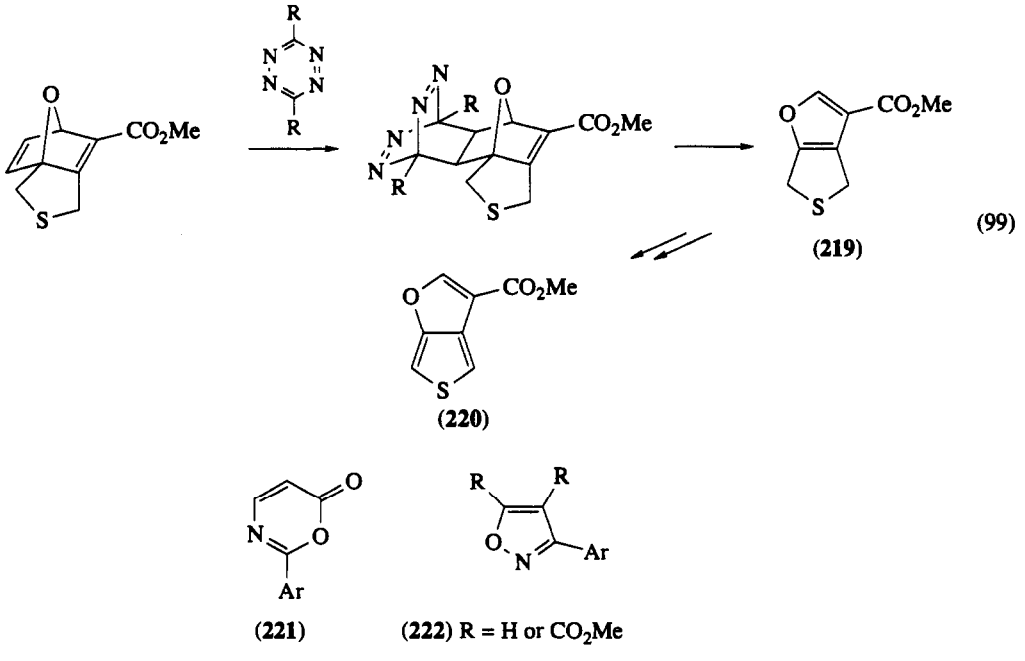
4.5.5.6 Heterocycles with Two Different Heteroatoms

The synthesis of heterocycles *via* rDA processes includes the preparation of heterocycles with two different heteroatoms. Furo[3,4-*c*]pyridine (**218**), a previously unknown polyheterocyclic, has been achieved by FVP of adduct (**217**) (equation 98).[192] The heteropentalene thieno[3,4-*b*]furan (**220**) has been synthesized by a reaction pathway based upon rDA formation of polyheterocycle (**219**) (equation 99).[193] Other heterocycles prepared *via* rDA reactions that contain two different heteroatoms include 6*H*-1,3-oxazin-6-one (**221**)[194] and 3-arylisoxazoles (**222**).[195]



(98)

(**217**) (**218**)



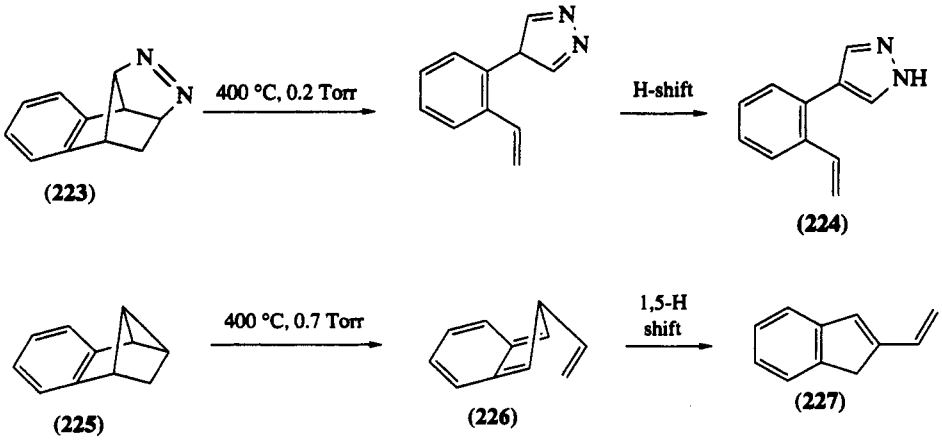
(99)

(**221**) (**222**) R = H or CO_2Me

4.5.6 INTRAMOLECULAR CYCLOREVERSIONS

4.5.6.1 Cyclic Compounds

Intramolecular rDA processes have been used to produce a variety of cyclic compounds. Thermolysis of azoalkane (**223**) followed by tautomerization gives 4-(2′-styryl)pyrazole (**224**) as shown in equation (100).[196] Apparently the C-1—C-6 and C-4—C-5 bonds are sufficiently weakened compared with the C-1—N-2 and N-3—C-4 bonds in strained (**223**) that the rDA process is preferred over expected molecular nitrogen extrusion. An investigation of the thermal stability of (**225**) led to production of 2-vinylindene (**227**) *via* an intramolecular cycloreversion to intermediate (**226**), which underwent a 1,5-hydrogen shift to yield the more stable aromatized product (equation 101).[197]

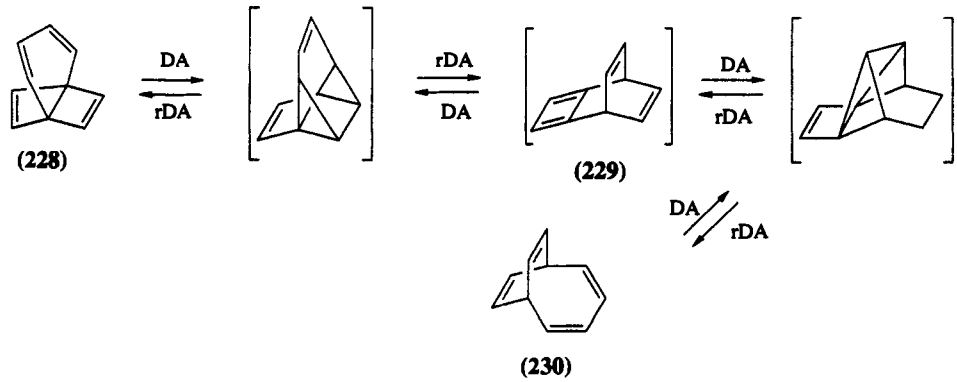


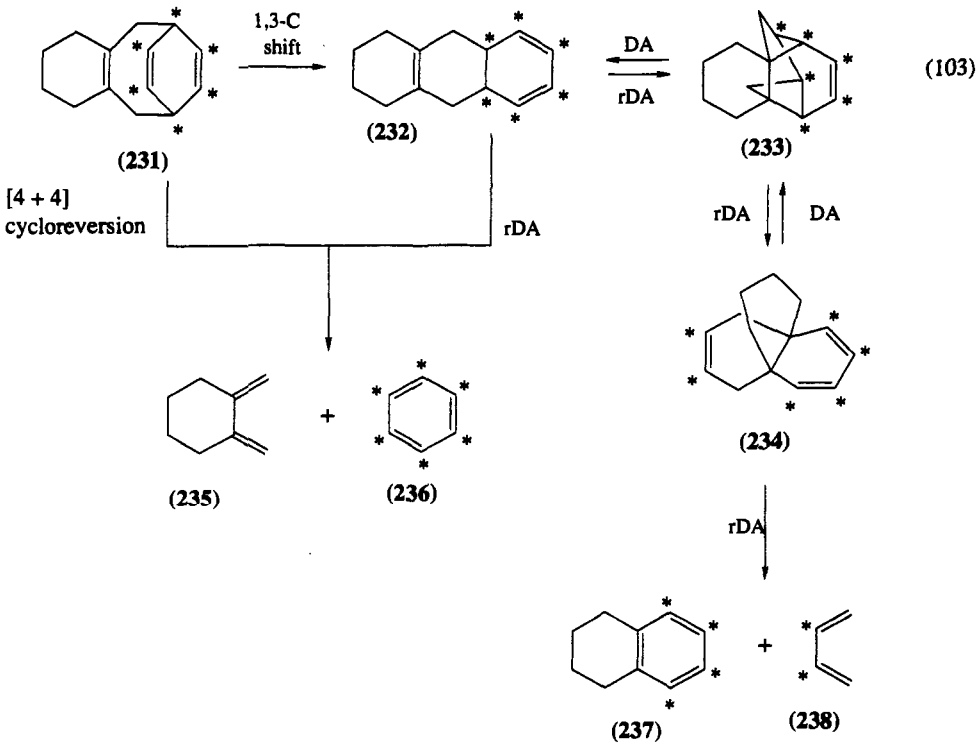
4.5.6.2 Isomerizations

Often an intramolecular rDA cycloreversion is involved in a series of DA–rDA reactions in an isomerization or an automerization process. In the automerization of [4.2.2]propella-2,4,7,9-tetraene (**228**), a DA–rDA sequence occurred twice to produce bicyclic (**230**) (equation 102).[198] A remarkable facet of this thermal molecular rearrangement process is the formation of the highly energetic cyclobutadiene intermediate (**229**), whose presence was evidenced by trapping with methanol. Another isomerization involving a series of rDA reactions is observed for the thermal decomposition of tricyclo[6.4.2.0.$2^{3,6}$]tetradeca-1(8),4,13-triene (**231**). This thermal decomposition produces 1,2-dimethylenecyclohexane (**235**), tetralin (**237**), benzene (**236**) and butadiene (**238**) as shown in equation (103).[199] The mechanism shown was based on thermal decomposition of the hexadeutero analog of (**231**) (asterisks are deuterated positions). The suspected driving force for this molecular rearrangement is the aromatization occurring during the rDA reactions of (**232**) and (**234**). Tricyclic acetate (**239**) is converted to acetate (**240**) by a thermally initiated intramolecular rDA reaction (equation 104).[200] Relief of ring strain is cited as contributing to the low temperature required for this rDA reaction.

4.5.6.3 Solvolysis Reactions

Very few well-documented cases of intramolecular rDA reactions are known that occur during solvolysis. Three examples that exist are: the aqueous ethanolysis of (**241**) in excess sodium cyanide (equation 105),[201] the hydrolysis of a related *p*-nitrobenzoate in aqueous acetone,[202] and a related tosylate in TFA.[203] In each case a cyclopentadienyl derivative is formed by an intramolecular rDA process, which can then be trapped as a DA adduct, tautomerize or dimerize.





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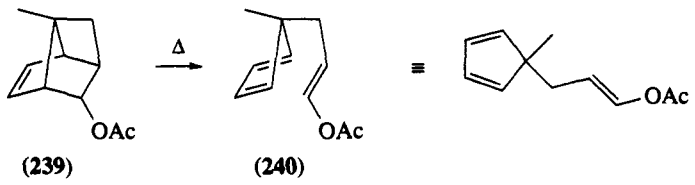

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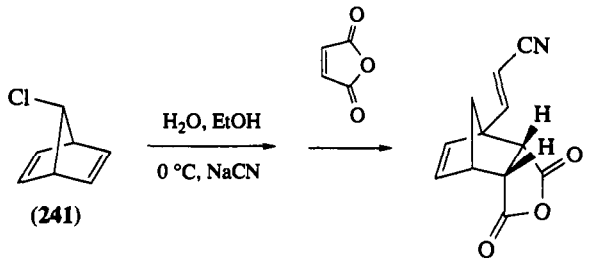
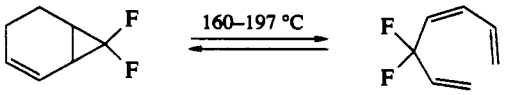


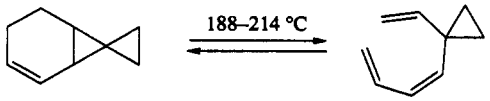
(105)

4.5.6.4 Acyclic Species

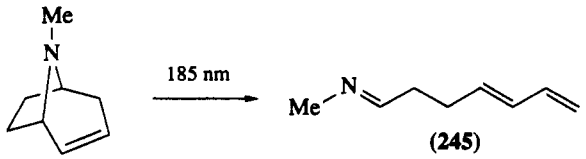
Intramolecular rDA reactions are also known that generate acyclic compounds. The thermal isomerizations of bicyclo[4.1.0]hept-2-enes (**242**) and (**243**) were found to occur *via* an intramolecular rDA process as depicted in equations (106) and (107), respectively;[204] *gem*-difluoro substituents of (**242**) and the spiropentyl substituent of (**243**) give rise to similar kinetic enhancements of ring cleavage and an incremental strain of the ring system.[204] The kinetic parameters for these reversible intramolecular rDA processes demonstrate that almost all of the entropy lost upon product formation is lost on reaching the transition state. A final example of the formation of acyclic species by an intramolecular rDA cycloreversion involves the photochemistry of tropidine (**244**). Irradiation of tropidine in pentane with 185 nm light (6.7 eV photons) gave only product (**245**) in greater than 90% yield (equation 108).[205]



(242) (106)



(243) (107)



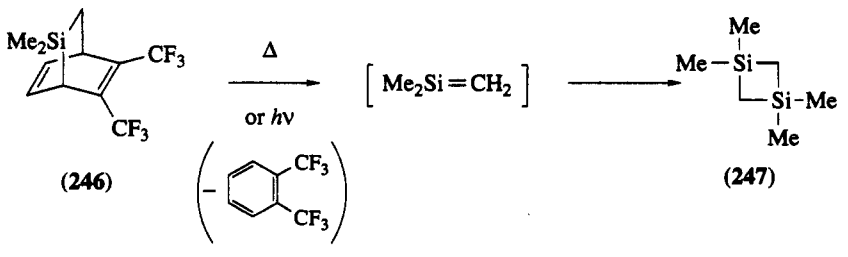
(244) (245) (108)

4.5.7 GENERATION OF REACTIVE INTERMEDIATES

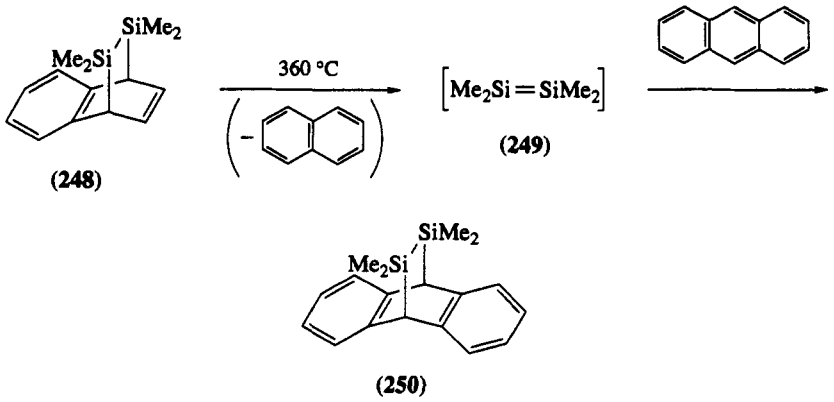
4.5.7.1 Silenes, Disilenes and Silanones

The generation of reactive species by a retrograde Diels–Alder pathway has proven a powerful tool for the study of chemical intermediates. The generation of intermediates containing doubly bonded silicon, such as silenes, disilenes and silanones, has been achieved. Silenes, molecules containing a silicon–carbon double bond, can be obtained by the thermolysis or photolysis of an appropriate adduct. A very efficient silaalkene generator is the 7-silabicyclo[2.2.2]octadiene (**246**), which upon thermolysis or photolysis yields 2-methyl-2-silapropene (**247**) as shown in equation (109).[206] Disilenes, compounds with a silicon–silicon double bond, have been similarly obtained. The disilene intermediate tetramethyldisilene (**249**) has been produced by the thermal decomposition of 7,8-disilabicyclo[2.2.2]octa-2,5-dienes such as (**248**). The existence of these reactive intermediates is often substantiated by trapping with an appropriate diene. To be suitable, the diene must be stable at the decomposition temperature and the product formed after the reaction with the diene must also be thermally stable at this temperature. Direct evidence for the existence of tetramethyldisilene was obtained by trapping with anthracene as shown in equation (110).[207]

Silanones, the silicon analogs of ketones, are produced *via* rDA reactions. One attempt to prepare a suitable DA precursor for retrograde decomposition to a silanone met with unexpected results. The desired DA reaction between 2,2-dimethyl-1-oxa-2-silacyclohexa-3,5-diene (**251**) and perfluoro-2-butyne was complete in one day at room temperature. The observed product was *o*-bis(trifluoromethyl)benzene, as the initial adduct apparently underwent retrodiene decomposition to yield the intermediate dimethylsilanone (**252**) (equation 111). The occurrence of this retrodiene process at room temperature was not consistent with the analogous extrusions of silenes and disilenes that require elevated temperatures. However, the reaction sequence was substantiated by comparison with its carbon analog in which tetramethylpyran and dimethyl acetylenedicarboxylate react at room temperature to afford only acetone and the corresponding phthalate.[208] Stable adducts that extrude silanones are also known. Reactions of 2-silapyrans and maleic anhydride provide stable adducts, such as (**253**), that decompose upon thermolysis

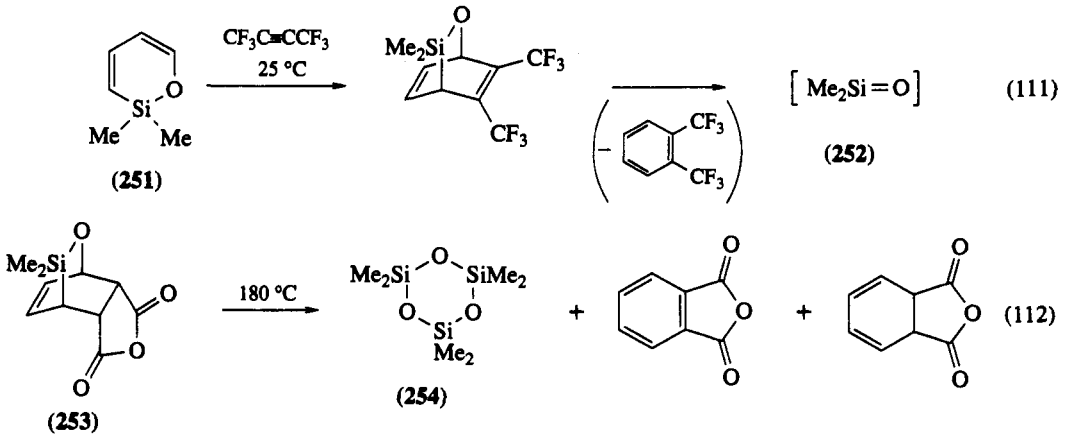


(246) (247) (109)



(110)

or photolysis to yield silanones. The existence of these reactive intermediates is based on the formation of cyclosiloxanes, for example (**254**), from the cyclic oligomerization of the silanone in the absence of a trapping agent. The product of silanone insertion is obtained when a suitable trap such as dimethoxydiphenylsilane is present.[208]

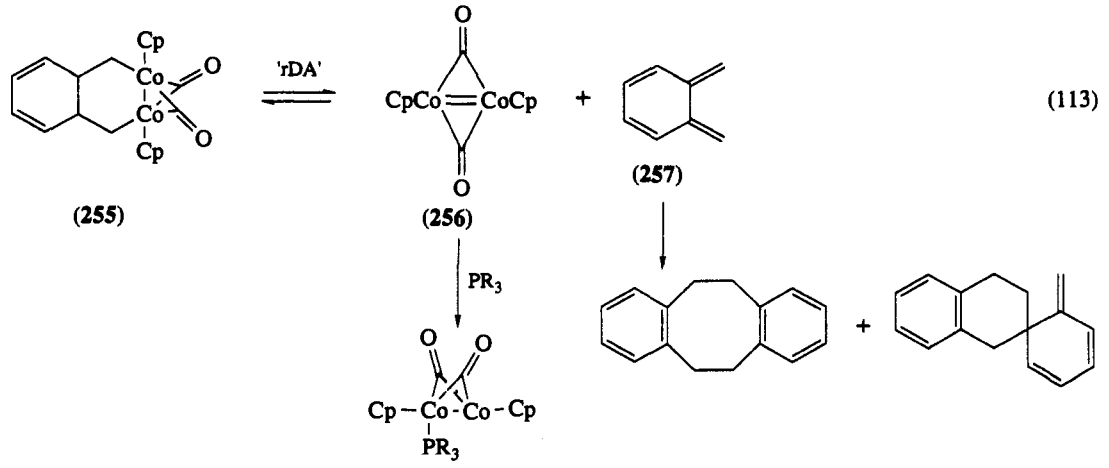


(111)

(112)

4.5.7.2 *o*-Xylylene *via* Retro-dimetalla-DA Reaction

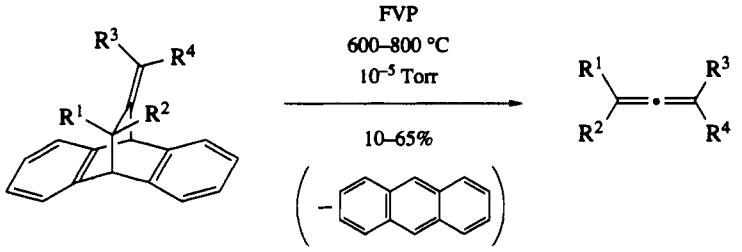
An interesting variation of the rDA reaction is the retro-dimetalla-Diels–Alder reaction that generates two reactive intermediates, *o*-xylylene (**257**) and the metal–metal double bonded dimer (**256**), *via* a dinuclear elimination. Performing this equilibrium reaction in the presence of reagents that react with (**256**), such as trialkylphosphines, yields the dinuclear monophosphine adducts. Consumption of (**256**) allows the *o*-xylylene to dimerize as shown in equation (113).[209]



(113)

4.5.7.3 Cumulenes

Cumulenes, generally regarded as difficult to prepare, can be obtained readily *via* rDA methods. Allenes, the most basic cumulenes, with a wide range of substituents on the allenic carbon, can be obtained by FVP of anthracenic DA adducts as shown in equation (114).[210] Butatriene (**258**), the next in the series of cumulenes, has been produced by FVP of a variety of adducts that includes 9,10-ethano-9,10-dihydroanthracene,[211] cyclohexyne[212] and fulvene, furan and benzene cycloadducts.[213] Pentatetraene (**260**), a compound that is stable enough to be purified by GLC at room temperature, has also been obtained by the FVP of vinylallene (**259**).[214]

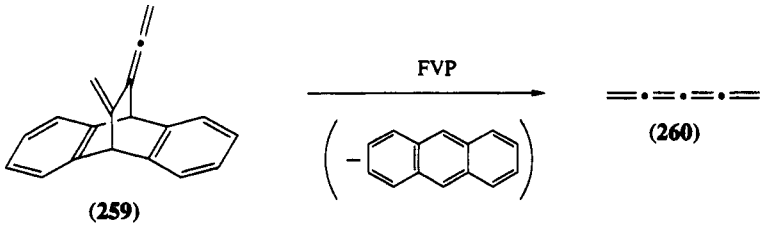


(114)

R^1 = H, Me; R^2 = H, Me, CHO; R^3 = H, Me, CN, CO_2R; R^4 = H, alkyl, CHO, CN, CO_2R, $OSiMe_3$, NH_2

$CH_2{=}{\bullet}{=}{\bullet}{=}CH_2$

(**258**)



(115)

(**259**)

(**260**)

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5.1
[4 + 3] Cycloadditions

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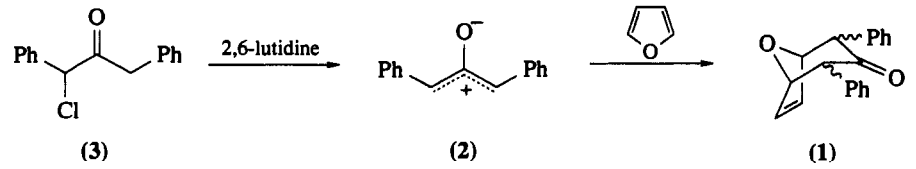
5.1.1 INTRODUCTION

Seven-membered carbocycles are an important class of organic compounds that are of practical and theoretical interest. They are more elusive and have been studied less in depth than their lower homologs, probably because of entropy reasons, ring strain, and synthetic difficulties. Before discovery of the [4 + 3] cycloaddition reaction, methods for preparing seven-membered carbocycles were limited to enlargement of six-membered rings and some cyclization reactions. However, [4 + 3] cycloadditions of reactive three-carbon species with dienes should prove to be the most convenient and straightforward method for the synthesis of a wide range of seven-membered rings. Recently, various routes to reactive three-carbon species have rapidly developed and therefore [4 + 3] cycloadditions using these species

have come to be widely investigated, although not yet to the level of [4π (4C) + 2π (2C)] cycloadditions. The latter processes constitute one of the most useful and successful processes in organic synthesis, leading to six-membered carbocycles.[1]

5.1.2 PREPARATION OF REACTIVE THREE-CARBON UNITS

In 1962, Fort first reported the preparation of an 8-oxabicyclo[3.2.1]oct-6-en-3-one derivative (**1**) by reaction of α-chlorodibenzyl ketone (**3**) with furan in the presence of 2,6-lutidine as a base.[2] The 2-oxyallyl unit (**2**) coupled with furan in this reaction (Scheme 1). Soon after, Cookson and his coworkers reported an improved method for the synthesis of (**1**).[3]



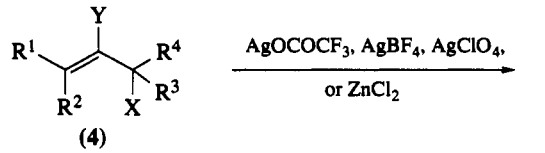
(3) (2) (1)

Scheme 1

The discovery of allyl cations (**2**) that serve as 2π components in [4π (4C) + 2π (3C)] cyclocoupling reactions provides considerable innovation for the elaboration of seven-membered ring carbocycles. The [4 + 3] cyclocoupling reaction of allyl cations with 1,3-dienes is an efficient and easy method for the stereoselective synthesis of seven-membered ring compounds. New methodology for generating allyl cation species continues to evolve and annulations using these species have opened easy access to a wide range of organic frameworks that have been utilized for preparing natural products, pharmacologically active compounds, and key intermediates for various useful organic molecules. These reactive species also undergo [3 + 2] cycloadditions across simple alkenic bonds, thereby giving rise to five-membered carbocycles. Mechanistic and synthetic aspects of the [4 + 3] and [3 + 2] cycloaddition reactions using allyl cations have been elegantly reviewed by Hoffmann,[4] Noyori[5] and Mann.[6] Recently, vinylcarbenes and 1,3-dipolarophiles consisting of three-carbon species have also been used as 2π components in [4 + 3] cycloaddition reactions.[7]

5.1.2.1 β-Heteroatom-substituted Allylic Cations

Much attention has been directed to the chemistry of β-heteroatom-substituted allylic cations (**5**), especially oxyallyl cations (**7**), from both synthetic and mechanistic viewpoints. One of the characteristic reactions of oxyallyls (**7**) is their [4 + 3] → 7 cycloadditions with conjugated dienes, which provide a unique and important route to seven-membered rings (Schemes 2 and 3).



(4) (5)

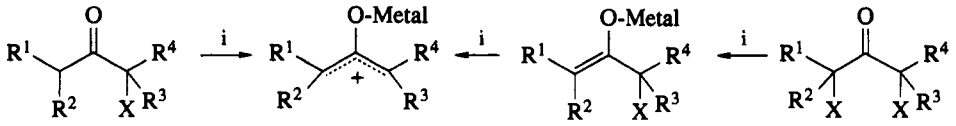
X = Cl, Br, OH, $OCOCF_3$,; Y = $OSiMe_3$, OR, NR_2, alkyl

	R^1	R^2	R^3	R^4
a:	H	H	H	H
b:	Me	Me	H	H
c:	H	H	Me	Me
d:	H	Me	Me	Me
e:	Me	Me	Me	Me
f:	H	$-(CH_2)_2-$		H
g:	H	$-(CH_2)_3-$		H

Scheme 2

5.1.2.1.1 α,α′-Dihalo ketones and reducing agents

One of the most useful routes to 2-oxyallyl cations (**7**) is the reaction of α,α′-dihalo ketones (**9**) with reducing agents (Scheme 3). Initially, halogenated metal enolates of type (**8**) are formed and oxyallyl cations (**7**) are then generated by subsequent elimination of the halide ion. Copper–sodium iodide in ace-



(6) (7) X = Cl, Br (8) (9)

i, $Fe_2(CO)_9$ and related iron carbonyl species, Zn–Cu couple (Me_3SiCl), Zn–Ag couple, $Zn/(EtO)_3B$, or Cu/NaI

	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a:	Me	H	H	H	**j:**	Me	Me	Ph	H
b:	Pr^i	H	H	H	**k:**	Me	Me	Me	Me
c:	Pr^i	H	H	Pr^i	**l:**	H	$-(CH_2)_2-$		H
d:	Ph	H	H	H	**m:**	H	$-(CH_2)_3-$		H
e:	Ph	H	Me	H	**n:**	H	Br	H	H
f:	H	Me	Me	H	**o:**	H	Br	Br	H
g:	H	Ph	Ph	H	**p:**	H	Cl	Cl	H
h:	Me	Me	H	H	**q:**	I	H	Me	Me
i:	Me	Me	Me	H					

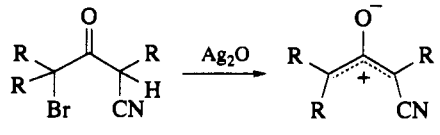
Scheme 3

tonitrile,[8] zinc dust–triethyl borate in THF,[9] zinc–copper couple in DME or acetone,[10] diiron enneacarbonyl [$Fe_2(CO)_9$] in benzene,[11] and sodium iodide in acetone or acetonitrile[3] have seen use. In addition, copper–isonitrile complexes,[12] Grignard reagents,[13] organocuprates,[13] and dissolved electrons[14] are also capable of promoting the reaction with open-chain dibromides. The reaction of (**9**) with zinc–copper couple has been accelerated by the addition of chlorotrimethylsilane. Moreover, the yield of cycloadduct dramatically increases, presumably due to formation of an α-haloalkyl-substituted silyl enol ether (**8**; M = $SiMe_3$) followed by a cation of type (**7**), which is more electrophilic than (**8**; M = ZnBr).[15] A summary of the main features of various methods for preparing 2-oxyallyl cations is given in Table 1.

5.1.2.1.2 α-Halo ketones and base

After Fort's and Cookson's reports, a variety of combinations between α-halo ketones (**6**) and bases has evolved for the generation of 2-oxyallyl cations (**7**). Simple α-bromobenzyl and α-bromoalkyl ketones can be converted to the corresponding oxyallyl cations, which are trapped with 1,3-diene derivatives. Reactions using triethylamine proceed smoothly in methanol and 2,2,2-trifluoroethanol.[16] The dehalogenation can also be efficiently promoted by silver tetrafluoroborate and triethylamine in acetonitrile, or in furan which serves as both solvent and trapping agent.[17] Readily available, inexpensive lithium perchlorate–triethylamine in diethyl ether is also effective for reaction with α-chloro and α-bromo ketones, owing to the formation of insoluble triethylammonium halide.[18] The base-induced reaction of α-halo ketones turns out to generate weakly electrophilic 2-oxyallyl intermediates (**7**), which react specifically with furan and other nucleophilic dienes.[19]

The more acidic γ-bromo-β-oxonitriles (**10**) have been easily dehydrohalogenated with Ag_2O (Scheme 4).[20]



(10) (11)

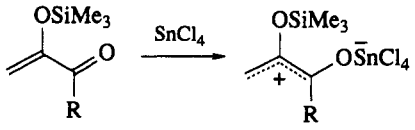
Scheme 4

Table 1 Preparation of Reactive Three-carbon Units

Section	*Stating material*	*Reagent*	*Solvent*	*Reaction time*	*Reaction temp.*	*Ref.*
5.1.2.1.1	α,α′-Dihalo ketone	Cu, NaI	MeCN	4–24 h	r.t. → 60 °C	3, 8b, 15
		$Zn/(EtO)_3B$	THF	24 h	r.t.	9
		Zn–Cu	DME or acetone		–10 °C → r.t.	15, 53
		Zn–Ag	THF	4–12 h	r.t.	11b
		$Fe_2(CO)_9$ or $Fe(CO)_5$	Benzene	2–48 h	r.t.	11a, 49
		Cu, Bu^tNC	Benzene			12
		Grignard or cuprate reagent				13
		Electron reduction				14
5.1.2.1.2	α-Bromo ketone	$AgBF_4/Et_3N$	CH_2Cl_2 or MeCN	5–6 h	r.t.	17
	γ-Bromo-β-oxonitrile	Ag_2O	CH_2Cl_2 or ether	3–64 h	r.t.	20
	α-Chloro and α-bromo ketone	$LiClO_4/Et_3N$	Ether	2 h–117 days	r.t	18
		Et_3N	$MeOH/CF_3CH_2OH$	1 h–29 days	–20 °C → r.t.	16
		NaH	Ether			19
5.1.2.1.3	Siloxyallyl chloride	$LiClO_4$	MeOH			21
		$AgClO_4$	$MeNO_2$	1 h	0–20 °C	21
		$AgClO_4$	THF/ether	1 h	0 °C	21
	Siloxyallyl bromide	$ZnCl_2$	CH_2Cl_2	50 min	–78 °C → r.t.	22
	Siloxyvinyl aldehyde	$SnCl_4$	CH_2Cl_2	5 h	–78 °C	23a
	Siloxyvinyl ketone	$TiCl_4$	CH_2Cl_2	1 h	–78 °C	23b
	Alkoxyallyl bromide	CF_3COOAg or $ZnCl_2$	Benzene	10 hr	r.t.	24, 25
	Aminoallyl chloride	$AgBF_4$	CH_2Cl_2		–60 °C	26
5.1.2.1.4	Cyclopropanone allenoxide		CH_2Cl_2	5–6 days	r.t.	27, 28
5.1.2.2.1	Allyl iodide	CCl_3COOAg	Liquid SO_2	3 h	–60 °C → r.t.	31
			CH_2Cl_2	1.5 h	–50 °C → r.t.	32
		CF_3COOAg	Isopentene	6 h	–78 °C	32
5.1.2.2.2	Allyl alcohol	H_2O–TsOH	Pentane	24 h	0 °C → r.t.	34
		$(CF_3CO)_2O$	$EtNPr_2$			36
		$PhNHMe/TiCl_4$	CH_2Cl_2		–20 °C	37

5.1.2.1.3 β-Heteroatom-substituted allylic halides and silver salts or Lewis acids

2-(Trimethylsiloxy)allyl cations (**5**; Y = $OSiMe_3$) are obtained by the reaction of 2-(trimethylsiloxy)allyl chlorides (**4**; X = Cl, Y = $OSiMe_3$) with silver perchlorate in nitromethane (Scheme 2).[21] These intermediates are also obtained with the aid of a Lewis acid.[22] It has been reported that 2-siloxyacrolein (**12a**; R = H), but not the less electrophilic (**12b**; R = Me), when activated by an equimolar amount of $SnCl_4$ serves as a 1-hydroxy-2-oxidoallyl synthon (**13**) (Scheme 5).[23]



(**12a**) R = H (**13a**) R = H
(**12b**) R = Me (**13b**) R = Me

Scheme 5

2-Methoxyallyl cation (**5a**; Y = OMe), derived from 2-methoxyallyl bromide (**4a**; X = Br, Y = OMe) and silver trifluoroacetate in the presence of sodium carbonate, reacts with benzene, toluene, *p*-xylene or mesitylene.[24] 2-Ethoxyallyl alcohol (**4c**; X = OH, Y = OEt) in the presence of trifluoroacetic anhydride generates the 2-ethoxyallyl cation (**5c**; Y = OEt).[25] 2-Ethoxyallyl alcohol (**4c**) is probably more advantageous than the corresponding 2-methoxyallylic species (**4a**; Y = OMe) because dealkylation of the intermediary oxonium ion seems to be less facile, and the ethyl enol ether is more nucleophilic than the methyl enol ether. Treatment of cyclic α-chloroenamines (**4f**; X = Cl, Y = morpholino) and (**4g**; X = Cl, Y = pyrrolidino) with $AgClO_4$ or $AgBF_4$ in THF or dichloromethane generates 2-aminoallyl cations (**5f**; Y = morpholino) and (**5g**; Y = pyrrolidino).[26]

5.1.2.1.4 Cyclopropanones and related compounds

Cyclopropanones act as three-carbon sources in [4 + 3] cycloadditions. However, these small-ring compounds are impractical for preparative scale experiments, because they are generally inaccessible and also must be handled with special precautions, in contrast to other oxyallyl species. One of the early descriptions of the synthesis of cyclopropanones appeared in 1932.[27] Nevertheless, the development of the chemistry of cyclopropanones proceeded at quite a slow pace until the late 1960s when Turro reported their utilization in [4 + 3] cycloaddition reactions.[28] 2,2-Dimethylcyclopropanone (**14**) adds to furan, cyclopentadiene, 6,6-dimethylfulvene and the relatively nucleophilic *N*-methylpyrrole to give the corresponding cycloproducts, but fails to react with anthracene and 1,3-butadiene. Parent cyclopropanone cannot be used.

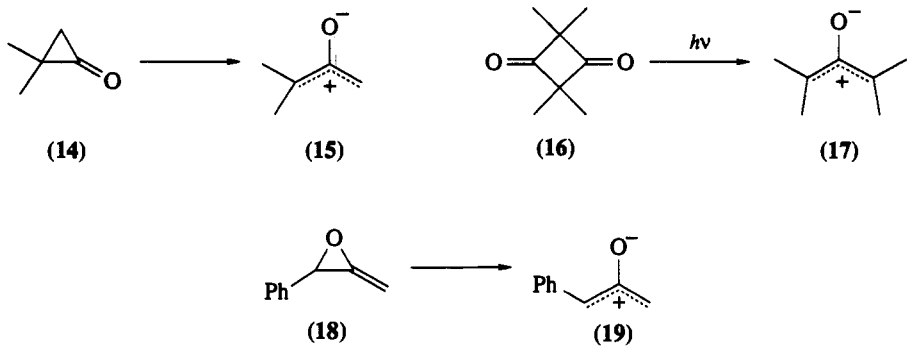
Irradiation of tetramethylcyclobutanedione (**16**) in furan gives an 8-oxabicyclo[3.2.1]oct-6-en-3-one derivative *via* oxyallyl cation (**17**).[29] This reaction is the first example of the cycloaddition of cyclopropanones. Although the syntheses of a few seven-membered ring compounds have been subsequently carried out by means of this photoreaction, interest in cyclopropanone chemistry has been directed to structure and reactivity relationships, but not to organic synthesis.[30]

Allenoxide (**18**) also reacts with 1,3-dienes to give seven-membered ring adducts (**19**) (Scheme 6).[31]

5.1.2.2 Other Allylic Cations

5.1.2.2.1 Allylic halides and Lewis acids or silver salts

Treatment of β-methallyl iodide (**4a**; X = I, Y = Me) with a silver salt gives a methallyl cation (**5a**; Y = Me) which reacts with 1,3-dienes such as 1,3-butadiene, 1,3-cyclopentadiene or 1,3-cyclohexadiene to give the corresponding seven-membered ring compounds (**20**) and (**21**) and their isomers.[32] However, cycloaddition of the parent allyl cation (**5a**) with 1,3-dienes generally produces satisfactory results. In fact, (**5a**; Y = H) derived from allyl iodide (**4a**; X = I, Y = H) and silver trifluoroacetate reacts with 1,3-cyclopentadiene to yield bicyclo[3.2.1]octa-2,6-diene (**21**; Y = H, *n* = 1) though in poor yield, along with

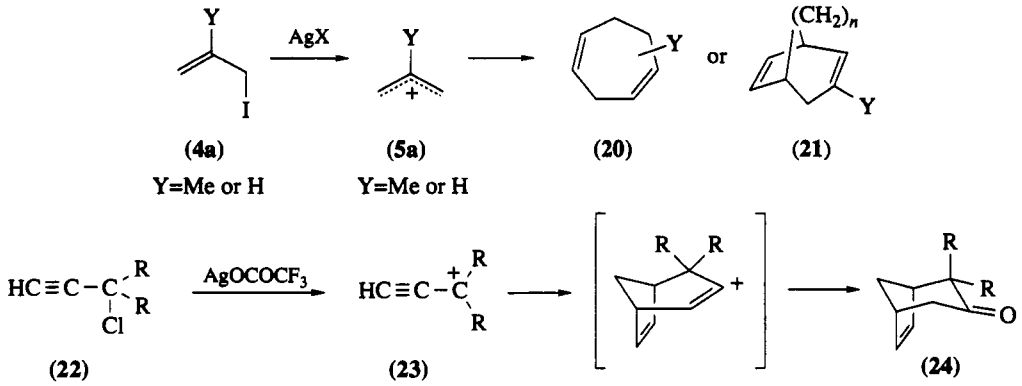


(14) (15) (16) (17)

(18) (19)

Scheme 6

2-propenyl trifluoroacetate as a major product.[32b] Similarly, propargyl cation (**23**) also gives a seven-membered ring product (**24**) (Scheme 7).[33]



(**4a**) (**5a**) (**20**) (**21**)

Y=Me or H Y=Me or H

(**22**) (**23**) (**24**)

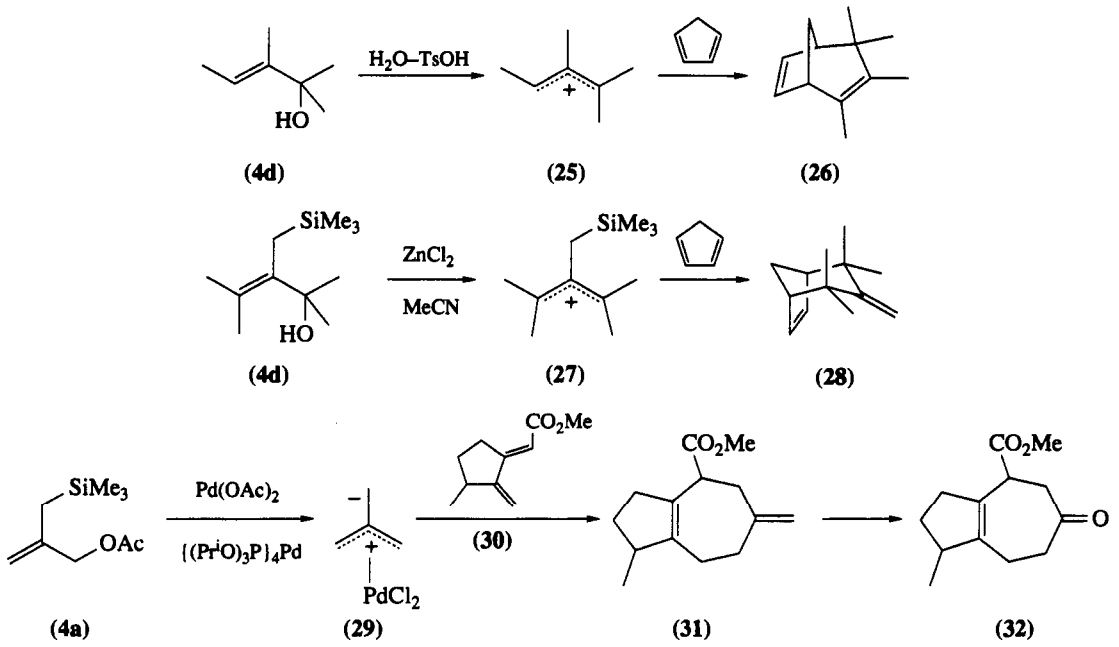
Scheme 7

5.1.2.2.2 Activation of allylic alcohols and allylsilanes

Allyl alcohol with three terminal methyl groups, such as (**4c**; X = OH, Y = Me), reacts with cyclopentadiene under two-phase conditions (in an aqueous *p*-toluenesulfonic acid/pentane solution) to give a seven-membered ring product (**26**) (Scheme 8).[34]

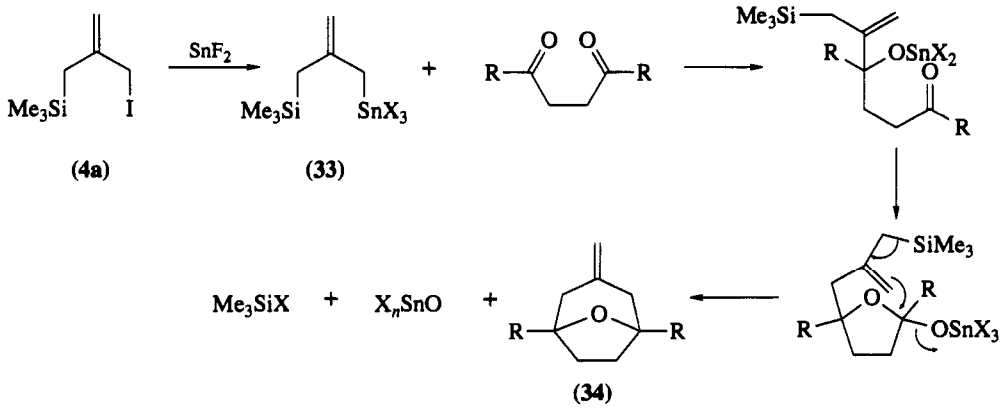
Allylsilanes are important synthetic reagents for the introduction of allyl groups and act as otherwise inaccessible synthetic equivalents.[35] Although allylsilanes are relatively stable and isolable, they react with a variety of electrophiles in the presence of a Lewis acid. When 2-(trimethylsilylmethyl)allyl alcohol or its trifluoroacetate is treated with a Lewis acid, the 2-(trimethylsilylmethyl)allyl cation that can participate in [4 + 3] cyclization is formed.[36] The reaction proceeds in a symmetry-allowed suprafacial manner. For example, when a highly substituted 1,3-bifunctional silyl alcohol (**4d**; X = OH, Y = CH_2SiMe_3) is exposed to a Lewis acid, the intermediate 2-(trimethylsilylmethyl)allyl cation (**27**) reacts with cyclopentadiene and furan to give the corresponding cycloadduct (**28**), though the yields are modest (Scheme 8).[36]

Recently, Trost reported on [4 + 3] cycloadditions of trimethylenemethane fragments by palladium-catalyzed reaction of 2-(trimethylsilylmethyl)allyl acetate (**4a**; X = OAc, Y = CH_2SiMe_3) and related compounds with electron-deficient alkenes. An exciting approach to methylenecycloheptenes (**30**) is realized.[37] These interesting reagents have been elegantly reviewed by Trost.[38] The reaction of trimethylenemethane-palladium intermediate (**29**) with dimethyl (*E,E*)-muconate gives as cyclized products a 1:1 mixture of the five- and seven-membered carbocycles. Treatment of exocyclic diene (**30**) with (**29**) in the presence of a Pd^0 catalyst leads to perhydroazulenes (**31**) in good yields. Best results are obtained by using *N,N'*-benzylideneethylenediamine as a ligand. The *exo* methylene group of the adduct is chemoselectively oxidized to a ketone (**32**) by the portion-wise addition of benzyltriethylammonium permanganate. The ketone (**32**) corresponds to the [4 + 3] cycloadduct of the 2-oxyallyl zwitterion.[37]



Scheme 8

Molander *et al.* have reported on the dianionic [4 + 3] annulation reaction of 1,4-dicarbonyl compounds with 3-iodo-2-[(trimethylsilyl)methyl]propene (**4a**; X = I, Y = CH_2SiMe_3) promoted by tin(II) fluoride.[39] The extraordinary efficiency of this novel stereoselective seven-membered ring forming process, coupled with the simplicity of the procedure, promises to provide an expedient route to innumerable cyclic organic molecules (Scheme 9).

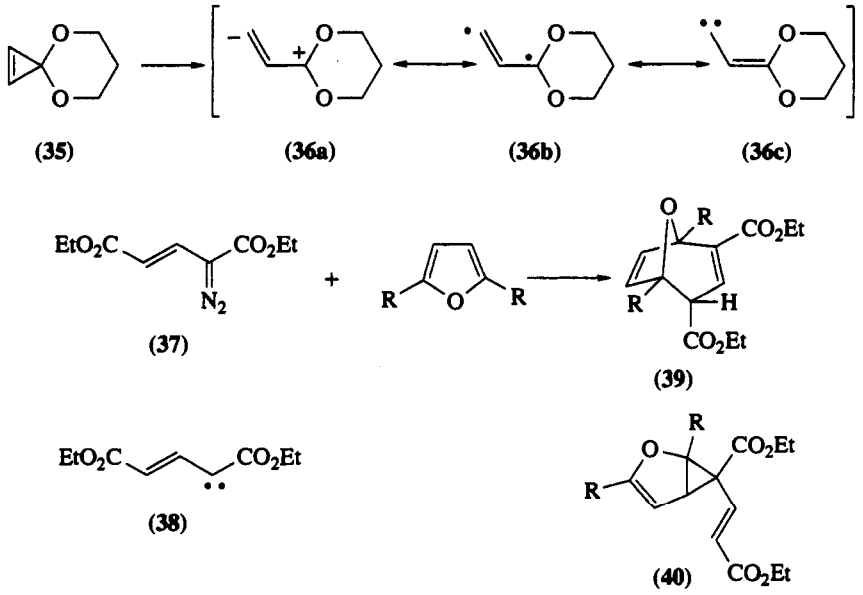


Scheme 9

5.1.2.3 Singlet Vinylcarbenes and Vinylcarbenoids

Cyclopropenone ketals (**35**) on thermal reaction give π-delocalized singlet vinylcarbenes (**36c**), which serve as three-carbon 1,1-/1,3-dipoles (**36a**) lacking octet stabilization that cycloadd to α-pyrones effectively.[7]

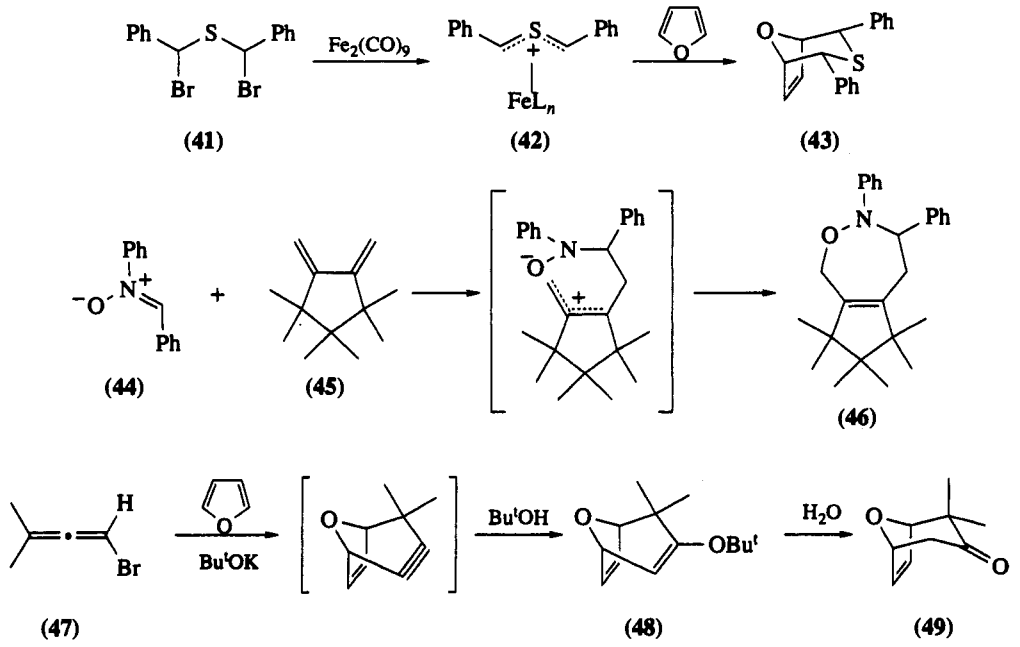
Davies *et al.* have reported that the formal [4 + 3] cycloaddition reaction of vinylcarbenoids (**38**) with furan to give (**39**) *via* (**40**) proceeds satisfactorily (Scheme 10).[40]



Scheme 10

5.1.2.4 Miscellaneous Methods

The dehydrogenation of bis(α-bromobenzyl) sulfide (**41**) with $Fe_2(CO)_9$ in the presence of furan affords (**43**). The iron-stabilized sulfur ylide (**42**) has been proposed as intermediate.[41] Reaction of *C,N*-diphenylnitrone (**44**) with 1,2-bis(methylene)-3,3,4,4,5,5-hexamethylcyclopentane (**45**) in benzene at 80 °C gives a [4 + 3] cycloadduct (**46**; 18%), along with some other products.[42] Landor *et al.* have shown that the dehydrobromination of allenyl bromide (**47**) in the presence of furan affords bicyclic ketone (**49**) in 9% yield.[43] Apparently, a strained alkyne intermediate reacts with *t*-butyl alcohol to afford an enol ether (**48**), which is then converted to (**49**) (Scheme 11).

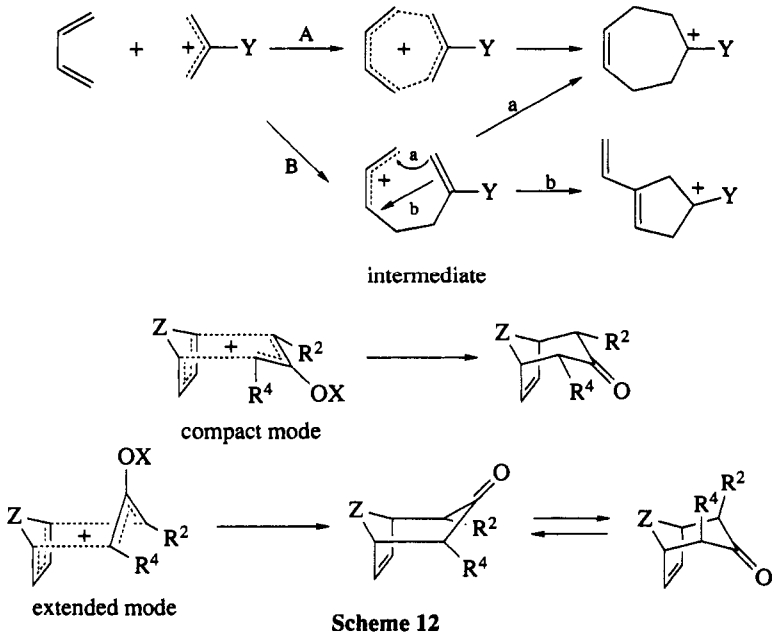


Scheme 11

5.1.3 REACTIONS WITH DIENES

The β-heteroatom-substituted allylic cations shown in Section 5.1.2 serve as active three-carbon units toward 1,3-dienes to afford the corresponding seven-membered ring compounds selectively, though five-membered rings are obtained in some cases.[21,44]

[4 + 3] Annulations of allylic cation species with diene moieties are formally classified according to a mechanistic descriptor (Class A and B), where Class A is a concerted mechanism and Class B is the stepwise one as shown in Scheme 12.

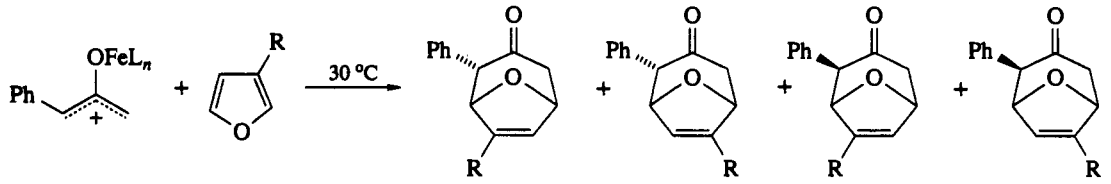


Scheme 12

The precise mechanism of [4 + 3] cycloadditions involving allyl cations depends upon the nucleophilicity of the dienes, the electrophilicity of the allyl cations, and the electronic property of the substituent Y on the allylic moiety. For example, the cycloaddition of 2-oxyallyliron(II) cation species (**7**), generated from a dibromo ketone and iron carbonyl, with 1,3-dienes is classified as a [4π (4C) + 2π (3C)] process.[44] This cationic cycloaddition, which is symmetry allowed, proceeds in a concerted manner *via* the cyclic transition state, and the regioselectivity should be controlled by frontier molecular orbitals (FMOs) of the cycloaddends. Indeed, the experimental findings by Noyori *et al.* are not consistent with the stepwise mechanism *via* zwitterions but agree with the concerted process that occur *via* a cyclic transition state (Class A).[45] Thus the reaction of 1-phenyl-2-oxyallyl (**7d**) with 3-methylfuran generates a mixture of (**50**)–(**53**), in which the ratio of both (**50a**)/(**51a**) and (**52a**)/(**53a**) is 56:44. Similarly, the addition of (**7d**) and ethyl 3-furoate leads to a 55:45 mixture of (**50b**)/(**51b**). The observed regioselectivity is best accounted for by considering the primary interaction between the FMOs of each cycloaddend, namely the LUMO of the electron-accepting oxyallyl and the HOMO of the electron-donating furan substrates. Thus the transition state formed through dominant interaction between the termini with the larger MO coefficient (primary MO interaction) results in the production of the major isomer. Interesting is the behavior displayed by 2-furoates that have comparable MO coefficients at the two reaction sites, C-2 and C-5. The trend toward the production of the major regioisomer (**54**) is far greater than that expected from the degree of MO inclination. This bias is presumably due to the presence of secondary MO interactions between the substituents of each cycloaddend in the transition state. There exists only a narrow energy gap between the FMOs of the cationic oxyallyl and furans. Therefore the two cycloaddends can achieve pericyclic interaction even at a long distance. Consequently, such secondary MO interactions become much more significant than in the ordinary nonpolar [4π (4C) + 2π (C2)] process (Scheme 13).[1]

The unsymmetrically substituted oxyallyl intermediates (**7i**) and (**7j**), generated from the corresponding dibromo ketones, are trapped by styrene to give a regioisomeric mixture of 3-phenylcyclopentanones (**56a,b**) and (**57a,b**), respectively.[46] The results are summarized in Scheme 14.

Apparently the preferred orientation in the cationic [3 + 2] cycloaddition is the one that realizes the maximum stabilization within the zwitterionic intermediates (Class B, route b). The same trend has been observed in the reaction that employs enamines.[47]



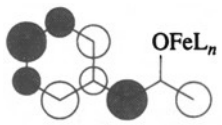
(7d)

R = Me (50a)
R = CO_2Et (50b)

(51a)
(51b)

(52a)
(52b)

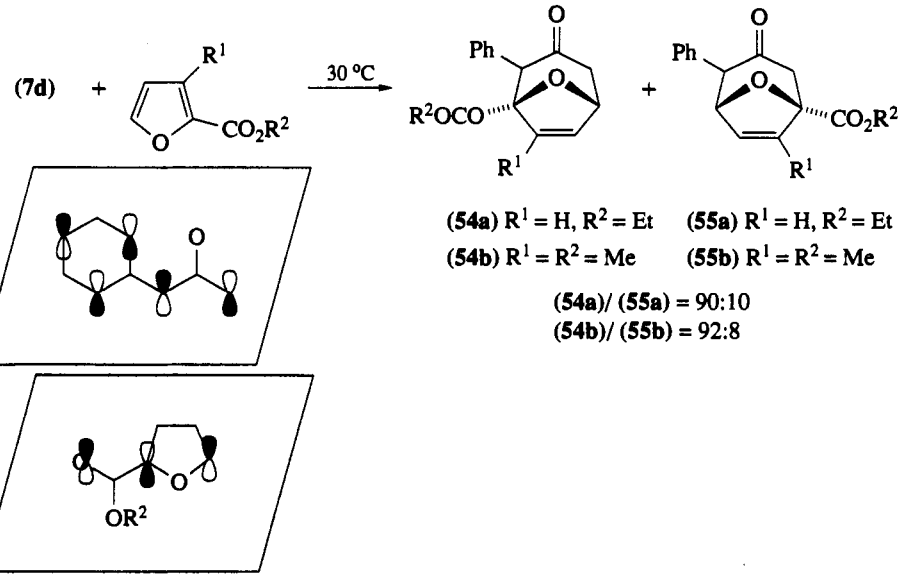
(53a)
(53b)



LUMO of (7d)

HOMO of 3-methylfuran

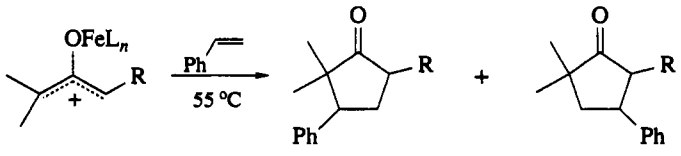
HOMO of ethyl 3-furoate



(54a) R^1 = H, R^2 = Et (55a) R^1 = H, R^2 = Et
(54b) R^1 = R^2 = Me (55b) R^1 = R^2 = Me

(54a)/ (55a) = 90:10
(54b)/ (55b) = 92:8

Scheme 13



(7i) R = Me
(7j) R = Ph

(56a) R = Me
(56b) R = Ph

(57a) R = Me
(57b) R = Ph

(56a)/ (57a) = 94:6
(56b)/(57b) = 0:100

Scheme 14

Since mechanistic considerations in these areas have been discussed in detail by Hoffmann,[4] a variety of regio- and stereo-selective [4 + 3] cycloaddition and cyclization reactions are described in this section.

5.1.3.1 Open-chain 1,3-Dienes

Oxyallyl cations give cycloadducts (**58**) in the presence of a variety of open-chain 1,3-dienes in generally good yields, provided that the diene exists primarily in an *s-cis* conformation. Noyori and his coworkers found that the reaction of α,α′-dibromo ketones and $Fe_2(CO)_9$ in the presence of 1,3-dienes afforded the corresponding 4-cycloheptenones in moderate to good yield.[47] This simple one-step procedure reveals wide applicability for the regioselective synthesis of seven-membered ketones in preparative scale experiments. Although reactions of 1,3-dienes with α,α′-dibromoacetone fail to give cycloheptenone adducts, unlike dibromides that possess long alkyl side chains, condensation with tetrabromoacetone proceeds smoothly.[48] Thus the iron carbonyl-promoted reaction of polybromoacetone and 1,3-dienes, followed by zinc–copper reduction, formally corresponds to [4 + 3] cyclocoupling of dibromoacetone to dienes.[48] This modification has wide applicability and can also be used for reactions involving other methyl ketone polybromides. Thus 2-oxyallyls with various kinds of substitution patterns can be obtained in a formal sense. Additionally, tetrasubstituted dibromo ketones and disubstituted dibromo ketones such as 2,4-dibromopentan-3-one (**9f**) and 3,5-dibromo-2,6-dimethylheptan-4-one (**9c**) can be employed. A variety of 1,3-dienes, including 1,3-butadiene, isoprene and 2,3-dimethyl-1,3-butadiene, can serve as open-chain 1,3-dienes.

Since the present [4 + 3] → 7 reaction can be regarded as a concerted [4π + 2π] cycloaddition, it is expected that dienes having high equilibrium concentrations of the *s-cis* conformer should serve as efficient acceptors of the reactive three-carbon unit. As expected, 1,2-dimethylenecyclohexane is recognized to be one of the most effective dienes.[22,48] It should be further noted that the use of diene–iron carbonyl complexes in place of the free dienes results in remarkable increases in the yields of cycloadducts, presumably owing to fixing the *s-cis* conformation within the diene.[48]

Compound (**4c**; X = Cl, Y = $OSiMe_3$) reacted with isoprene to give a mixture of karahanaenone (**59**) and its regioisomer (**60**), irrespective of the reaction conditions.[21] The regioselectivity is slightly higher in THF-ether or benzene than in nitromethane. 2-Siloxyallyl cation (**5c**), generated from 2-siloxyallyl bromide (**4c**; X = Br, Y = $OSiMe_3$) with the aid of zinc chloride in dichloromethane, adds to isoprene regioselectively to give karahanaenone (**59**) and its regioisomer (**60**) in a ratio of *ca.* 2:1.[22] With *p*-methylstyrene the aromatic sesquiterpene α-cuparenone is obtained. These results strongly suggest that the reaction proceeds in a stepwise manner in rather nonpolar solvent systems. These two monoterpenoids may also be obtained from the appropriate α,α′-dihalo ketone and zinc–copper[49] or zinc dust–triethyl borate.[9]

Compound (**13a**) also reacts with butadiene in the presence of $SnCl_4$ to give 2-hydroxy-4-cycloheptenone (**61**) directly (Scheme 15).[23]

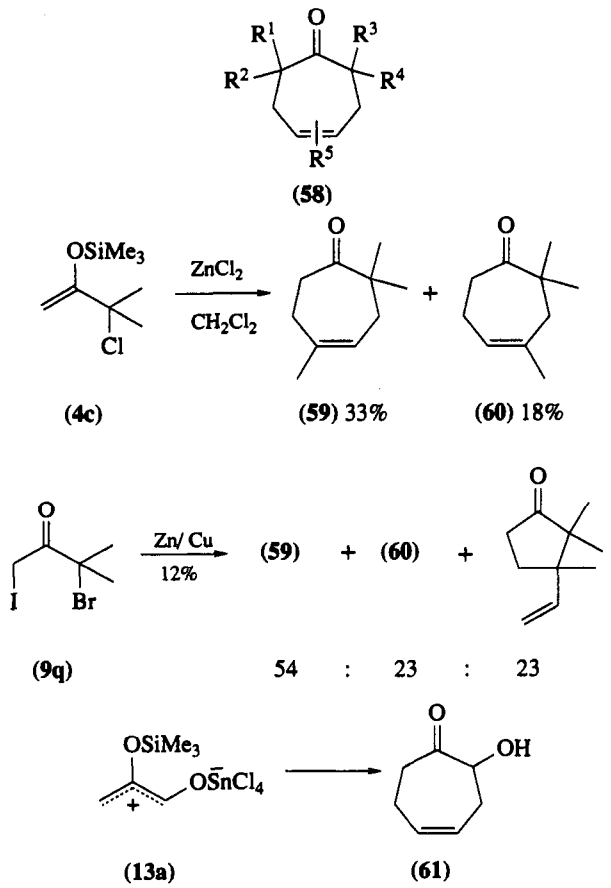
5.1.3.2 Cyclic 1,3-Dienes

5.1.3.2.1 Cyclopentadienes and related compounds

Cyclopentadiene gives rise to bicyclo[3.2.1]oct-6-en-3-ones (**62**) upon reaction with 2-oxyallyl cations (**7**) in generally high yields. The adducts are important precursors to natural products, as discussed in a later section. The 2,4-disubstituted products (**64a,b**), obtained stereoselectively *via* the extended and compact mode, respectively, are usually a mixture of two *cis* isomers except for the diphenyl adduct.[3] A similar conformational change can be seen for cycloadducts involving oxyallyl cation (**7f**) from 2,4-dibromopentan-3-one (**9f**; X = Br) and cyclohexa-1,3-diene. A tricyclic ketone (**63**) is obtained by a reaction using 2,5-dibromocyclopentanone (**91**; X = Br).[50] Tri- and tetra-bromo ketones (**9n**) and (**9o**) also react with cyclopentadiene with the assistance of $Fe(CO)_5$ in benzene or THF–benzene.[48a,e,51] The extra bromine atoms in the resulting cycloadducts are quantitatively removed by treatment with zinc–copper couple in ammonium chloride-saturated methanol.[48,52] In this case, less satisfactory results are obtained with $Fe_2(CO)_9$ or zinc–copper couple–triethyl borate. Compound (**4c**) also reacts with 1,3-cyclopentadiene to give a cyclized product (**66**), which is the key intermediate for the synthesis of camphenic acid (Scheme 16). Iron carbonyl-promoted reactions of α,α′-dibromo ketone (**9**) with various substrates, including alkenes, enamines and 1,3-dienes have been reviewed in detail by Noyori.[5]

Hoffman *et al.* have reported that reaction of the 2-methylallyl cation with cyclopentadiene affords seven-membered ring products.[32]

Cycloadditions of cyclopentadienones (**67a–d**) with (**9f**) and (**9k**) in the presence of $Fe_2(CO)_9$ in dry benzene has given the corresponding [4 + 3] cycloadducts (**68a–d**) and (**69a–d**) in moderate yields.[53]

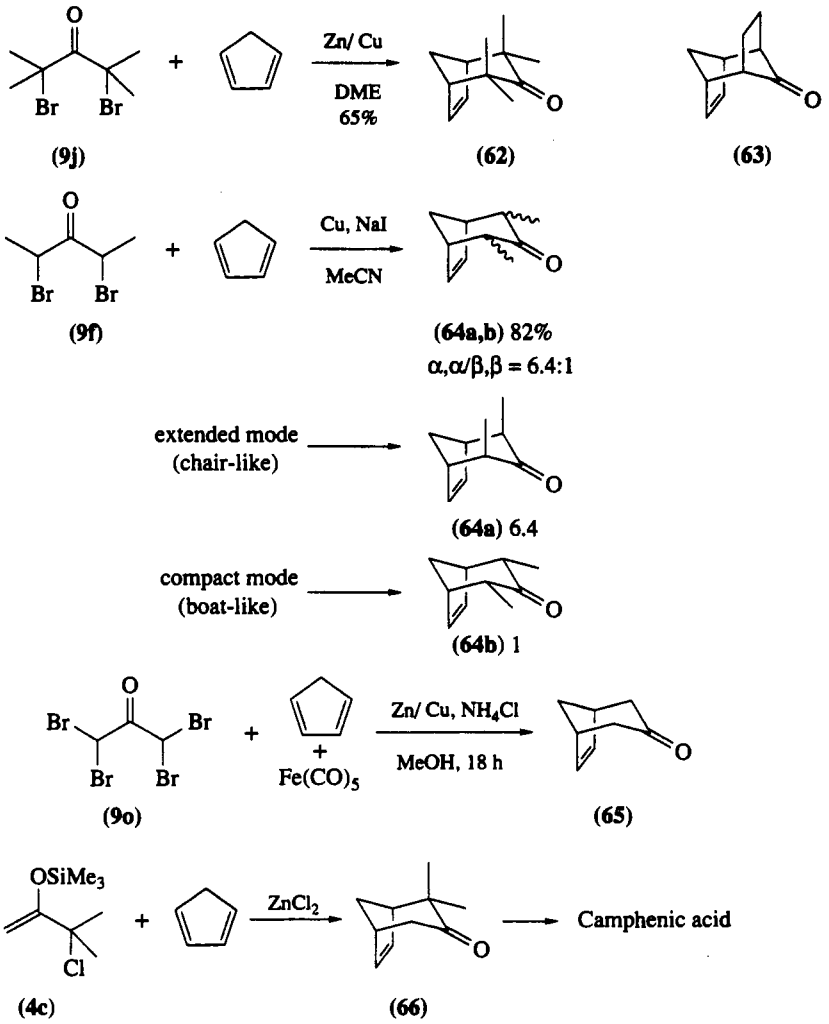


Scheme 15

However, a similar cycloaddition reaction of (**9f**) with tetraphenylcyclopentadienone (**67e**) did not take place even under more drastic conditions, presumably owing to the steric hindrance of the phenyl groups at the 2,5-positions in the cyclopentadienone moiety. Adducts (**68**) and (**69**) probably arise *via* a half-boat conformation.[53] The rate constants of these reactions are second order and reveal low sensitivity to the ionizing power of the reaction medium, suggesting that a concerted mechanism may be involved. Fulvenes also enter into cyclocoupling with dibromo ketones (**9f**) aided by copper–sodium iodide in acetonitrile,[52] zinc–copper couple in DME,[8b] or sodium iodide in acetonitrile,[52] giving 8-alkylidenebicyclo[3.2.1]oct-6-en-3-ones (**70**) (Scheme 17). Reactions with 6,6-dialkylfulvenes generally give good results, though hetero substituents at the C-6 position depress the yields. 6-(Dimethylamino)fulvene acts as a 6π component, giving a different type of cyclic adduct (**71**) in the presence of $Fe_2(CO)_9$.[53]

5.1.3.2.2 Cyclohexadiene and other cyclic dienes

Diels–Alder reactions of 2-pyrone with various dienophiles are well known to give the corresponding [4 + 2] cycloadducts in good yields.[1,54] Although the reaction of allyl cations with 2-pyrones has not, to our knowledge, been reported, Boger *et al.* have recently described the reaction of delocalized singlet vinylcarbenes with 2-pyrones to give [4 + 3] cycloaddition products.[7] Vinylcarbene species (**36**) acts as a 2π component in [4π (4C) + 2π (3C)] cycloadditions with selected dienes, suitable for the preparation of functionalized cycloheptadienes that are capable of further elaboration to tropones (**73**).[7b] This reaction has been applied to the formal total synthesis of colchicine (**74**) (Scheme 18).



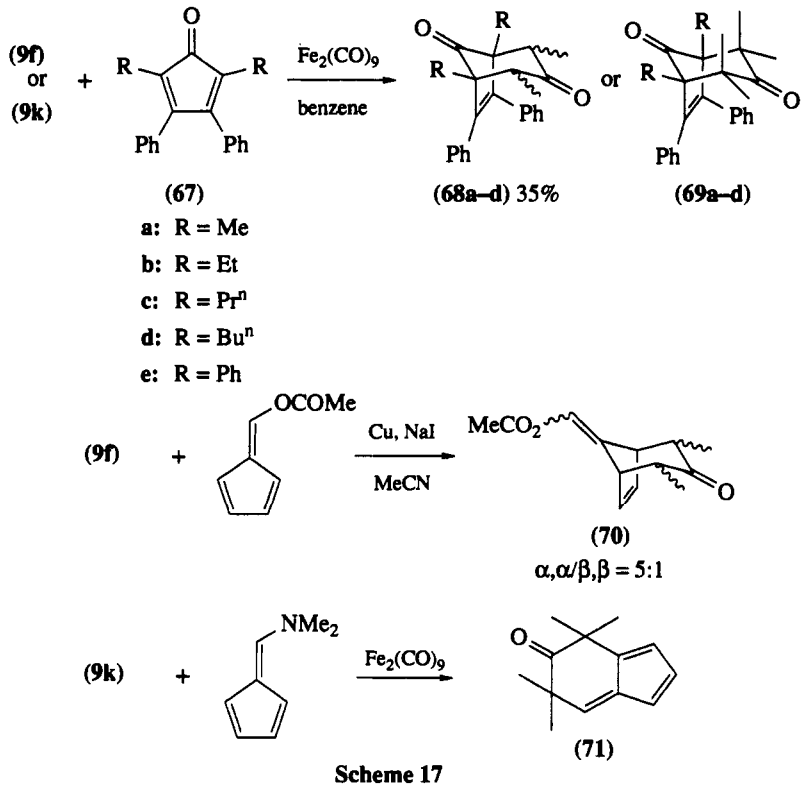
Scheme 16

5.1.3.3 Heterocycles

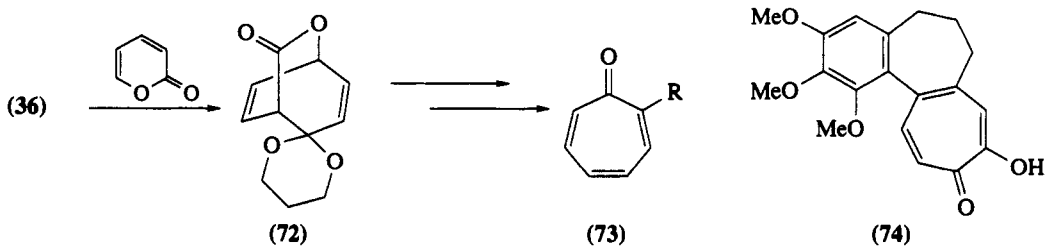
5.1.3.3.1 Furans

Cycloaddition reactions of allylic cations with furans (**76**) have been extensively studied for the preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**75**), which have served widely as starting materials for the synthesis of a number of natural products and their congeners such as thromboxane A_2[55] and B_2[56] analogues, *C*-nucleosides,[57] muscarine analogues,[58] pyrrolizidine alkaloids,[59] and troponoids,[49e,60] as well as theoretically interesting molecules (Scheme 19).[60a,b,61]

For the cyclocouplings of open-chain dibromo or polybromo ketones and cyclic bromo ketones with furans, iron carbonyls and zinc–copper couple are the most widely used reducing agents to afford the corresponding adducts, generally in fair to high yields and significantly high stereoselectivity. Thus (**75**) can be prepared by reductive cyclocoupling of dibromo or polybromo ketones with furan or its alkyl, alkoxycarbonyl or halogeno derivatives. For example, the stereochemical outcome in the reaction of (**9f**) with furan was 48:10:0 for the α,α/β,β/α,β-isomers of (**75d**).[62] Cyclic dibromides undergo somewhat erratic transformation accompanied by α-substitution reactions to give 2-substituted furans. Reactions using α,α′-dibromomethyl alkyl ketones are generally efficient. When cyclocoupling reactions of 1,3-dibromo-1-phenylpropan-2-one (**9d**; X = Br) with substituted furans are promoted by $Fe_2(CO)_9$ and zinc–copper couple, regioisomeric mixtures of [4 + 3] adducts are obtained (Scheme 19).[5,46,63] The



Scheme 17

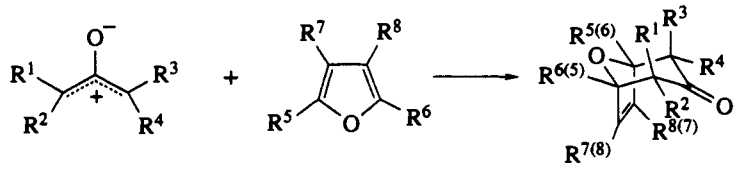


Scheme 18

regioselectivity, which is moderately good, is controlled by the FMOs of the intermediary oxyallyl species (LUMOs) and furan (HOMOs) (see Section 5.1.3).[45]

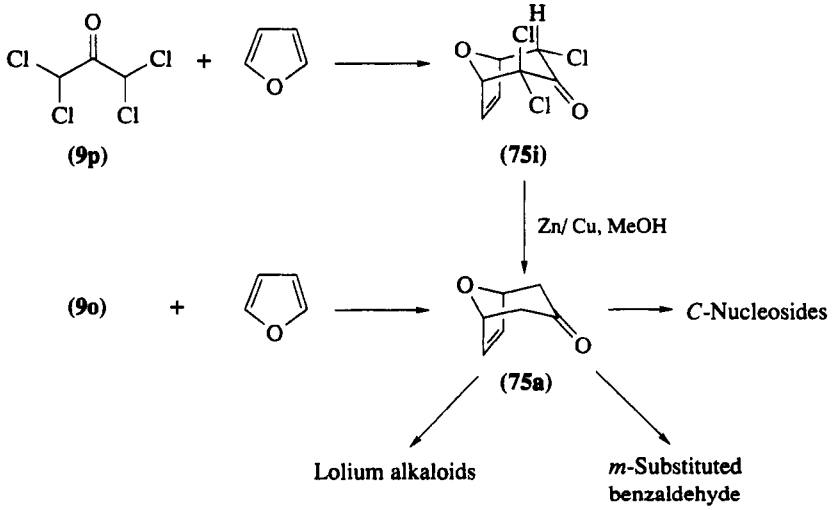
It has been recently reported that 2-(trimethylsiloxy)acrolein (**12a**; R = H), but not the less electrophilic (**12b**; R = Me), can serve as a 1-hydroxy-2-oxidoallyl synthon (**13**) in the presence of an equimolar amount of $SnCl_4$.[23] Interestingly, furan affords only the *exo* adduct (**77**). This stereoselectivity can be explained by postulating that the cycloaddition belongs to Class B, the formation of the second σ-bond being late or product-like and assisted by chelation to oxygen.

2-(Trimethylsiloxy)allyl cations (**5**; Y = $OSiMe_3$), generated from the corresponding siloxyallyl chlorides (**4**; X = Cl, Y = $OSiMe_3$) and silver perchlorate, smoothly react with furan and cyclopentadiene in nitromethane to give [4 + 3] cycloadducts in good yields.[21] The cycloaddition with furan proceeds in a stereospecific manner with retention of the allyl cation configuration, in accord with the concerted mechanism (Class A). In contrast, the reactions in THF–ether are nonstereospecific and the yields strongly dependent upon the structure of the allyl cation (**5**; Y = $OSiMe_3$) because of competition with electrophilic substitution. The reaction of (**4c**; Y = $OSiMe_3$, X = Cl) with 2-methylfuran proceeds in a highly regioselective manner in THF–ether, giving (**78a**) overwhelmingly, compared with nitromethane where two regioisomers (**78a**) and (**78b**) are formed in comparable amounts. The findings in THF–ether are reasonably explained by a stepwise mechanism (Class B, route a) (Scheme 20).

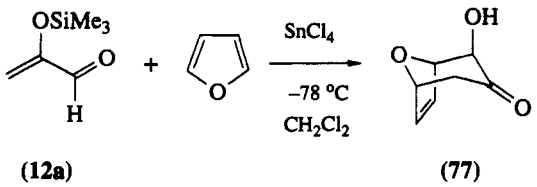


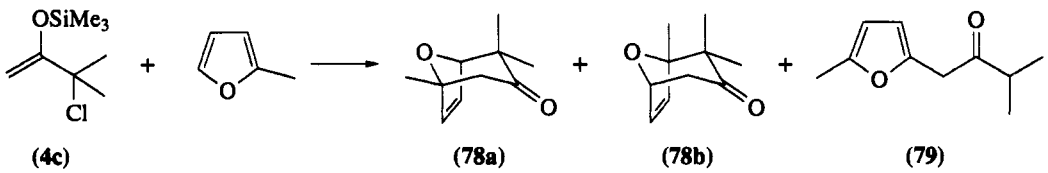
(5) or (7) (76) (75)

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
75a:	H	H	H	H	H	H	H	H
b:	H	H	Me	Me	H	H	H	H
c:	H	H	Me	Me	H	Me	H	H
d:	H	Me	Me	H	H	H	H	H
e:	H	Me	Me	H		H	H	H
f:	H	Pr^i	H	H	H	H	H	H
g:	H	H	H	H	H	Pr^i	H	H
h:	H	H	H	H	H	H	Pr^i	H
i:	H	H	Cl	Cl	Cl	H	H	H



Scheme 19

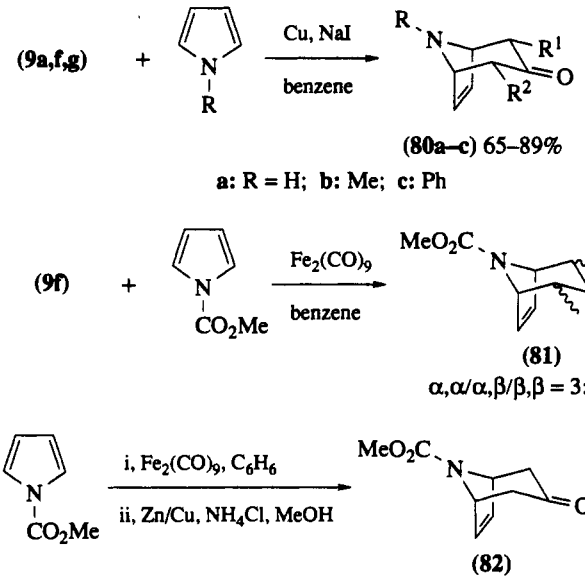




Scheme 20

5.1.3.3.2 Pyrroles

Pyrrole and its *N*-alkyl derivatives can be employed as diene components for the copper–sodium iodide promoted [4 + 3] cyclocoupling reaction of open-chain dibromo ketones.[8b,64] Reactions with cyclic dibromo ketones such as 2,6-dibromocyclohexanone (**9m**; X = Br) afford only substitution products. Treatment of both acyclic and cyclic dibromo ketones with zinc or iron carbonyls only results in substitution.[49c,e,64] In contrast, pyrrole derivatives bearing an electron-withdrawing substituent such as acetyl or methoxycarbonyl on the nitrogen atom undergo the cyclocoupling reaction with di- or more highly brominated ketones (**9**; X = Br).[65] As a reducing agent, $Fe_2(CO)_9$ is used since $Fe(CO)_5$ or zinc–copper couple give less satisfactory results in these cases. Attempts to use copper–sodium iodide were unsuccessful (Scheme 21). Allenoxide also reacts with *N*-methylpyrrole to give the corresponding seven-membered adducts.[31]



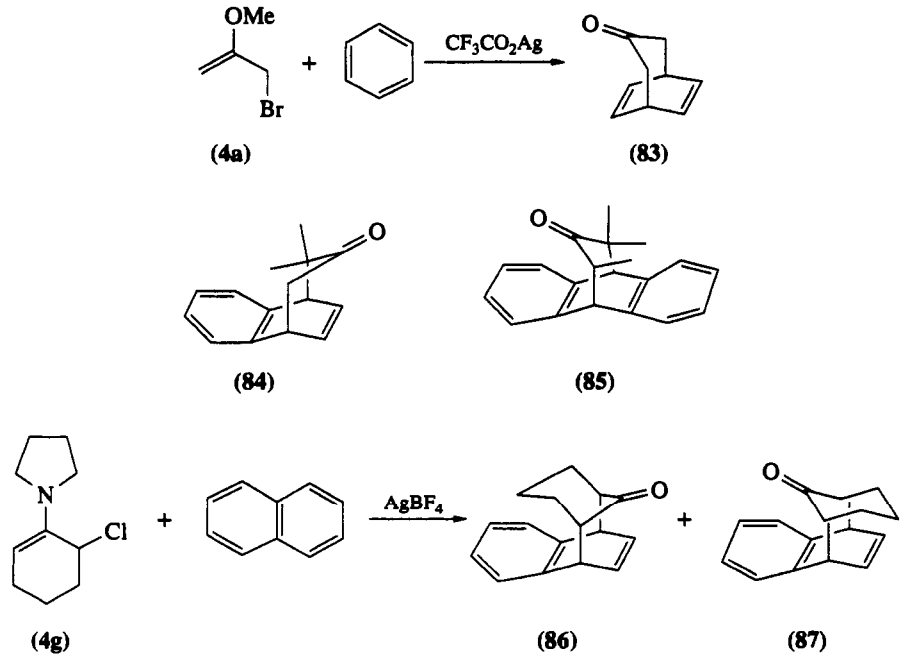
Scheme 21

5.1.3.4 Arenes

Oxyallyl, alkoxyallyl, siloxyallyl, aminoallyl and alkylallyl cations react with arenes to give cycloadducts (**83**)–(**87**). Methoxyallyl bromide (**4a**) reacts with benzene in the presence of CF_3COOAg to give bicyclo[3.2.2]nona-6,8-dien-3-one (**83**), though the yield is not always good.[24a] The reactive species obtained from (**4c**) is captured by naphthalene to give a small amount of 1,4-addition product (**84**) together with a substitution product.[21] The reduction of α,α′-dibromo ketones (**9**; X = Br) with zinc–copper couple in dioxane containing anthracene affords 6,7,8,9-dibenzobicyclo[3.2.2]nonan-3-one (**85**) in 3–25% yields.[66] However, the addition of chlorotrimethylsilane to the system along with a solvent change to benzene results in substantially increased yields of (**85**) (71–97%).[66] Schmid *et al.* have shown that in the presence of $AgBF_4$ and naphthalene, cyclic α-chloroenamine (**4g**; X = Cl, Y = pyrrolidino) affords (**86**) and (**87**), in 24 and 0.4% yields, respectively (Scheme 22).[26a]

5.1.4 SYNTHETIC APPLICATIONS

There now exist many procedures for the generation of allyl cations, and various reactions of these with 1,3-dienes are known. The products have been conveniently applied as precursors in synthesis of important naturally occurring products, inaccessible by other methods.[4–6]



Scheme 22

5.1.4.1 Intramolecular Cyclization

Despite the copious literature dealing with bimolecular [4 + 3] cycloaddition reactions, intramolecular reactions are not plentiful. Probably the most attractive feature of the internal cycloaddition is the opportunity to control the stereochemistry of the products at several centers. Polybromo ketones bearing a functional group are extremely important substrates for the synthesis of novel seven-membered fused-ring compounds. The first example of such a process was reported for the synthesis of (**89**) from (**88**) by Paquette *et al.* in 1973,[67] though they did not isolate the intermediate. Noyori *et al.* have reported that the intramolecular dibromo ketone–iron carbonyl reaction permits the direct synthesis of an oxidoperhydroazulenone (**91**), a ring system found in naturally occurring daucon.[68] Thus treatment of dibromo ketone (**90**) with $Fe_2(CO)_9$ produced (**91**; 38%). A similar conversion of (**92**) to (**93**) was carried out by Föhlisch and Herter.[69] Hoffmann *et al.* have also reported an intramolecular variant to generate (**95**) and (**96**) by starting from (**94**) (Scheme 23).[70]

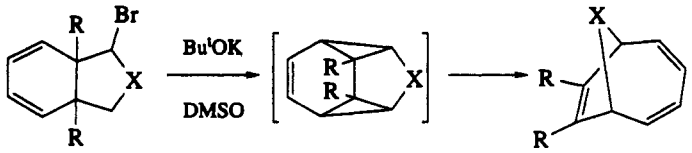
5.1.4.2 Troponoid Compounds

2,7-Dialkylated 4-cycloheptenones such as (**58**) are utilized as key intermediates in the preparation of various kinds of troponoid compounds, including 2,7-dialkylated tropones (**97**),[49a,60c] γ-tropolones (**98**) and 4,5-homotropones (**99**),[49a,60c] which exist as hydrohomotropylium ions (**100**) in concentrated sulfuric acid.[60,61]

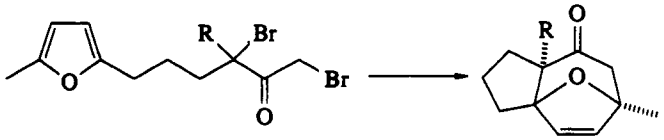
8-Oxabicyclo[3.2.1]oct-6-en-3-ones (**75**) are also readily transformed to tropones (**97**) or γ-tropolones (**98**) in a few steps. The tricyclic adduct (**75**; R = $(CH_2)_9$) can be readily converted to troponophane (**101**). Successful use of tetrabromoacetone and tribromo derivatives of methyl alkyl ketones in these reactions opens a new route to various naturally occurring troponoid compounds, *viz.* nezukone (**102**),[60b,c] α-thujaplicin (**103**)[49d,60] and hinokitiol (β-thujaplicin) (**104**),[49d,60c] respectively (Scheme 24).

5.1.4.3 Tropane Alkaloids

The synthesis of a variety of tropane alkaloids has been achieved *via* 6,7-dehydrotropines (**105**), derived from (**82**) by stereoselective reduction with diisobutylaluminum hydride. Subsequent appropriate modification of the double bond leads to several naturally occurring tropane alkaloids, including tropine (**106**), scopine (**107**), tropanediol (**108**) and teloidine (**109**) (Scheme 25).[49,64]

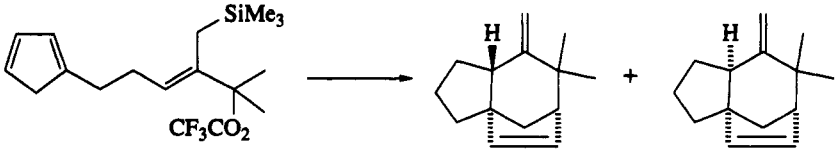


(88) X = CO, SO_2 (89)



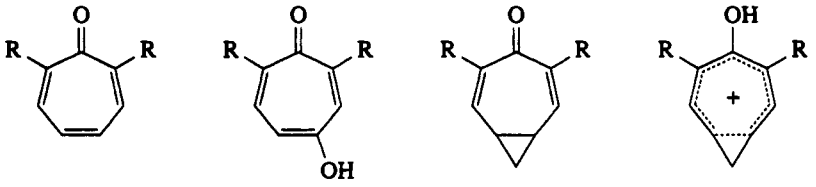
(90) (91)

(92) (93)

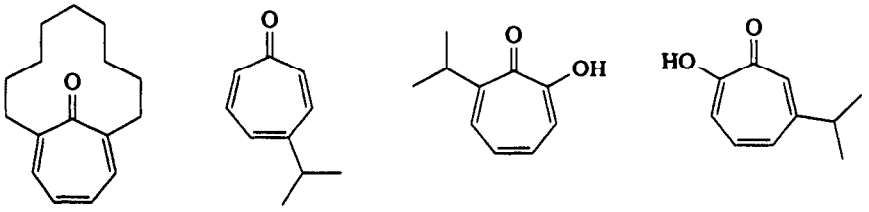


(94) (95) (96)

Scheme 23

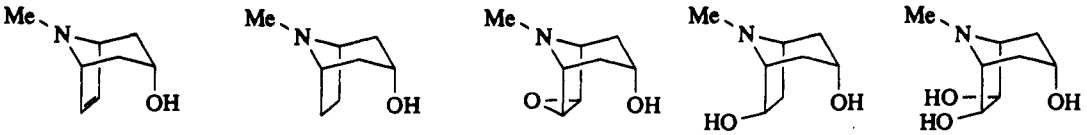


(97) (98) (99) (100)



(101) (102) (103) (104)

Scheme 24

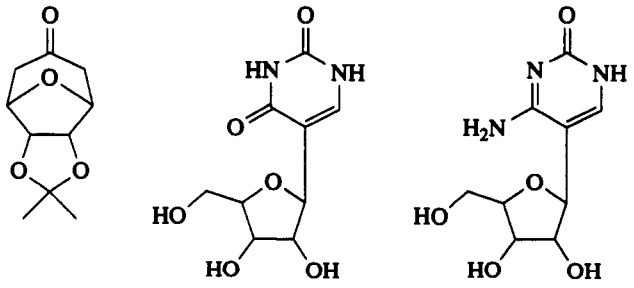


(105) (106) (107) (108) (109)

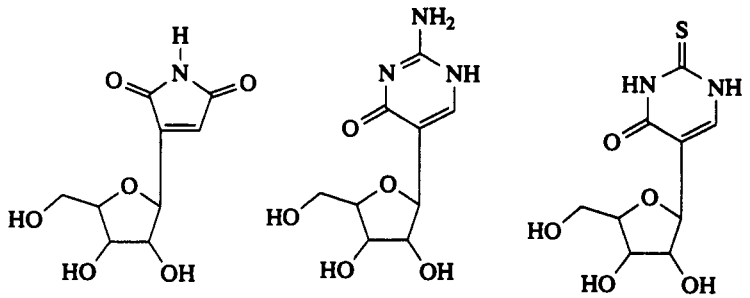
Scheme 25

5.1.4.4 *C*-Nucleosides

The oxabicyclic ketone (**75a**) is converted to (**110**) with high stereoselectivity, the methodology providing an efficient entry into *C*-nucleosides.[5b,57] The stereocontrolled synthesis of natural products such as pseudouridine (**111**), pseudocytidine (**112**) and showdomycin (**113**) has been accomplished along with a number of unnatural analogs such as pseudoisocyctidine (**114**) and 2-thiopseudouridine (**115**). Apparently the efficiency of this direct approach to *C*-nucleosides is based on the ready availability of (**75a**) from tetrabromoacetone and furan (Scheme 26).[5b]



(**110**) (**111**) (**112**)

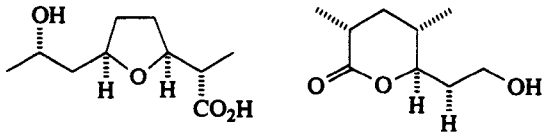


(**113**) (**114**) (**115**)

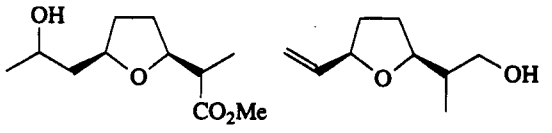
Scheme 26

5.1.4.5 Nonactic Acid, Lilac Alcohol and Prelog–Djerassi Lactone

The cycloadduct (**75d**) has been utilized for the synthesis of nonactic acid (**116**) and lilac alcohol (**119**) *via* (**118**).[71] The Prelog–Djerassi lactone (**117**), a pivotal intermediate in Masamune's methymycin synthesis, has been prepared from the key compound (**75e**) (Scheme 27).[72]



(**116**) (**117**)

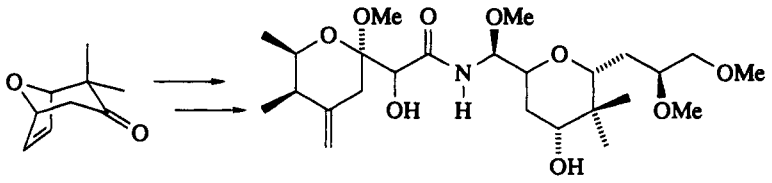


(**118**) (**119**)

Scheme 27

5.1.4.6 Pederin

The bicyclic ketone (**75b**) has been used as a starting material for a multi-step synthesis of the 'eastern half' of pederin (**120**), which is the most complex, nonproteinaceous insect defensive compound known (Scheme 28).[73]



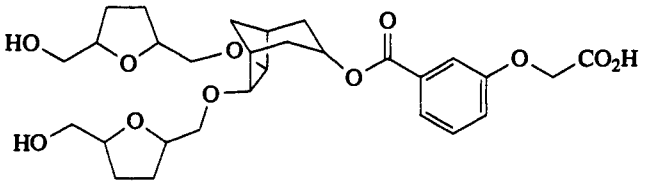
(**75b**) (**120**)

Scheme 28

5.1.4.7 Noncyclic Ionophore and Barbaralanes

The parent bicyclic compound (**65**), prepared from (**9o**) and cyclopentadiene, has been elaborated in only a few steps into the noncyclic ionophore (**121**), which transports Ca^{2+} efficiently.[74] Its 2,4-dimethylated homolog (**64**) has been used by Wierenga *et al.* as the starting material to prepare functionalized barbaralanes (**124**) (Scheme 29).[75]

(**65**) (**121**)



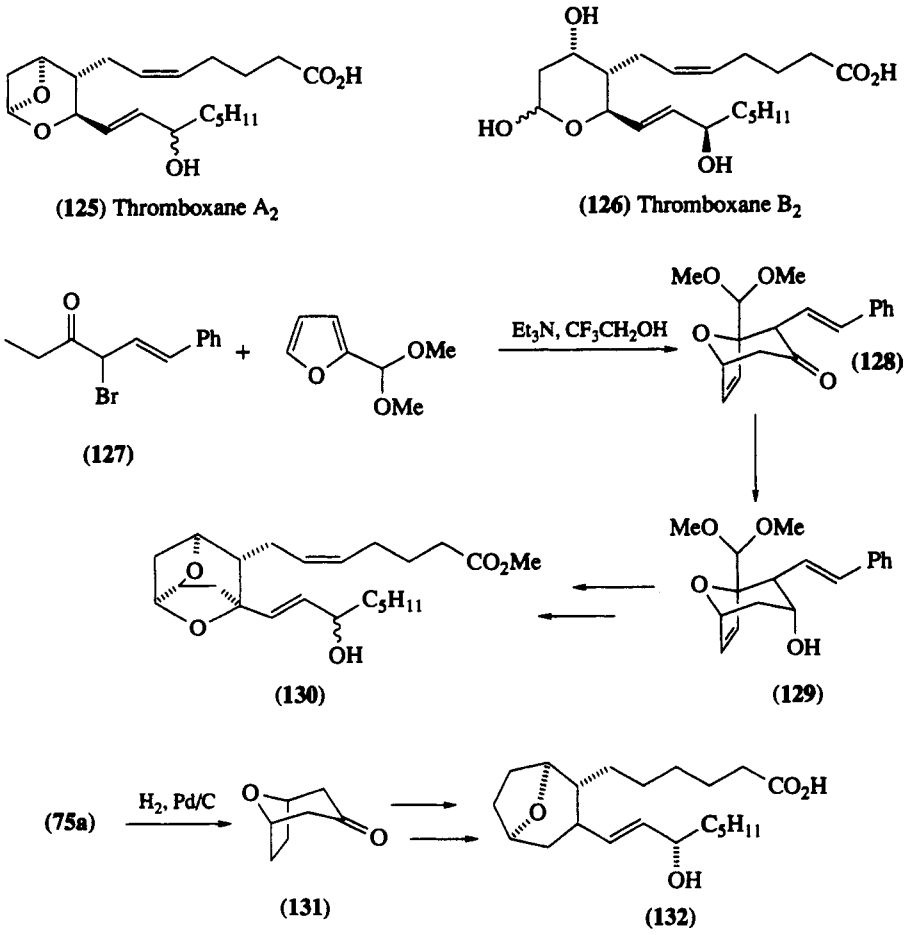
(**122**) Nonproteinaceous

(**64**) (**123**) (**124**) Barbaralanes

Scheme 29

5.1.4.8 Thromboxane A_2 and B_2

Thromboxane families (**125**) and (**126**) were prepared from the cycloadduct (**128**) between a bromo ketone (**127**) and 2-furfural dimethyl acetal, though the yields were not good (Scheme 30).[76,77]



Scheme 30

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5.2
[4 + 4] and [6 + 4] Cycloadditions

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5.2.1 INTRODUCTION

The potential utility of higher-order cycloaddition reactions in complex syntheses has only been recognized relatively recently. To a large extent, cycloaddition processes involving the interaction of two polyene addends have been restricted to somewhat specialized molecular systems selected for examining particular mechanistic and theoretical issues. This has been a very fruitful endeavor since the observations concerning the behavior of higher-order cycloaddition reactions have been instrumental in providing insight into the underlying principles of the cycloaddition reaction in a general sense.

Various early studies in this area have provided a sound and fundamental comprehension of the basic mechanistic tenets and limitations of the [6 + 4] and [4 + 4] cycloaddition reactions. However, the scope of this broad class of reactions has yet to be fully established, particularly within the context of preparative chemistry. A number of these reactions display qualities that are traditionally desirable in synthetically useful transformations. Typically, many examples proceed with attendant high levels of predictable stereoselectivity; furthermore, the nature of these cycloadditions is such that they are eminently suitable for rapid and efficient assembly of complex polycyclic carbon systems.

The fundamental variable that must be addressed to employ profitably either the [6 + 4] or [4 + 4] cycloaddition in a synthetic scheme is the general propensity for systems that possess extensive conjugated unsaturation to participate in multiple, competitive pericyclic reactions. The ability to control which of several thermally or photochemically allowed processes will prevail in a given situation is the principal challenge confronting successful synthetic design based on a higher-order cycloaddition reaction as the key bond-forming step. A number of interesting and effective themes for manipulating both [6 + 4] and [4 + 4] cycloaddition processes in a predictable fashion have emerged. These include the well-established technique of tying the reacting centers together to exploit the advantages of intramolecularity. A particularly powerful approach for controlling periselectivity has been to employ the templating effect of

complexation to transition metals. This strategy has resulted in a number of useful advances in the synthetic application of these cycloaddition reactions and points the way for future investigations in this area.

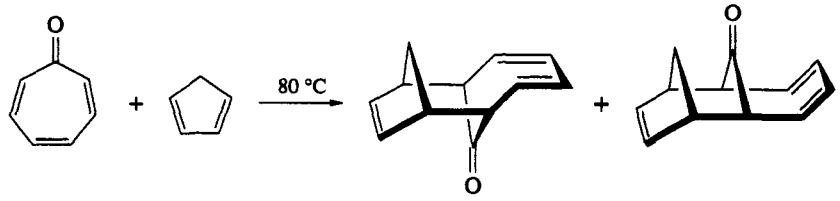
5.2.2 [6 + 4] CYCLOADDITION REACTIONS

5.2.2.1 2,4,6-Cycloheptatrien-1-one (Tropone) as the 6π Addend

5.2.2.1.1 Dienes as 4π addends

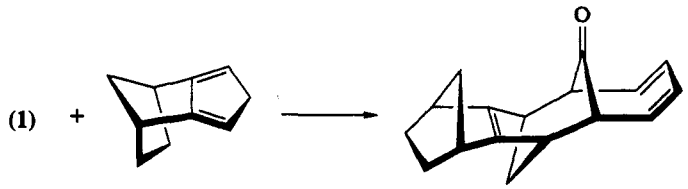
The thermally induced [6 + 4] cycloaddition of 2,4,6-cycloheptatrien-1-one (tropone) (**1**) with a variety of diene partners has played a central role in the development of the mechanistic precepts and preparative utility of the entire class of higher-order pericyclic processes. The relatively well-defined reaction parameters for these cycloadditions render them particularly well-suited for the rapid assembly of relatively complex polycyclic carbon arrays.

Tropone (**1**) and cyclopentadiene form a single 1:1 adduct (**2**) in high yield when heated together at 80 °C.[1,2] Of particular note in this transformation is the production of the *exo* oriented adduct to the virtual exclusion of the corresponding *endo* product (**3**). This experimentally established preference for the *exo* mode of addition was one of the early triumphs of the Woodward–Hoffmann orbital symmetry rules, which correctly predicted this stereoselectivity a year earlier.[3,4]

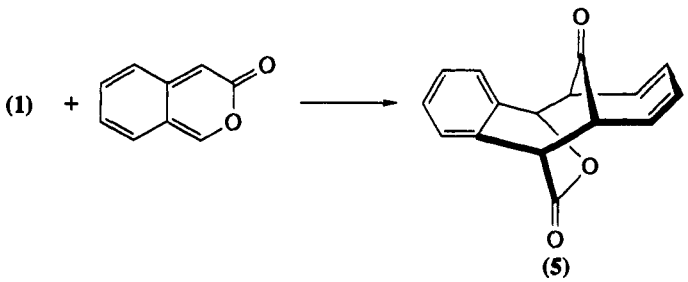


(**1**) (**2**) 100% (**3**) 0%

Numerous examples of *exo* selective cycloadditions employing a diversity of diene partners attest to the generality of this manner of combination. Isodicyclopentadiene can be added to tropone to give principally ketone (**4**)[5] and *in situ* generated 2-benzopyran-3-one provided *exo*-lactone (**5**) in 28% yield.[6] 1-Substituted butadienes have proven to be particularly useful 4π partners, which give the *exo* adducts (**6**) exclusively when reacted with tropone at moderate temperatures.[7,8] Furthermore, the intramolecular vari-

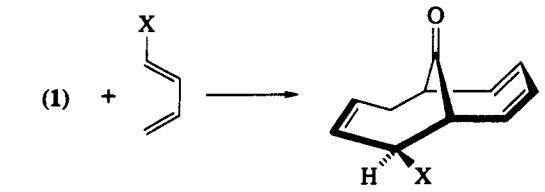


(**4**)

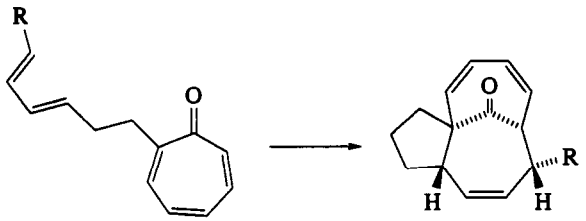


(**5**)

ant of the diene–tropone [6 + 4] cycloaddition also proceeds smoothly at temperatures between 80–110 °C to generate *exo* products (7) in high yields.[8,9]

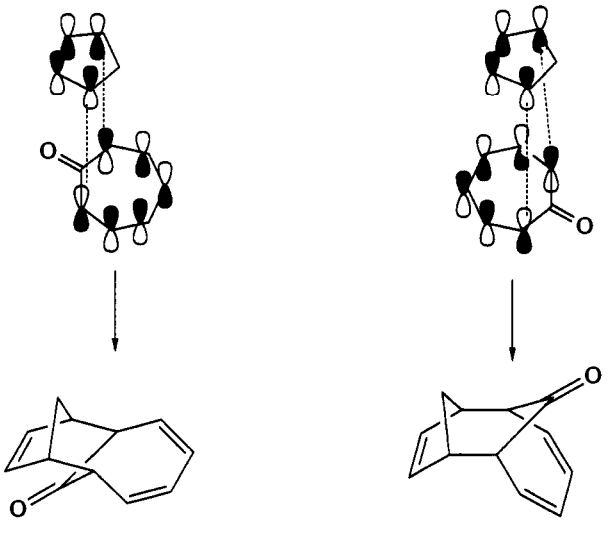


(6)



(7)

The observed stereochemical course of the [6 + 4] diene–tropone cycloaddition has been explained by consideration of the interactions of the HOMO and LUMO of the diene and triene participants, respectively. The appropriate orbital combinations for the *exo* transition state and the alternative *endo* transition state are depicted in Figure 1.[3] A repulsive secondary orbital interaction develops when the diene engages the tropone triene system in an *endo* fashion. This unfavorable situation is avoided in the *exo* transition state; hence the experimentally observed preference for production of the *exo* stereoisomer in these reactions. An intriguing recent study of the reaction of tropone and cyclopentadiene at high pressure indicated that the transition state of the cycloaddition is somewhat smaller than the final state, a result paralleling observations in certain Diels–Alder reactions in which favorable secondary orbital interactions were operative.[10] From these results it was concluded that an attractive interaction between the diene LUMO and the carbonyl portion of the tropone HOMO may be partially responsible for the high degree of *exo* stereoselectivity exhibited by these transformations. Work from other laboratories, however, has suggested only a minimal contribution by attractive secondary orbital interactions in these reactions.[11–13]

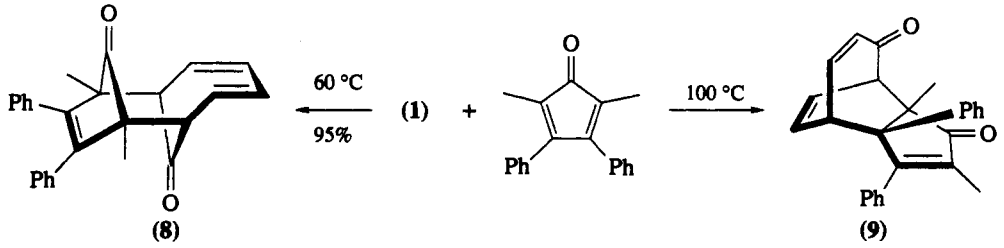


Exo transition state *Endo* transition state

Figure 1 Frontier molecular orbitals for the cycloaddition of cyclopentadiene to tropone

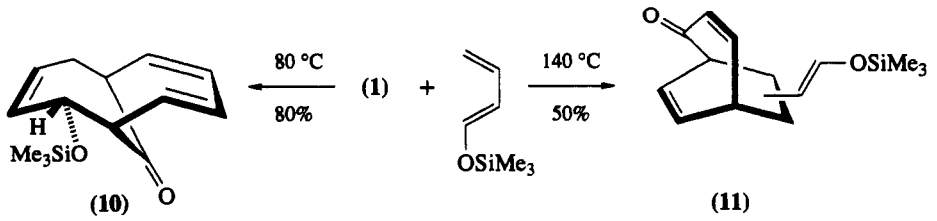
The relative complexity of the extended π-systems present in these reactants suggest that a variety of potentially competitive pericyclic processes could be operative in the thermal reaction of a given diene with tropone. Consequently, the question of periselectivity in these reactions has been examined in some detail in recent years and a number of useful generalizations have been enumerated for predicting products in a variety of circumstances.

From the earliest investigations it was noted that tropone in combination with a number of dienes would provide the *exo* [6 + 4] cycloadduct at relatively low reaction temperatures (≤80 °C), whereas higher temperatures and prolonged reaction times produced, in most cases, the corresponding *endo* [4 + 2] species with tropone serving as the 4π reactant and the diene participating as the 2π partner.[14,15] For example, heating tropone (**1**) and 2,5-dimethyl-3,4-diphenylcyclopentadienone together at 60 °C in THF or acetone gave a 95% yield of the *exo* [6 + 4] product (**8**). In contrast, performing the same reaction at 100 °C or higher provided only the *endo* [4 + 2] product (**9**) in high yield.[15] A qualitatively similar observation had been made with cyclopentadiene and tropone.[14] Formation of these two adducts has been attributed to the operation of concerted *exo* [6 + 4] (kinetic) and *endo* [4 + 2] (thermodynamic) pathways, respectively. A number of kinetic studies on the tropone–diene [6 + 4] cycloaddition have concluded that the reaction possesses a late transition state, which is consistent with a concerted process and mechanistically resembles the classical Diels–Alder reaction.[10–13]

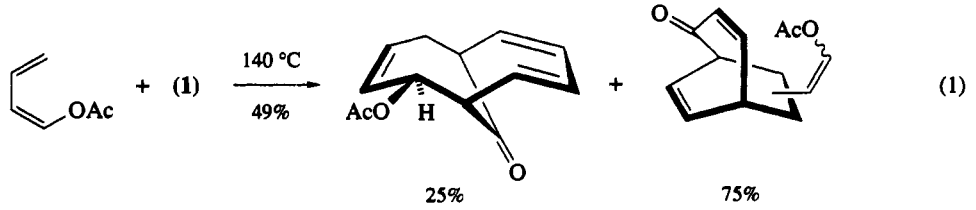


(8) (9)

The periselectivity of the reaction of a given diene with tropone is critically dependent on temperature. The variable course of the cycloaddition of (*E*)-1-trimethylsilyloxybutadiene with tropone as a function of reaction temperature is a dramatic illustration of this phenomenon. At 80 °C the major adduct is bicyclo[4.4.1]undecenone (**10**), whereas in refluxing xylene the [4 + 2] cycloadduct (**11**) prevails as a mixture of regioisomers.[7] A further example of the dichotomy between [6 + 4] and [4 + 2] reaction pathways can be seen with (*Z*)-1-acetoxybutadiene, which provides some [6 + 4] cycloadduct along with larger quantities of various [4 + 2] products as depicted in equation (1).[7] In contrast to these results, dienes such as ethyl 2,4-hexadienoate and furan do not yield any [6 + 4] or [4 + 2] products when heated with tropone.[7] The latter result, in particular, may be reflective of the reversibility of the furan cycloadducts. Various furan derivatives do provide modest yields of mixtures of *endo* and *exo* [4 + 2] cycloadducts with tropone when reacted together at 3 kbar and 130 °C.[16]



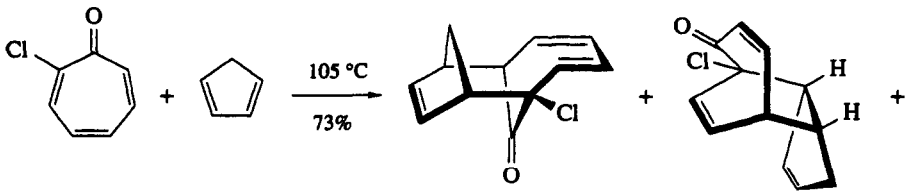
(10) (11)



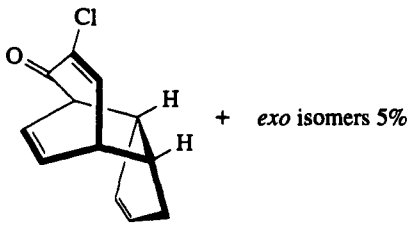
25% 75% (1)

Another important generalization in these systems is that the course of cycloaddition between tropone and dienes appears to be particularly sensitive to substitution patterns in either addend. 2-Chlorotropone

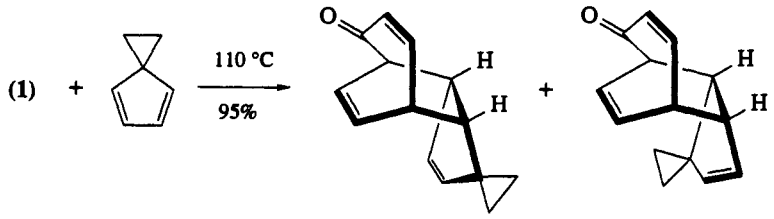
(**12**), for example, gives rise to a mixture of four 1:1 adducts when exposed to cyclopentadiene at 105 °C for 3 h. In this instance the *endo* [4 + 2] species (**14**) and (**15**) were produced in excess.[17] A further interesting observation in this particular reaction was the prevalence of the regioisomer in which bonding occurred at the troponoid carbon bearing the chlorine substituent. Diene substitution also plays a significant role in determining the course of these reactions. None of the expected [6 + 4] products were detected in the reaction of spiro[2.4]hepta-4,6-diene with tropone. Regioisomeric *endo* [4 + 2] adducts (**16**) and (**17**) were the principal materials isolated in this case.[18,19] Apparently, the steric congestion provided by the quaternary center in the diene is sufficient to suppress the [6 + 4] option. In contrast, certain highly substituted but quite reactive dienes have been reported to undergo reasonably efficient [6 + 4] cycloaddition with tropone in selected situations. The formation of adduct (**8**) from a cyclopentadienone addend is a case in point.[15,20]



(**12**) (**13**) 25% (**14**) 45%

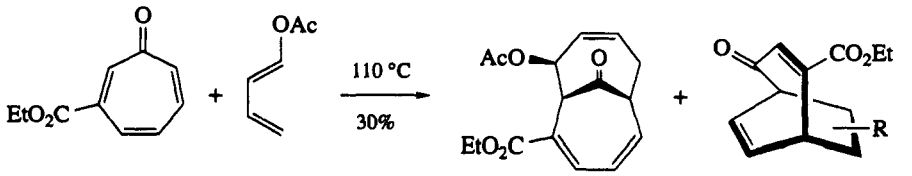


(**15**) 25%



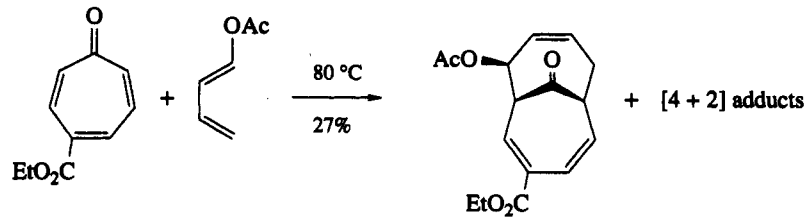
(**16**) 17% (**17**) 83%

Unsymmetrically substituted tropones wherein the substitution is remote from the actual bonding centers have also been the subject of regioselectivity studies.[21] Modest chemical yields accompanied high regioselectivities in the resultant products isolated from the addition of various dienes to 3- and 4-ethoxycarbonyltropones, (**18**) and (**21**). So-called 'even' regioselectivity, which completely parallels the regioselectivity observed in the Diels–Alder reaction, prevailed in these cases. Lower selectivities characterized the reactions of 3- and 4-methoxytropones with the same set of electron-rich diene partners.



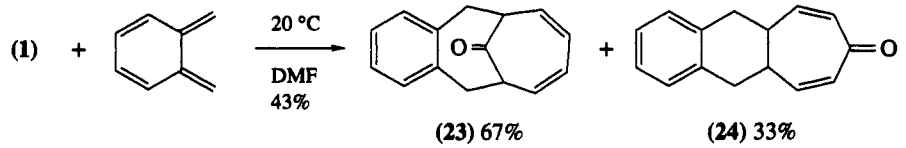
(**18**) (**19**) 67% (**20**) 33%

While the primary modes of cycloaddition between tropone and a given diene can normally be classified as following one of two distinct pathways, in which tropone serves either as the 6π or as the 4π

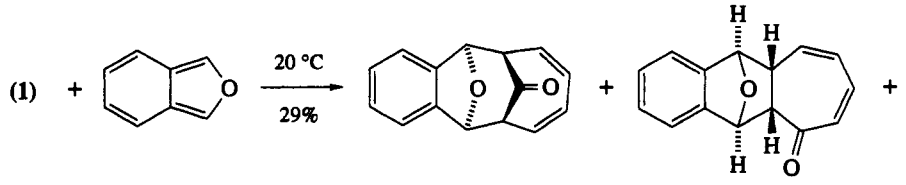


(21) (22) 81%

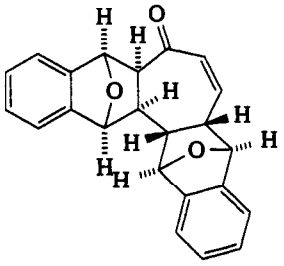
partner, a few cases have been reported in which other reactivities have been revealed. *o*-Xylylene has been described as giving two products, (**23**) and (**24**), when reacted with tropone (**1**) at room temperature.[22] The major product (**23**) was the normal [6 + 4] adduct. On the other hand, the minor species appeared to arise from a [2 + 4] cycloaddition process with tropone participating as the 2π component. A similar phenomenon was observed in the reaction of isobenzofuran and tropone to give (**25**)–(**27**)[23] and an [8 + 2] adduct has been observed in the reaction of 2,5-dimethyl-3,4-diphenylcyclopentadienone with tropone.[15] While mechanistically interesting, these latter examples appear to be exceptions to the dual pathways normally available to tropone in its reactions with dienes.



(23) 67% (24) 33%

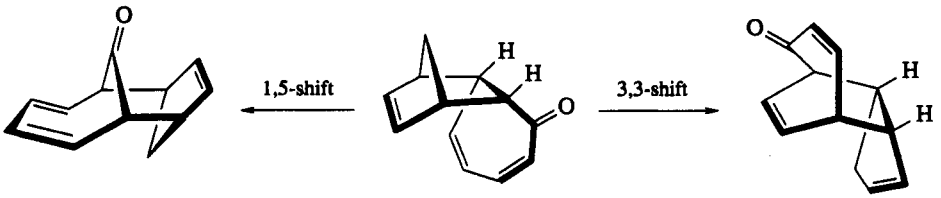


(25) 41% (26) 18%



(27) 41%

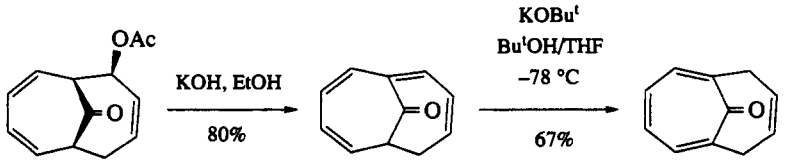
Although the characteristics of the thermal reaction of tropone with dienes can be accommodated by the operation of concerted *exo* [6 + 4] and *endo* [4 + 2] pathways, an alternative mechanistic scenario that would lead with equal stereoselectivity to the observed [4 + 2] and [6 + 4] products can be envisioned as depicted in Scheme 1. This pathway would involve initial [2 + 4] cycloaddition of cyclopentadiene to tropone to give dienone (**28**) followed by thermally allowed 1,5- and 3,3-sigmatropic carbon migrations which would lead to the *exo* [6 + 4] adduct (**2**) and *endo* [4 + 2] adduct (**29**), respectively. Recently a test of this scheme was conceived and executed by Franck-Newmann and Martina.[24] Cycloaddition of cyclopentadiene to tricarbonyl(tropone)iron provided access to the critical [2 + 4] intermediate (**28**) after metal decomplexation. Heating of the resultant cycloadduct at 60–75 °C led exclusively to compound (**29**) *via* a Cope rearrangement. No evidence for the production of the [6 + 4] product (**2**) in this reaction was indicated. These results suggest that ketone (**2**) probably arises directly from a concerted [6 + 4] cycloaddition. In an interesting contrast, compound (**26**) has been reported to rearrange to [6 + 4] adduct (**25**) when heated at 160–165 °C for several hours.[23]



(2) (28) (29)

Scheme 1

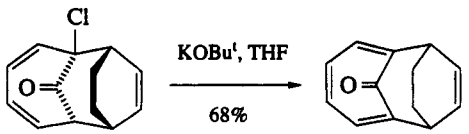
Application of the *exo* [6 + 4] tropone–diene cycloaddition protocol to the construction of specific target molecules has begun to receive attention only recently. The high level of stereocontrol and ease of assembling polycyclic carbon frameworks afforded by this technology is particularly appealing for complex synthesis. Several members of the highly strained troponophane series have been efficiently assembled by the use of tropone–diene [6 + 4] cycloaddition.[25] Cycloadduct (**30**), derived from tropone and 1-acetoxybutadiene, can be converted into the dehydro analog of [4](2,7)troponophane (**31**) through the action of a remarkable base-mediated double bond migration[26] as depicted in Scheme 2.



(30) (31)

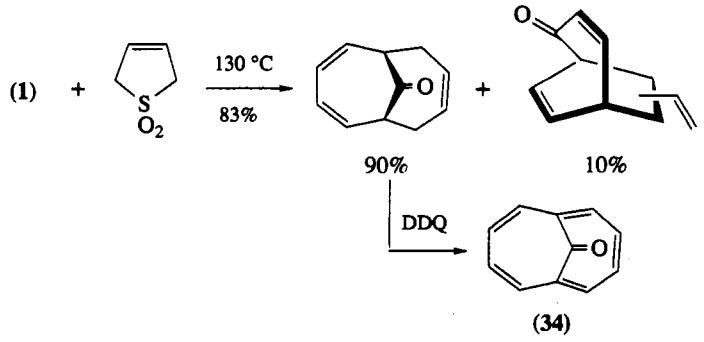
Scheme 2

Other highly distorted troponoid species have been accessed through related [6 + 4] cycloaddition–dehydrohalogenation protocols as well. For instance, bridged troponophane (**33**) was prepared from cycloadduct (**32**) in 68% yield.[27] An interesting aspect of this particular work is the remarkable efficiency of the cycloaddition between 2-chlorotropone and cyclohexadiene, which proceeded smoothly to form ketone (**32**) in 58% yield.



(32) (33) (2)

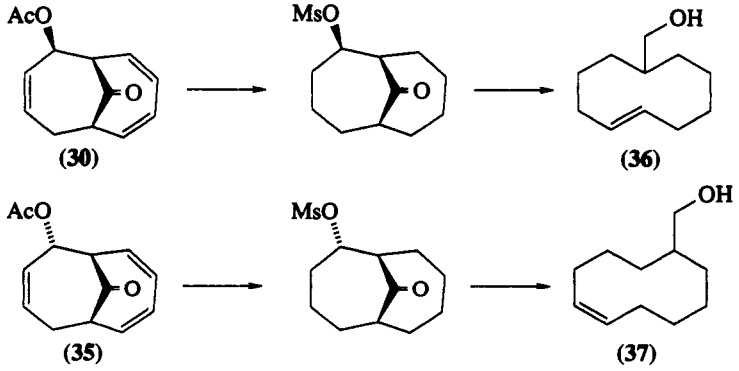
Ito and coworkers have employed the simple cycloadduct of butadiene and tropone to prepare the theoretically interesting 1,6-methano[10]annulen-11-one (**34**).[28] Although a number of dehydrogenation procedures were examined, direct treatment of the cycloadduct with DDQ was of only modest value in delivering the desired [10]annulene derivative.



(34)

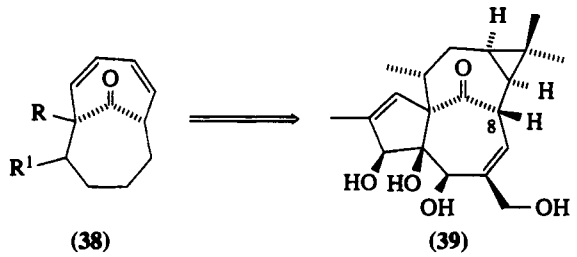
Scheme 3

The potential utility of the stereocontrol available through *exo* [6 + 4] cycloaddition in the tropone series can be seen in Garst's stereoselective cyclodecene synthesis.[29] This methodology is predicated on the efficient translation of the double bond geometry from stereochemically homogeneous (*E*)- and (*Z*)-1-acetoxybutadiene *via* cycloadducts (**30**) and (**35**) into (*E*)-cyclodecene (**36**) and (*Z*)-cyclodecene (**37**), respectively. Reduction of cycloadducts (**30**) and (**35**) to the corresponding fully saturated ketoacetates, followed by conversion to the mesylates and hydride reduction, led to the desired 10-membered ring products (**36**) and (**37**) in 78% and 40% yields, respectively.

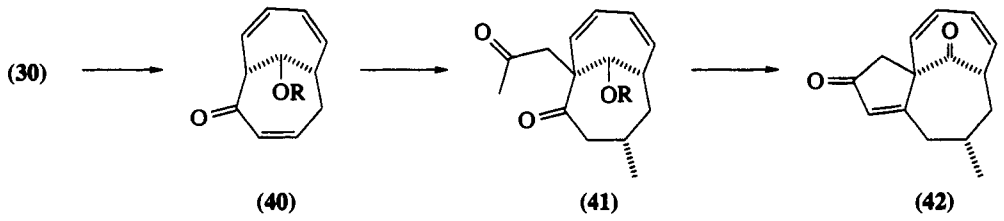


Scheme 4

The [6 + 4] cycloaddition strategy is ideally suited for constructing the basic bicyclo[4.4.1]undecanone carbon skeleton (**38**) which is characteristic of the potent co-carcinogenic diterpene ingenol (**39**). This cycloaddition strategy rapidly assembles the requisite bicyclo[4.4.1]undecanone system which is initially epimeric to the naturally occurring ingenol at the C-8 position. Thus this technology is particularly useful for the construction of the important so-called 'isoingenol' series. The resultant cycloadducts afford further advantages by retaining a number of strategically located functional handles for subsequent elaboration of the ample array of substituents displayed throughout this target molecule. Both inter-[8] and intra-molecular[8,9] approaches into this complex natural product have been developed that employ a [6 + 4] tropone–diene cycloaddition as the key ring-forming step. Initial efforts to assemble the basic tricycle through [6 + 4] cycloaddition of 1-acetoxybutadiene with a substituted tropone bearing the elements of the A ring at the 2-position were thwarted by the production of only [4 + 2] cycloadducts in modest yields, a result that is in complete concurrence with established precedent in these reactions. Cycloaddition with the parent tropone gave adduct (**30**) which was smoothly transformed into enone (**40**) through a routine oxidation level adjustment protocol (Scheme 6).[8] Bridgehead enolate alkylation with 2-methoxyallyl bromide, conjugate addition of a methyl substituent and enol ether hydrolysis gave dione (**41**) in good yield. Subsequent base-mediated cyclopentannulation provided the key tricycle (**42**) after deprotection and oxidation at the one-carbon bridge.

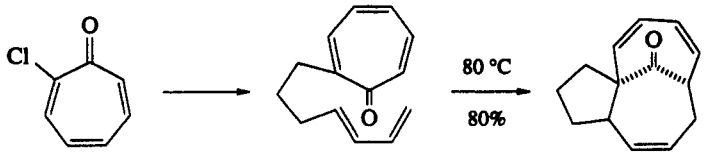


Scheme 5



Scheme 6

A complementary strategy into the ingenane skeleton exploited the first reported intramolecular [6 + 4] tropone–diene cycloaddition[8] for the one-step construction of an intermediate with the A, B and C rings of the target molecule intact.[8] The successful implementation of the intramolecular version was made possible by tethering the diene partner to the tropone moiety in straightforward fashion. This accomplishment was achieved by incorporating the requisite diene side-chain *via* an addition–elimination sequence starting with 2-chlorotropone (Scheme 7).[8] Subsequent to this initial disclosure, a second report of a similar strategy appeared which featured an alternative addition–elimination protocol for constructing the tethered diene species.[9]



(43)

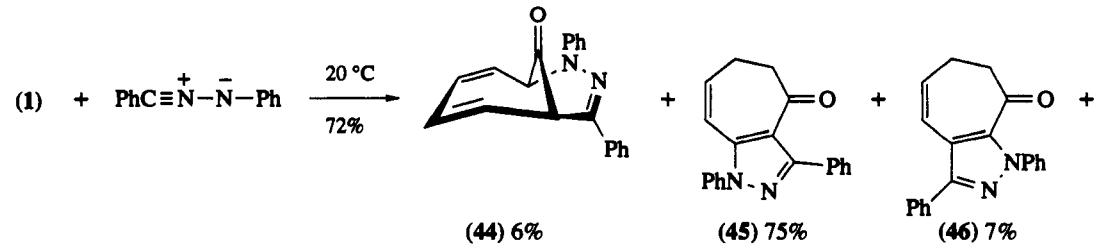
Scheme 7

Clearly, the utilization of the [6 + 4] tropone–diene cycloaddition for synthetic applications has just begun to develop and many new opportunities for exploiting the unique combination of stereocontrol and synthetic convergency afforded by these reactions is certain to be forthcoming in the near future.

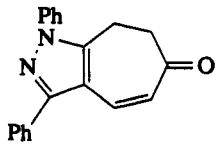
5.2.2.1.2 1,3-Dipoles as 4π addends

In stark contrast to the relative abundance of dienes that are known to provide synthetically useful yields of [6 + 4] cycloaddition products when reacted with tropone, relatively few examples of viable [6 + 4] additions have been documented in which the 4π addend has been a 1,3-dipolar species. This situation is somewhat surprising since 1,3-dipoles and dienes are normally quite similar in their respective cycloaddition behavior.

The initial disclosure of a [6 + 4] cycloaddition between tropone (**1**) and a 1,3-dipole involved diphenylnitrilimine as depicted in Scheme 8.[30,31] In this instance the [6 + 4] pathway competed rather poorly with various alternative [4 + 2] pathways and only a small quantity of the adduct in which the dipole added across the 2- and 7-positions of (**1**) was recovered. The three [4 + 2] adducts (**45**)–(**47**) that were isolated from the reaction mixture presumably arose from a base-catalyzed hydrogen shift that occurred subsequent to the initial cycloaddition. Efforts to account for the divergent behavior of dienes and 1,3-dipolar species in their reactions with tropone have included invoking a dipole repulsion between the large positive charge located on the central atom of the 1,3-dipole and the partial positive charge on tropone, which must come into close proximity in the transition state of a concerted [6 + 4] cycloaddition.[32] A ca-



(44) 6% (45) 75% (46) 7%

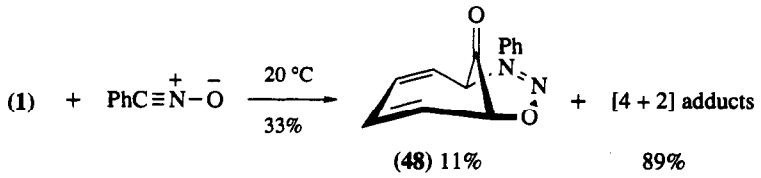


(47) 7%

Scheme 8

veat to this argument has been issued, however, since the energetics of this repulsion appear insufficient to explain the almost total lack of [6 + 4] adducts in these reactions. The regioselectivity observed in the formation of the corresponding [4 + 2] adducts can be satisfactorily interpreted based on the interaction of the LUMO of the electron-deficient nitrilimine with the HOMO of tropone.[32]

Nitrile oxides have also been reported to combine with tropone in a [6 + 4] fashion.[33] Again this mode of addition does not compete well with various [4 + 2] alternatives as can be seen from inspection of equation (3). The room temperature addition of benzonitrile oxide to tropone (**1**) provided the [6 + 4] adduct in quite low yield and at least five [4 + 2] cycloadducts of various structures were also formed during this reaction. In contrast, the hindered mesitonitrile oxide displayed somewhat greater periselectivity than did the parent nitrile oxide in combination with tropone. Almost no [6 + 4] adduct was isolated, however, and a single [4 + 2] species (**49**) emerged as the principal product of this reaction. The higher periselectivity exhibited by the more hindered mesityl derivative was rationalized as reflecting a higher steric demand in the [6 + 4] transition state relative to the [4 + 2] process.[33]



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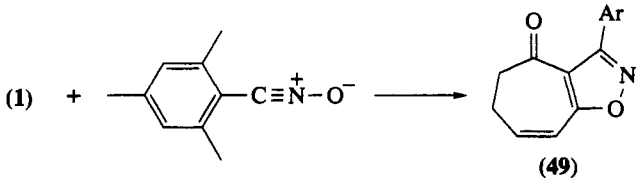


(**49**)

Based on the existent data, it appears that the reaction of 1,3-dipolar species with tropone in a [6 + 4] sense does not hold much promise as a viable tool for applications to synthetic problems.

5.2.2.2 Fulvenes as 6π Addends

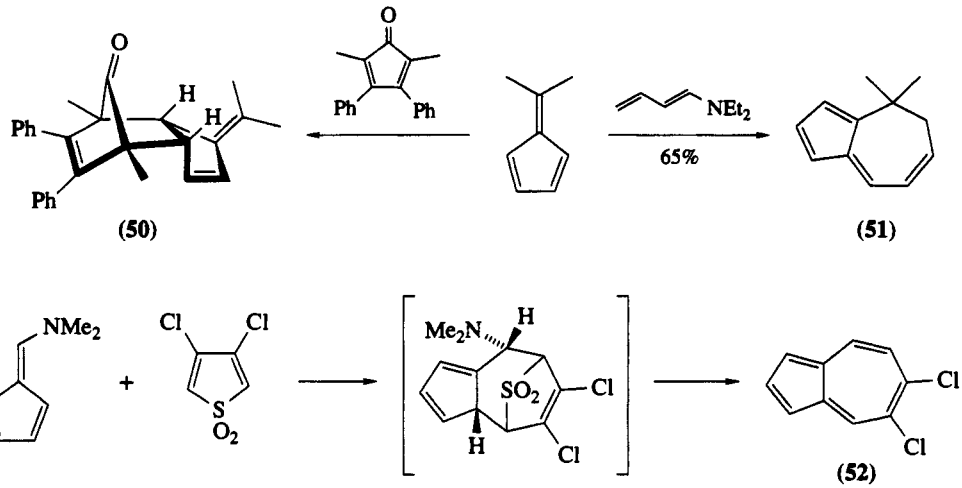
5.2.2.2.1 Dienes as 4π addends

Fulvenes, like their troponoid counterparts, are capable of engaging dienes in a number of different pericyclic reactions. A reasonably well-defined reactivity profile of these systems has emerged as the result of extensive scrutiny of the cycloaddition behavior of the fulvene nucleus. To a large extent, fulvenes undergo concerted cycloadditions to dienes as either the 6π or 2π participant and the factors governing which of these reactivities is expressed in a particular circumstance has been elucidated employing frontier molecular orbital considerations.[34]

The reactions of electron-deficient dienes with fulvenes tend to favor addition across one of the endocyclic double bonds where the fulvene is the 2π component, as illustrated in the cycloaddition of 6,6-dimethylfulvene with 2,5-dimethyl-3,4-diphenylcyclopentadienone in refluxing THF to give adduct (**50**).[35] Cyclopentadiene exhibited a similar periselectivity in its reactions with several fulvenes. In contrast, [6 + 4] adducts are the major products when electron-rich dienes are used in these reactions. For example, hydroazulene (**51**) was isolated in good yield from the combination of 1-diethylaminobutadiene and 6,6-dimethylfulvene subsequent to the elimination of diethylamine from the initially formed cycloadduct.[36]

Reversing the polarity of the reacting partners has also proven to be an effective ploy for promoting [6 + 4] periselectivity.[37–39] The room temperature reaction of 6-dimethylaminofulvene with 3,4-dichlorothiophene dioxide is typical, giving azulene (**52**) in 60% yield.[37,38] 6-Aminofulvenes have also been successfully added in a [6 + 4] sense to α-pyrones, resulting in low yields of azulenes.[39]

The variations of periselectivity exhibited in the cycloadditions of fulvenes to dienes have been rationalized by application of frontier molecular orbital theory. The fulvene orbitals of interest in these reactions are depicted in Figure 2.[34,40] The controlling orbitals in the reaction of fulvene with an



electron-deficient diene are the fulvene HOMO and the diene LUMO. The relatively large coefficients at C-2 and C-3, as well as the node through positions 1 and 6 in the fulvene HOMO, dictate that this species will participate as the 2π component in this case. HOMO-controlled electron-rich diene partners should add to fulvene at C-6 and to either C-1 or C-2 since the LUMO of this type of species possesses large coefficients at these locations. In the event, fulvene derivatives are indeed observed to react with dienamines as the 6π addend. Finally, strongly electron-donating substituents at the C-6 position on fulvene elevate the next highest occupied molecular orbital (NHOMO) sufficiently to permit the [6 + 4] mode of cycloaddition to prevail in reactions with electron-deficient 4π systems.

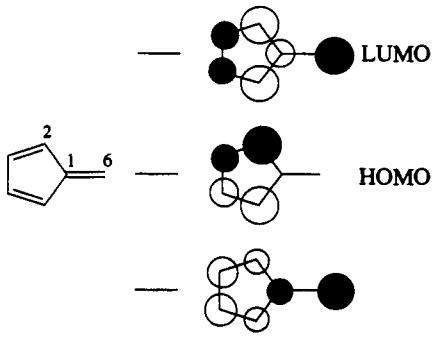
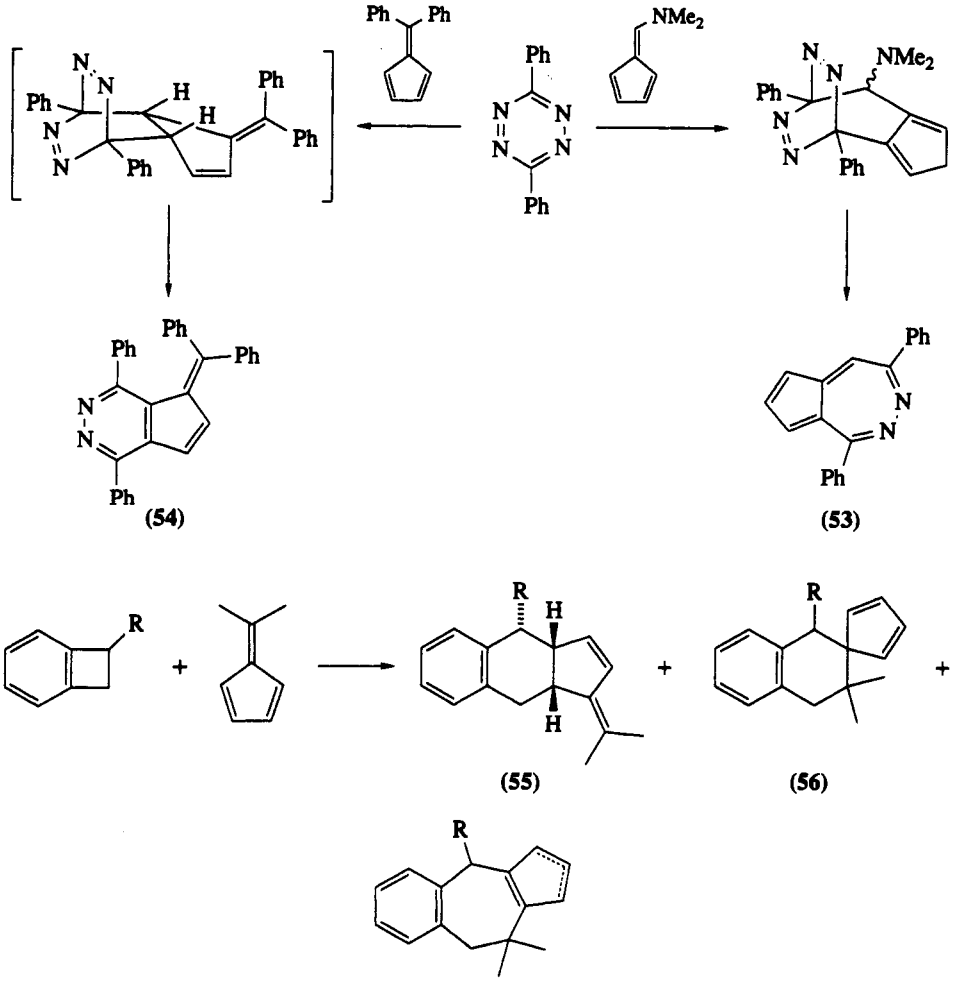


Figure 2 The frontier molecular orbitals of fulvene

An interesting example of the influence of electron-donating substituents at C-6 on reactivity in the fulvene series is the contrast in periselectivity displayed by 6-dimethylaminofulvene and 6,6-diphenylfulvene when exposed to the electron-deficient heterodiene 3,6-diphenyltetrazine.[41] The electron-rich fulvene derivative yielded only diazaazulene (**53**), which arose from an initial [6 + 4] cycloaddition followed by spontaneous loss of the elements of nitrogen and dimethylamine. The corresponding aryl-substituted system reacted exclusively as a 2π species to give compound (**54**). It has been suggested in some studies, however, that steric hindrance at C-6 in fulvenes can serve to inhibit reaction at that center.[42]

A series of interesting cycloadditions of substituted benzocyclobutenes with 6,6-dimethylfulvene has been detailed in regard to additional periselectivity effects.[43] The readily available cyano-substituted benzocyclobutene led exclusively to the endocyclic [4 + 2] adduct (**55**; R = CN) in 67% yield when exposed to 6,6-dimethylfulvene (Scheme 9), while the corresponding [(methoxycarbonyl)amino]benzocyclobutene gave a mixture of adducts, (**55**; R = $NHCO_2Me$) and (**56**; R = $NHCO_2Me$), in yields of 28% and 66%, respectively. Interestingly, pyrolysis of the methyl-substituted compound in the presence of the same fulvene resulted in the generation of a small quantity of [6 + 4] adduct (**57**; R = Me) along with the previously described [4 + 2] products.

The influence of intramolecularity on the benzocyclobutene–fulvene cycloaddition was illustrated in dramatic fashion when the two reactive units were tethered together by a three-carbon chain. Heating nitrile (**58**) gave only the [6 + 4] cycloadduct (**59**) as an inseparable mixture of cyclopentadiene isomers in



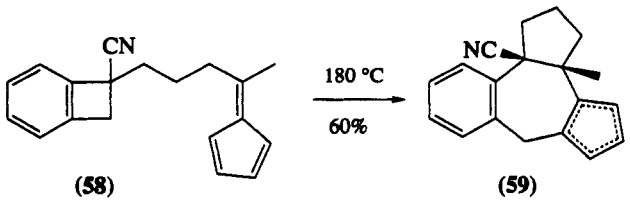
(54) (53)

(55) (56)

(57)

Scheme 9

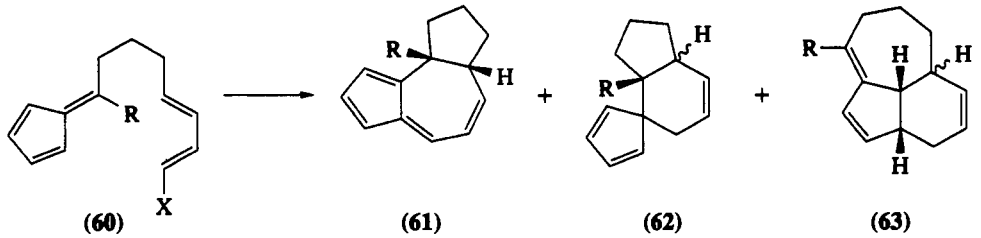
60% yield.[44] This change of periselectivity relative to the intermolecular series stems from conformational restrictions due to the carbon chain connecting the two addends. A further consequence of these constraints is that the reaction is proposed to occur through an *endo* transition state. A similar cycloaddition performed without the benefit of the cyano substituent on the benzocyclobutene moiety exhibited somewhat diminished periselectivity although the [6 + 4] mode still predominated.[44]



(58) (59)

An important ancillary study with significant synthetic implications revealed that electron-rich dienes attached to fulvenes by a multicarbon chain also exhibited a high degree of preference for forming the corresponding [6 + 4] adducts.[45] For example, when substituent X in compound (**60**) was either diethylamino or trimethylsiloxy, the [6 + 4] adduct (**61**) was the major product-type isolated. However, if no substituent was present on the diene portion of the molecule, a mixture consisting of [6 + 4], exocyclic [4 + 2] (**62**) and endocyclic [4 + 2] (**63**) cycloadducts was obtained.[45]

The regioselectivity of the reaction of unsymmetrical diene addends to various fulvene systems has also been explored in some detail. Heating 2-ethyl-5-methylthiophene dioxide in the presence of 6-di-

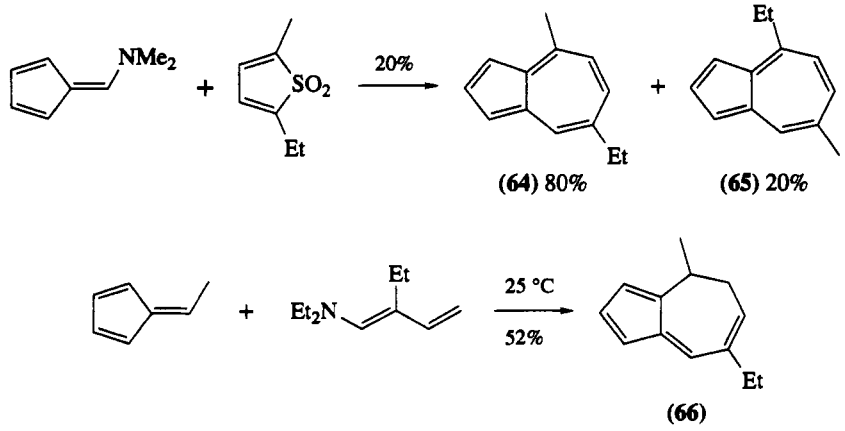


(60) (61) (62) (63)

X = NEt_2, OTMS, H
R = H, Me

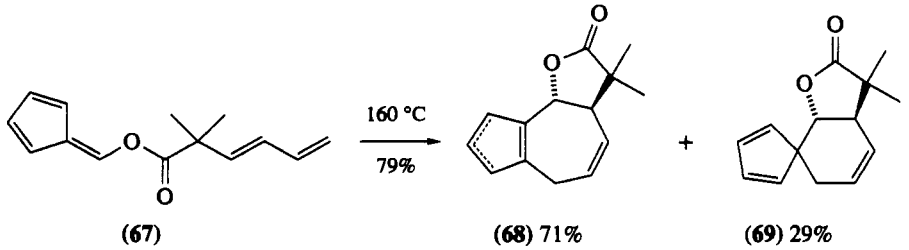
Scheme 10

methylaminofulvene at 80 °C gave a 4:1 mixture of azulenes (**64**) and (**65**) in low overall yield. Steric effects appear to be the critical factor for controlling the observed regioselectivity in this case.[46] However, electronic effects seem to be more potent in directing the course of these reactions. When 6-methylfulvene was reacted with 2-ethyldiethylaminobutadiene, a single hydroazulene (**66**) was obtained in 52% yield. In this situation the most nucleophilic end of the diene reacted with the most electrophilic center on the fulvene partner, as predicted by frontier molecular orbital theory.[47]



Scheme 11

The synthetic utility of the [6 + 4] cycloaddition of dienes to the fulvene system has been amply demonstrated by providing strategies which have greatly improved the available technology for accessing various substituted azulenes and related natural products.[36,38,46–48] A recent development in this area, which is particularly illustrative of the advantages offered by fulvene cycloaddition technology, involved the assembly of a hydroazulene lactone system in a one-step sequence (equation 4). Heating ester (**67**) gave hydroazulene (**68**) as a mixture of cyclopentadiene isomers in good yield along with lesser amounts of the spiro compound (**69**).[49] The general structural type exemplified by compound (**68**) is commonly observed in a variety of sesquiterpene lactones of medicinal interest.



(67) (68) 71% (69) 29% (4)

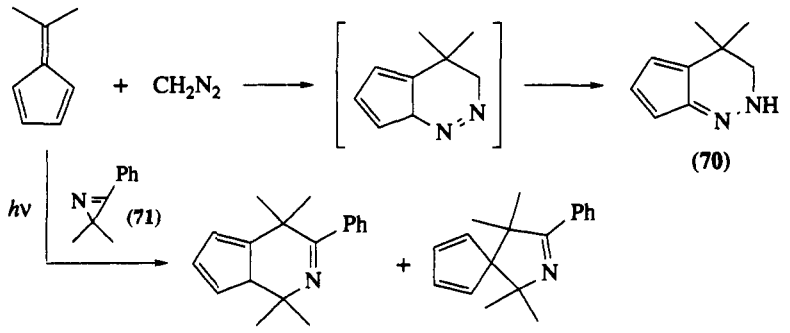
An important feature, characteristic of virtually all fulvene-mediated strategies thus far described in the literature, is the relative ease with which the addends can be assembled from readily available starting materials prior to cycloaddition. Customarily, a simple base-catalyzed condensation of an appropriate ketone substrate with a cyclopentadienide anion will suffice to provide good yields of the requisite ful-

venes. As a consequence, these reaction schemes lend themselves very nicely to synthetic applications and should be useful for the construction of a number of terpenoid natural products.

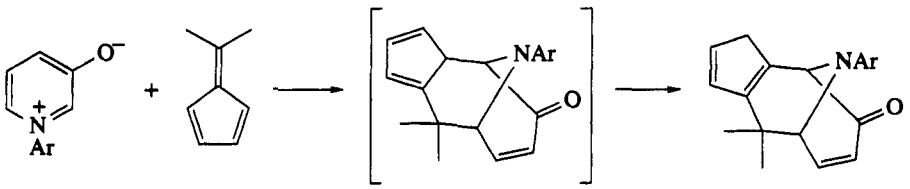
5.2.2.2.2 1,3-Dipoles as 4π addends

Cycloadditions between substituted fulvenes and 1,3-dipolar reagents have been the subject of considerably less study than the corresponding diene-mediated chemistry, paralleling the situation seen in the tropone series. For the most part, however, the reactivity patterns formulated in the fulvene–diene studies are repeated in the analogous 1,3-dipole reactions.

Diazomethane, a 1,3-dipole with well-established nucleophilic character, adds to 6,6-dimethylfulvene exclusively in a [6 + 4] fashion to give compound (**70**) after rapid tautomerism of the initially formed cycloadduct.[50] This observation is in complete accord with frontier orbital predictions for the interaction of a strongly HO-controlled 4π species with the LUMO of the fulvene partner.[40] Electron-rich nitrile ylides also are known to react primarily in a [6 + 4] fashion with substituted fulvene derivatives. A case in point is the irradiation of a 1:1 mixture of azirine (**71**) and 6,6-dimethylfulvene, which provided cycloadducts (**72**) and (**73**) in a ratio of 3:1.[51] The major adduct was quite labile and rapidly rearranged to two new species that were simply isomeric to the original cycloadduct with respect to the cyclopentadiene double bond regiochemistry. The orientation of the two reaction partners in adduct (**72**) is consistent with the preferential bonding of the position with the highest orbital coefficient in the fulvene LUMO to the position with the highest orbital coefficient in the dipole HOMO. 6-Dimethylaminofulvene was observed to be totally inert when exposed to a nitrile ylide in an effort to induce a cycloaddition between the two reactants.[51] This lack of reactivity was attributed to a significant raising of the fulvene LUMO energy, resulting in a decreased frontier orbital interaction.



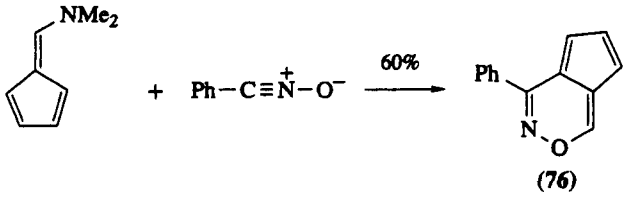
An interesting electron-rich 1,3-dipole, nitropyridyl betaine (**74**), smoothly cycloadded across positions 2 and 6 of 6,6-dimethyfulvene to generate the relatively unstable [6 + 4] cycloadduct. This labile intermediate experienced the now familiar 1,5-hydrogen shift to give the corresponding cyclopentadiene isomer (**75**) as the product which was, in fact, isolated from the reaction.[52] The reversed regioselectivity (the HOMO coefficient at the betaine C-2 was calculated to be slightly larger than at C-6) observed in this particular process has been rationalized in terms of attractive secondary orbital interactions.



(**74**) Ar = 5-NO_2-2-pyridyl (**75**)

A further illustration of the electronic influence of substituents on the course of reactions with 1,3-dipoles can be seen in the cycloaddition of an amino-substituted fulvene to benzonitrile oxide. Adduct (**76**) was obtained in 60% yield when the electron-rich dipolarophile 6-dimethylaminofulvene was exposed to benzonitrile oxide.[53] The structure of the resultant product can be conveniently explained by an initial [6

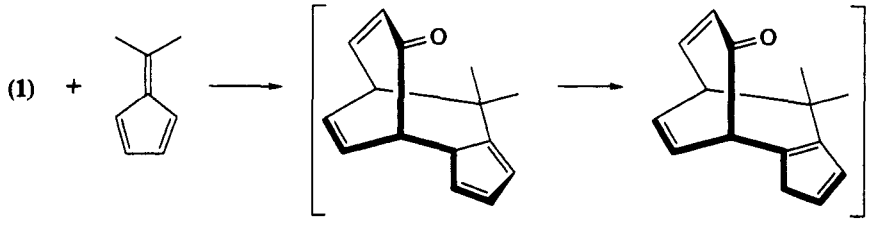
+ 4] cycloaddition followed by eliminative loss of dimethylamine. In contrast, benzonitrile oxide gave only products derived from various [4 + 2] cycloaddition processes when reacted with 6,6-dimethyl- and 6,6-diphenyl-fulvenes.[53]



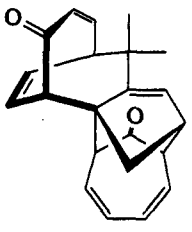
(76)

5.2.2.2.3 Tropone as the 4π addend

Among the earliest [6 + 4] reactions of fulvene to be studied involved tropone ostensibly participating as the 4π partner. Heating a solution of tropone and 6,6-dimethylfulvene in THF at 50 °C yielded the novel double [6 + 4] adduct (**77**) in up to 88% yield.[54,55] Performing the same reaction at room temperature provided relatively small quantities of several 1:1 adducts along with the 2:1 adduct (**77**) in 66% yield. Unfortunately, from a synthetic perspective, efforts to suppress the addition of the second molecule of tropone have met with limited success in this series. The primary course of this novel reaction was presumed to proceed *via* an initial [6 + 4] cycloaddition in which tropone participated as the 4π addend to give intermediate (**78**) which rapidly rearranged to the more stable cyclopentadiene isomer (**79**). This compound then experienced an apparently quite facile *exo* [6 + 4] cycloaddition with a second molecule of tropone to provide the isolated 'double' cycloadduct. When mono-substituted fulvenes were employed in this reaction, only the corresponding stereoisomer of the 2:1 adduct displaying the fulvene substituent oriented toward the three-carbon bridge of the tropone moiety was observed. This result was rationalized in terms of the fulvene addend approaching tropone so as to avoid unfavorable nonbonding interactions that were present during the production of the alternative stereoisomer.[56,57]



(78) (79)

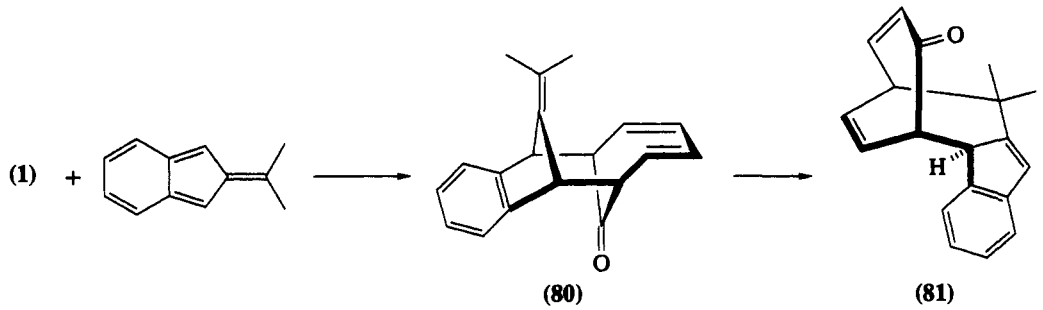


(77)

The steric consequences of substitutents at various locations on the tropone addend have also been described for this reaction. Substituents at the 2-position apparently provided sufficient steric hindrance to the approach of the fulvene addend that cycloaddition proceeded so as to completely avoid this center. Thus 2-chlorotropone gave cycloaddition products in which the chlorine substituent was always situated on the three-carbon bridge remote from the fulvene moiety in the initial [6 + 4] cycloadducts.[58] Furthermore, 2,7-dichlorotropone failed to cycloadd to substituted fulvenes under any conditions. From these results it is clear that steric hindrance plays a crucial role in determining the course of fulvene–tropone

cycloaddition much as it did in the corresponding cycloadditions of dienes to tropone (see Section 5.2.2.1.1).

Although many of the observed products from the [6 + 4] cycloaddition of tropone to various fulvenes can be explained by the concerted reaction of tropone as the 4π addend with fulvene participating as the 6π addend, an alternative mechanistic scheme for the production of species such as (**78**) and (**79**) can be envisioned. This pathway would necessitate the intervention of an *exo* [6 + 4] cycloadduct in which the fulvene behaved as the 4π addend. In this pathway, bond formation at the two termini of the tropone–triene system would initially occur across the C-2 and C-5 positions of the fulvene participant. Several reports have surfaced noting that some fulvene derivatives dimerize thermally in a [6 + 4] fashion in which one of the fulvene molecules reacts as a 4π species across the C-2 and C-5 positions, as required in this mechanistic scenario.[59,60] Subsequent, rapid 3,3-sigmatropic rearrangement of the thermodynamically unstable [6 + 4] adduct would deliver the products observed experimentally. The first substantive evidence for the operation of this alternative pathway in a cycloaddition was observed in the reaction of 8,8-dimethylisobenzofulvene with tropone in which the postulated [6 + 4] intermediate (**80**) was actually isolated.[61] This transient material rearranged rather rapidly to the final adduct (**81**) as required in the alternative mechanistic scheme. Other cycloadditions of substituted isobenzofulvenes have also been observed to proceed *via* the pathway depicted in Scheme 12.[62] Since the *exo* [6 + 4] tropone (6π)–fulvene (4π) adduct has not been observed to date in other examples of cycloadditions of tropone and substituted fulvenes, the question still remains open as to whether this intriguing tandem [6 + 4] cycloaddition–3,3-sigmatropic rearrangement process actually prevails in all fulvene–tropone cycloadditions.



(**80**) (**81**)

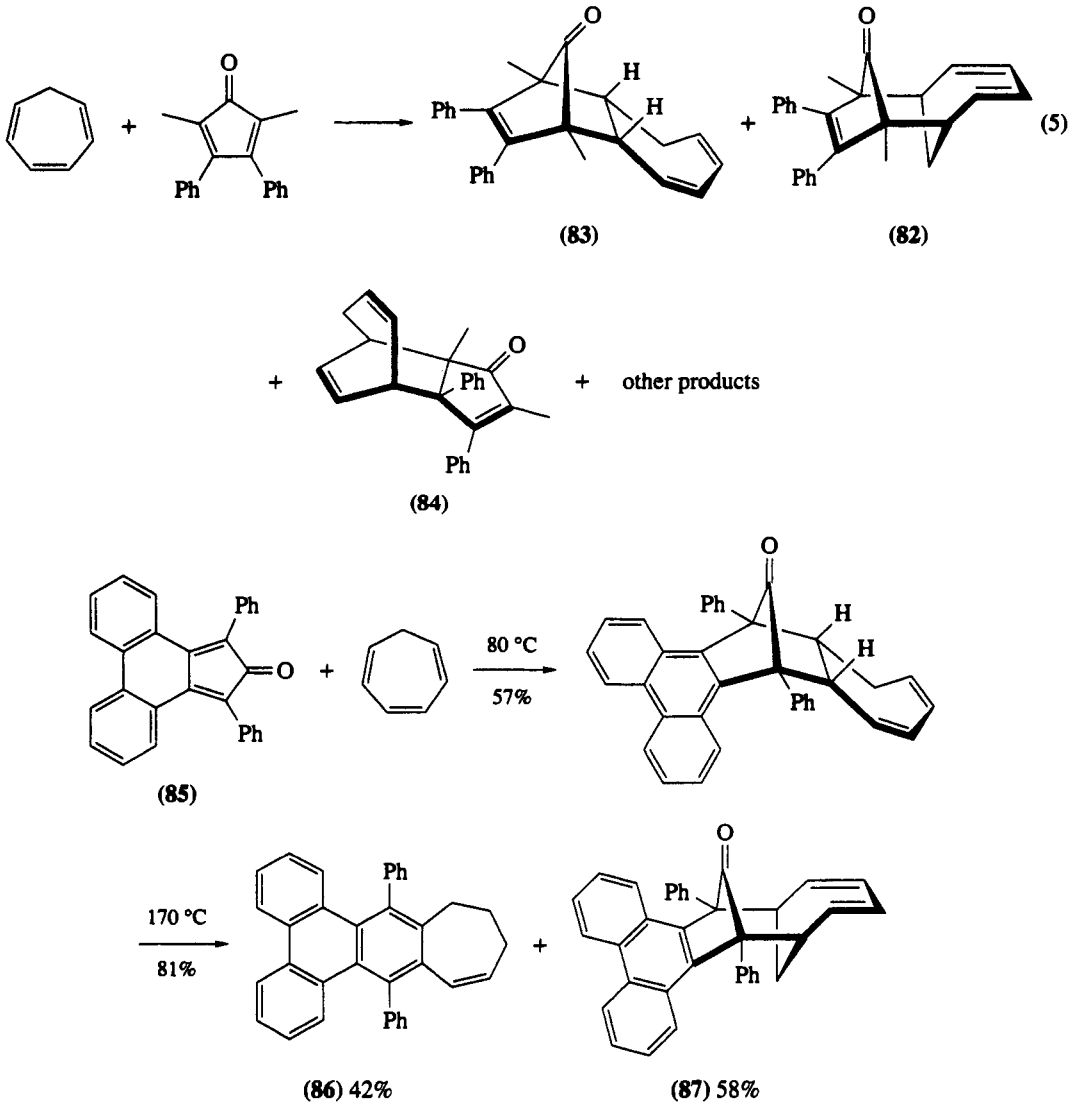
Scheme 12

5.2.2.3 Cyclic Trienes as 6π Addends

Cycloheptatriene and related heterocyclic analogs have been examined to some extent with regard to their reactivity with various conjugated diene partners. Characteristically, higher-order cycloaddition pathways often suffer relative to alternative modes of reaction in these systems and usually a select type of highly reactive diene partner is a prerequisite for viable cycloaddition to occur. Selectivity in these species can also be compromised by the intervention of the corresponding norcaradiene tautomer in certain circumstances. Modest periselectivity coupled with low chemical yields limit the potential synthetic utility of these cycloadditions.

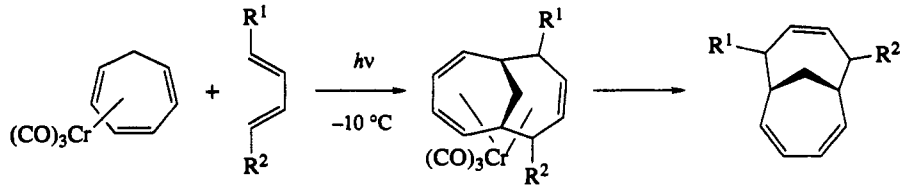
The reaction of cycloheptatriene with 2,5-dimethyl-3,4-diphenylcyclopentadienone is typical for this class of compounds, resulting in the formation of six distinct products.[63] Equation (5) displays the major products of interest, which include a modest quantity of the *exo* [6 + 4] adduct (**82**). The mechanistic details of this process were gleaned from monitoring an equimolar mixture of the two reactants maintained at 120 °C. This experiment revealed that both the [2 + 4] adduct (**83**) and the [6 + 4] adduct (**82**) were formed from the outset of the reaction. However, adduct (**83**) was subsequently converted quantitatively into the [4 + 2] cycloadduct (**84**) *via* a Cope rearrangement. This interconversion is reminiscent of a similar transformation in the tropone–diene series (see Section 5.2.2.1.1 and ref. 24).

The thermal cycloaddition of phencyclone (**85**) with cycloheptatriene offers additional mechanistic insight into these reactions (Scheme 13). In this case a 57% yield of the corresponding *endo* [2 + 4] adduct was isolated. Further pyrolysis of this material at 170 °C provided the decarbonylated pentacyclic material (**86**) along with an *exo* [6 + 4] adduct (**87**).[64] The course of this reaction can be contrasted with the thermolysis of compound (**83**). While neither of these examples is of great potential synthetic value, they do serve to illustrate some of the typical mechanistic themes which characterize these reactions.



Scheme 13

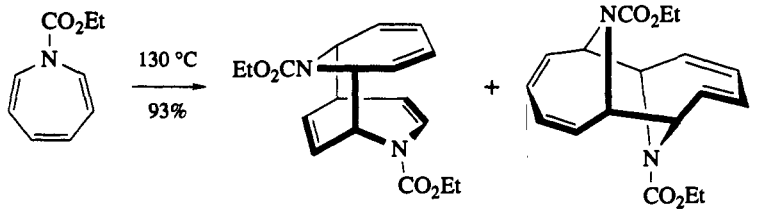
In dramatic contrast to the normal course of higher-order cycloadditions with most cyclic triene substrates, the photochemically induced [6 + 4] cycloaddition reactions exhibited by tricarbonyl(η-1,3,5-cycloheptatriene)chromium(0) complexes appear to be quite suitable for preparative applications. Yields of the resultant diene cycloadducts are usually good and the metal can be removed in high yield on treatment of the cycloadduct complex with triethylphosphine.[65–67] Scheme 14 shows the results of several cycloadditions between the complex and substituted diene addends. While not specifically delineated in the original work, these reactions provide the corresponding *endo* adducts exclusively.[67]



	(88)	(89)
R^1 = vinyl, R^2 = H	65%	63%
R^1 = Me, R^2 = CO_2Me	40%	85%

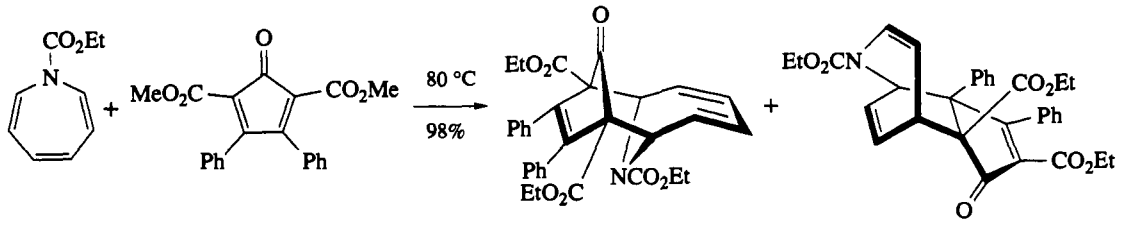
Scheme 14

The nitrogen and oxygen analogs of cycloheptatriene offer attractive potential 6π substrates for higher-order cycloadditions. Unfortunately, the reactions of these compounds with a variety of dienes usually result in low yields of [6 + 4] adducts. The mechanistic details of many of these processes are intriguing, however, and merit some attention. The dimerization of *N*-substituted azepines, for example, has provided numerous clues as to the actual pathways involved in these and related reactions.[68–70] Thermolysis of *N*-ethoxycarbonylazepine at 130 °C gave initially an *exo* [6 + 4] cycloadduct (**90**) and a small amount of a dimer ostensibly derived from a 'thermally forbidden' [6 + 6] cycloaddition process.[68] At 200 °C the azepine was converted into the [6 + 6] product in 83% yield. Apparently the [6 + 4] product isolated under milder conditions is an intermediate in the formation of the [6 + 6] dimerization product.

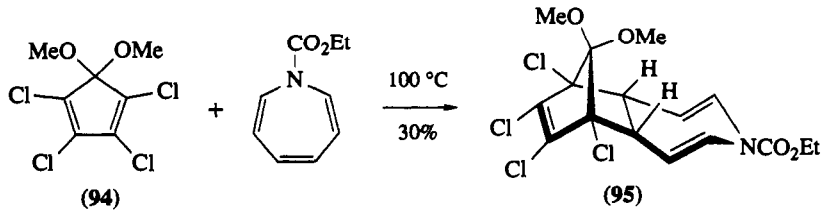


(**90**) 91% (**91**) 9%

A typical example of the reaction of *N*-ethoxycarbonylazepine with a reactive diene is illustrated by the addition of 2,5-dimethoxycarbonyl-3,4-diphenylcyclopentadienone. Heating a mixture of these reactants at 80 °C for several hours gave *exo* [6 + 4] adduct (**92**) and *endo* [4 + 2] adduct (**93**) in yields of 18% and 82%, respectively.[71,72] Alternatively, heating diene (**94**) in the presence of the same azepine gave only the [2 + 4] adduct (**95**).[73] Low-temperature examination of the cyclopentadienone reaction revealed the intervention of a cycloadduct similar in structure to compound (**95**), which rapidly led to the [4 + 2] adduct (**93**) *via* a facile 3,3-sigmatropic rearrangement.[71]



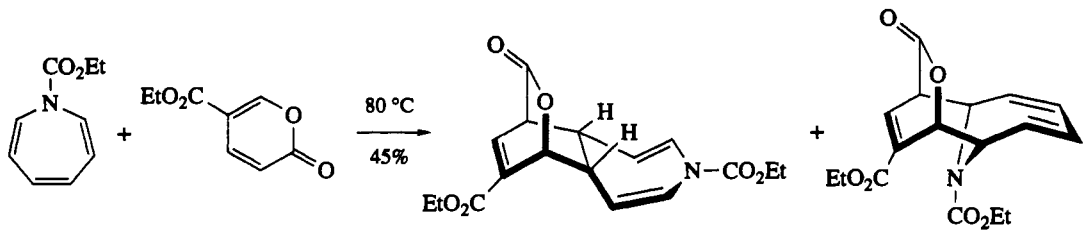
(**92**) 18% (**93**) 82%



(**94**) (**95**)

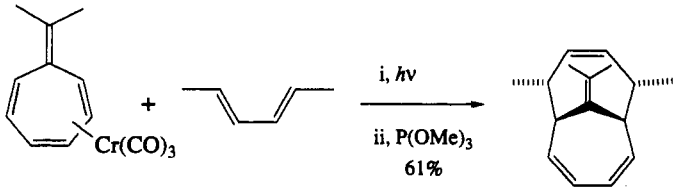
Heating *N*-ethoxycarbonylazepine with the electron-deficient diene (**96**) provided [2 + 4] adduct (**97**) and [6 + 4] adduct (**90**) in nearly equal quantities.[74] Other examples of relatively low conversion [6 + 4] cycloadditions of substituted azepines and various dienes have been reported but are of little synthetic consequence due to low periselectivity and modest chemical yields.[75,76] Oxepin heterocycles display a range of reactions with dienes which are similar in scope to the azepine series and, as such, will not be dealt with specifically in this review.[77–79] Other cyclic polyenes such as cyclooctatetraene are known to yield some [6 + 4] adducts when exposed to highly reactive diene species. For example, the potent electron-deficient diene 2,5-dimethoxycarbonyl-3,4-diphenylcyclopentadienone gives a modest amount of the corresponding [6 + 4] cycloadduct when reacted with cyclooctatetraene.[80,81]

In a very exciting series of studies, Kreiter and coworkers have established the viability of photochemically induced [6 + 4] cycloadditions of dienes to the chromium tricarbonyl complex of 8,8-dimethylheptafulvene.[82–84] These potentially useful transformations appear to be general with a wide range



(96) (97) 55% (98) 45%

of diene structures and, depending on the identity of the particular diene employed, proceed either through a direct cycloaddition pathway or alternatively *via* a novel π-allyl complex that subsequently collapses efficiently to the corresponding [6 + 4] adduct on addition of excess carbon monoxide. Decomplexation with trimethyl phosphite provided the free hydrocarbon product in good yields. In general, the peri- and stereo-selectivity of these reactions have been observed to be very high, making them particularly attractive for preparative applications. The stereochemistry of the resultant cycloadducts is derived from an *endo* approach of the diene to the complex. This selectivity is presumably a consequence of a metal–diene interaction prior to covalent bond formation. A typical cycloaddition using this chemistry is illustrated in the preparation of bicyclo[4.4.1]undecene (**100**). In this case the heptafulvene complex is photolyzed in the presence of (*E,E*)-2,4-hexadiene. The resulting cycloadduct is then liberated from the metal by decomplexation using trimethyl phosphite.[84] Table 1 displays the results of several cycloaddition reactions in this series. Clearly, this methodology offers numerous opportunities for preparative applications.



(99) (100)

Table 1 Photocycloadditions of Conjugated Dienes with Tricarbonyl[1–6-η-(8,8-dimethylheptafulvene)]chromium(0)[84]

Diene	*Yield of complex (%)*	*Yield of free cycloadduct (%)*
Butadiene	65	76
2,4-Pentadiene	73	85
2,4-Hexadiene	71	86
1,3-Cyclohexadiene	81	92
2-Methylbutadiene	56	90
4-Methyl-2,4-pentadiene	61	84

A number of interesting [6 + 4] cycloaddition processes involving ionic reactants have also surfaced recently. The bulk of examples reported to date involve charged heterocyclic systems with various reaction partners.[85–87]

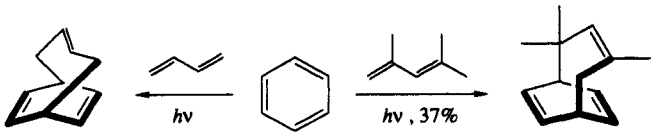
5.2.3 [4 + 4] CYCLOADDITION REACTIONS

5.2.3.1 Photocycloaddition Reactions of 1,3-Dienes and Arene Substrates

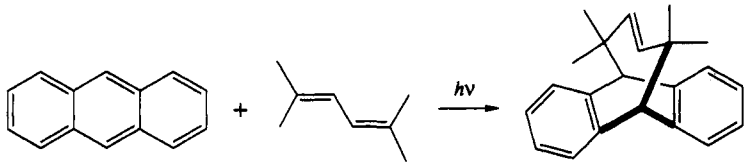
Reactions in which two 4π addends engage in a suprafacial cycloaddition process are generally photochemically allowed transformations.[3] The [4π + 4π] cycloaddition is an attractive strategy-level reaction from the perspective of the rapid construction of functionalized eight-membered carbocycles. The development of new methodology for eight-membered ring formation has been stimulated by the identification of numerous natural products of medicinal interest that display a cyclooctane ring as a prominent

structural feature.[88,89] [4 + 4] Cycloaddition-based strategies could play a significant role in this synthetic endeavor if appropriate protocols that proceed efficiently could be brought to bear on the problem. In practice, however, the photoinduced [4π + 4π] cycloaddition process is most frequently characterized by relatively low yields of adducts and by production of a plethora of different photoproducts. For example, the photoinduced intermolecular [4 + 4] cycloadditions of acyclic dienes in general provide low yields of cyclooctane products and are of little preparative value.[90] Competitive [2 + 2] processes prevail in these cases and in certain systems can be of considerable synthetic utility.[91]

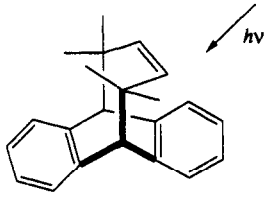
Photocycloaddition of dienes to benzene and most other arenes offer little respite from the low yields and complex product mixtures that plague the simple diene cycloadditions.[92,93] Typical of this genre of reaction is the photoaddition of butadiene to benzene which gives the corresponding *trans* cycloadduct (**101**) as the primary photoproduct in low yield. In an interesting contrast, the *cis* adduct (**102**) is a major product from the light-induced cycloaddition of benzene and 2,4-dimethyl-1,3-pentadiene. Based on these results, the ground-state conformation of the diene has been suggested as the controlling factor in determining the structure of the resultant adduct in these reactions.[94] Similarily, when anthracene was irradiated in the presence of 2,5-dimethyl-2,3-hexadiene, a metastable [4 + 4] adduct (**103**) exhibiting a *trans* double bond was initially isolated in 'high yield.' This compound was smoothly isomerized to the more stable *cis* isomer (**104**) by photosensitization. The observed stereospecificity of this cycloaddition is suggestive of a concerted process in which the diene participates in the *s-trans* conformation.[95] Cyclohexadiene also provides the corresponding [4 + 4] adduct in good yields.[95]



(**101**) (**102**)



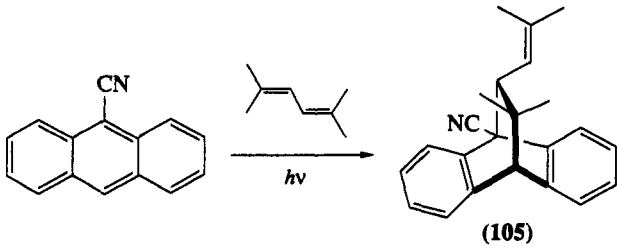
(**103**)



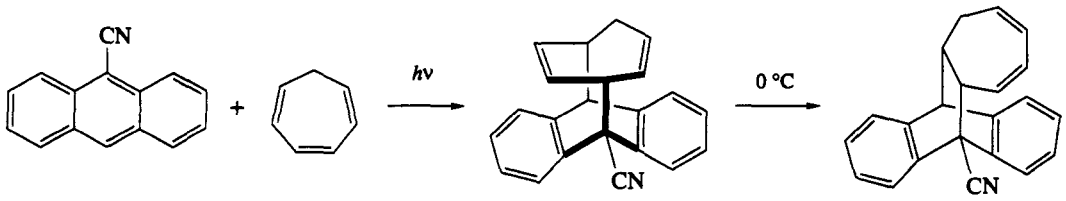
(**104**)

In contrast to the course of reaction with the parent anthracene, 2,5-dimethyl-2,4-hexadiene has been reported to yield chiefly the photochemically 'forbidden' [4 + 2] cycloadduct (**105**) when exposed to 9-cyanoanthracene.[96] The remarkable variability in periselectivity displayed by these systems has been rationalized in terms of the [arene*:1,3-diene] exciplex which is presumably involved in these transformations.[96,97] Polar exciplexes are described as leading to [4 + 2] products while less polar exciplexes are believed to be the precursors of [4 + 4] adducts. Of interest is the observation that cyclohexadiene provides principally the corresponding [4 + 4] adduct when reacted with both anthracene and 9-cyanoanthracene; thus it has been proposed that a less polar exciplex is involved in both of these reactions.[96]

Other results in this area point to an initial [4 + 4] cycloaddition step followed by a thermally or photochemically initiated rearrangement of the initial cycloadduct to give a '[4 + 2]' species as the final observed product. Irradiation of 9-cyanoanthracene and cycloheptatriene at low temperature initially produced the [4 + 4] adduct (**106**) which promptly rearranged to (**107**) at temperatures exceeding 0 °C.[98] Related diene–arene photocycloadditions have been reported in which comparable tandem processes were apparently operative.[99–101]

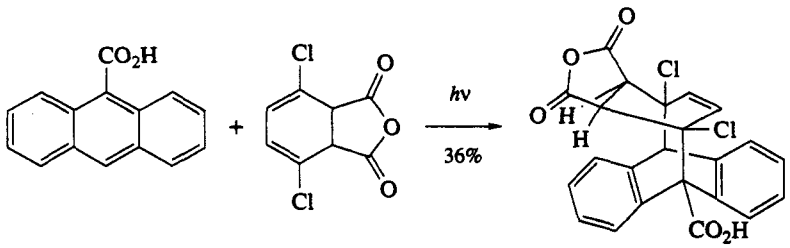


(105)



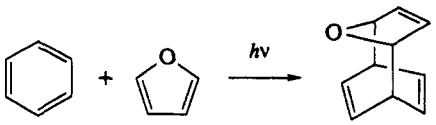
(106) (107)

A number of interesting studies have appeared in which somewhat more complex and highly substituted addends have been shown to participate in [4 + 4] photocycloadditions. As with the majority of [4 + 4] photocycloaddition reactions, the yields of adducts, *e.g.* (**108**), in these examples are, at best, modest.[102,103]



(108)

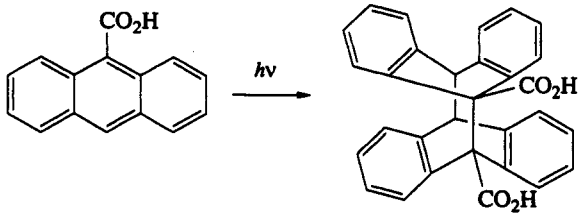
Photochemically excited arenes are also known to cycloadd to other aromatic species in a few cases. Furthermore, a growing body of literature attests to the relative ease of photoinduced dimerization of numerous aromatic species. Irradiation of benzene in furan as solvent provided cycloadduct (**109**) as the major isolable product.[104–106] The process was quite inefficient from a preparative perspective since a mixture of six products was formed during this reaction, of which (**109**) represented only 50% of this complex mixture.



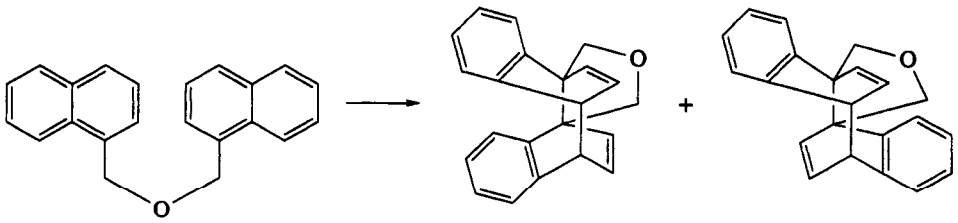
(109)

[4 + 4] Photodimers have been reported as the principal products from irradiation of numerous arene substrates.[107] While there is little selectivity to be considered in most of these reactions, it has been reported that almost all photolyses of 9-substituted anthracenes give head-to-head dimers as depicted in (**110**).[108] An intramolecular version of these photodimerizations has also been reported. Irradiation of di(α-2-naphthylmethyl) ether gave a mixture of the *endo* cyclomer (**111**) and the *exo* cyclomer (**112**).[109]

The photodimerization of 2-pyridones has been the subject of extensive investigation for a number of years.[110–114] In most instances the 'head-to-tail' or *trans-anti* isomer was the major or exclusive product in these reactions. Irradiation of *N*-methyl-2-pyridone for 15 h provided the *trans-anti* dimer (**113**) in 51% yield.[115] This material was accompanied by much smaller quantities of other dimeric species. Vari-

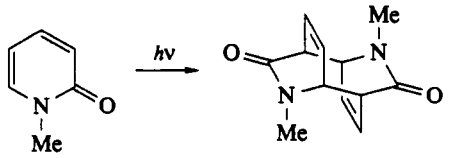


(110)



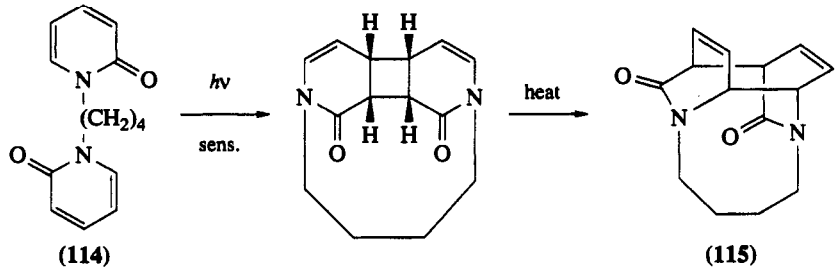
(111) (112)

ous substituted 2-pyrones have also been subjected to photoinduced dimerization and yield primarily the *trans* isomers as well.[116]



(113)

Intramolecular photodimerization of 2-pyridones provides a series of primary photoproducts, the structures of which were a function of the chain length connecting the two reactive centers.[117] The initially formed dimers were characterized as being derived from a photochemically allowed [2 + 2] cycloaddition process in each case examined. A particularly interesting example from this study in terms of [4 + 4] cycloaddition chemistry is the conversion of dipyridone (**114**) into the net [4 + 4] dimer (**115**) *via* a facile thermal rearrangement.[117] Further irradiation of the [4 + 4] species (**115**) produced a second [2 + 2] adduct that was isomeric with the initially formed metastable species.



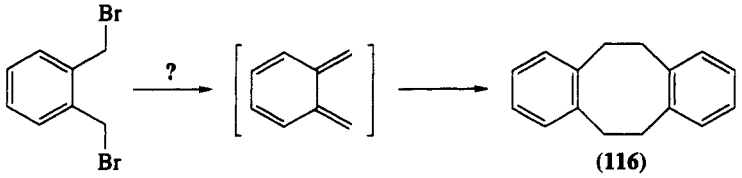
(114) (115)

Although a number of novel and mechanistically significant reactions have been reported in the area of polyene photocycloaddition, the inefficiency of these processes generally precludes their use for preparative applications.

5.2.3.2 Dimerization of *o*-Xylylene and 2,3-Dimethylenefurans

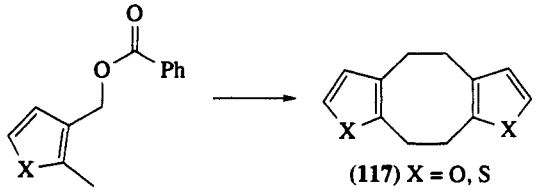
Ultrasound has been employed to promote the formation of *o*-xylylene from the reaction of zinc metal with α,α′-dibromo-*o*-xylene.[118] In the absence of reactive dienophiles, the transient diene produced in

this reaction dimerizes to generate the 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctadiene (**116**) in 5% yield. Dimer (**116**) can be produced in 80% yield from the same dibromide when it is treated with lithium and exposed to sonication. No [4 + 2] cycloadducts were observed in this reaction when it was performed in the presence of relatively reactive dienophiles, suggesting that *o*-xylylene is not an intermediate in the dimerization process.[119]



(**116**)

Similar [4 + 4] dimers have been reported during the flash vacuum pyrolysis of 2-methyl-3-furylmethyl benzoate in which 4*H*,5*H*,9*H*,10*H*-cycloocta[1,2-*b*:6,5-*b'*]difuran (**117**) is produced in virtually quantative yield.[120] A stepwise mechanism has been forwarded to rationalize the high-yield formation of the corresponding head-to-head [4 + 4] dimer.[121] Other examples of the [4 + 4] dimerization of 2,3-dimethylene furan[122] and 2,3-dimethylene thiophene[123] have been reported as well.



(**117**) X = O, S

It is apparent that these types of [4 + 4] dimerization, while normally high-yielding processes, are of limited potential for application to complex synthetic problems.

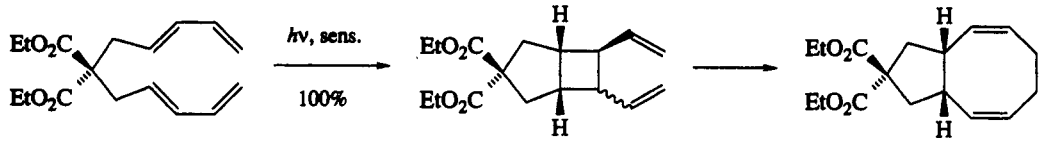
5.2.3.3 Applications of 'Indirect' [4 + 4] Cycloadditions to Synthesis

Direct application of [4 + 4] cycloaddition chemistry to problems in natural product synthesis is rare due to the general inefficiency of these processes. However, several variations on the theme of direct [4 + 4] cycloaddition have been developed and will be considered in this section.

As alluded to in Section 5.2.3.1, the intermolecular photoinduced [2π + 2π] cycloaddition of dienes is an efficient reaction in only a relatively few instances.[91] However, many of the liabilities normally associated with the intermolecular cycloaddition process can, in principle, be circumvented by employing the intramolecular version of the coupling. The requisite eight-membered ring could then be accessed from thermal rearrangement of the resultant divinylcyclobutane photoproduct.[124]

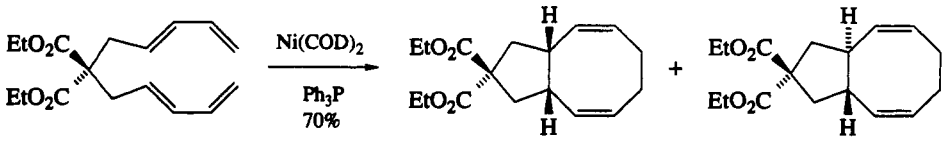
Wender and Correia have brought this concept to practice by tethering two 1,3-diene units together with a three-carbon chain.[125] Sensitized irradiation of the resultant tetraene provided a quantitative yield of two *cis*-fused bicyclo[3.2.0]heptane products that were isomeric with respect to the relative spatial disposition of the two vinyl side-chains. Thermolysis of the *cis*-divinylcyclobutane isomer at 130 °C for several hours gave a quantitative conversion to *cis*-cyclooctadiene (**118**). The *trans*-divinylcyclobutane, which proved to be more reluctant to rearrange, required higher temperatures (200 °C) and longer reaction times to give (**118**) as the major product. A modest quantity of a six-membered ring rearrangement product accompanied cyclooctadiene formation in this case. This reaction sequence was shown to be both versatile and general in scope. Tetraene analogs displaying heteroatom tethers, four-carbon connecting chains and functionalization all gave the corresponding products in good yields. Furthermore, the sequence has been employed as the key ring-forming step in a formal total synthesis of the antitumor and antibiotic triquinane coriolin.

In an extension of the indirect intramolecular [4 + 4] cycloaddition concept, Wender and coworkers have also developed a very powerful Ni^0 catalyzed cyclodimerization variant which is quite efficient at delivering cyclooctadiene products.[126] Exposure of the appropriate tetraene to catalytic amounts of Ni^0 in the presence of Ph_3P at 60 °C gave a mixture of two cyclooctadienes (**119**) and (**120**) in 70% total yield. In this instance the *cis*-fused isomer (**119**) prevailed in a ratio of 19:1 over the corresponding *trans* material. The proclivity for formation of the *cis*-cyclooctadiene, the result of a formal *endo* addition, was a

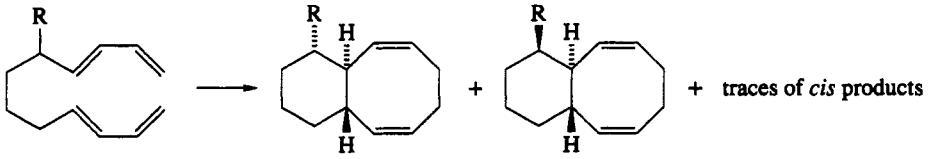


Scheme 15

general phenomenon for tetraenes joined by a three-carbon chain. It is clear that the overall process described here, while formally a [4 + 4] cycloaddition reaction, proceeds mechanistically through a series of intermediates.[127]



A particularly significant aspect of this reaction is the level of stereoinduction observed when certain substituents were appended to the carbon tether. When tetraene (**121**; R = CO_2Me) was treated with the standard $Ni(COD)_2/Ph_3P$ catalyst, cyclization proceeded smoothly to give (**122**; R = CO_2Me) in 84% yield along with a small amount of (**123**) and traces of *cis*-fused products. The equatorially substituted diastereomer (**122**) was formed with a preference of ≥70:1 over epimer (**123**), which exhibited an axially oriented methoxycarbonyl group. The *exo*/*endo* selectivity of the reaction was established as >95:5, now favoring formation of the *trans*-fused ring system. In contrast to the three-carbon analog, dienes connected by a four-carbon tether were found to display a high selectivity for formation of the *trans*-fused product.



(**121**) (**122**) (**123**)

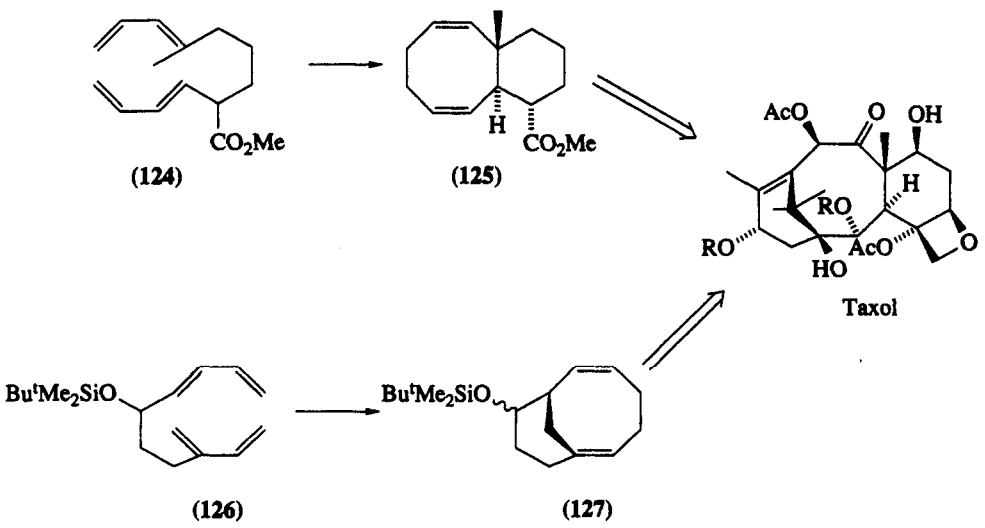
A number of different substituents (R) were positioned on tetraene (**121**) to evaluate the origins of the remarkable level of diastereoselection observed in these reactions. Table 2 summarizes the results of this study. The small cyano group had only a minor stereoinductive effect while the bulkier, noncomplexing methyl group showed a more pronounced effect. The influence of the acetoxymethyl group was essentially identical to the methyl group despite the possibility of coordination. Thus, it was concluded that the diastereoinduction observed was predominently steric in origin.[128]

Table 2 Substitutent Effects on the Diastereoselectivity of the Nickel(0) Catalyzed Intramolecular [4 + 4] Cycloaddition of (**121**)[128]

Substitutent (R)	*Yield (%)*	*Ratio (eq:ax)*
CN	66	1.5:1
Me	88	20:1
CH_2OAc	92	21:1
CO_2Me	84	≥70:1

The nickel-catalyzed intramolecular [4 + 4] cycloaddition strategy has been successfully applied to the construction of both the AB and BC ring systems of the taxane diterpenes.[129] These studies additionally served to establish the viability of this chemistry for the construction of angularly alkyl-substituted bicyclo[6.4.0]dodecanes. In an example typical of this class of transformations (Scheme 16), cyclooctadiene (**125**) was produced with greater than 97% diastereoselectivity and in 92% chemical yield when tetraene

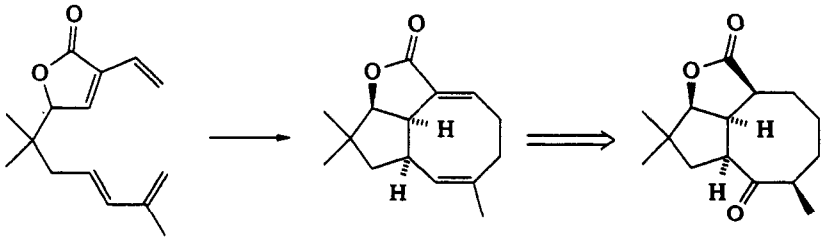
(**124**) was subjected to the standard Ni^0 cyclodimerization conditions. The complementary strategy for construction of the AB taxane ring system proceeded somewhat less effectively to give adduct (**127**) in 52% yield as a 1.3:1 mixture of *t*-butyldimethylsilyloxy epimers. Merging of these two sequences could, in principle, provide rapid entry into the taxane skeleton itself in a very efficient fashion.



(**124**) (**125**) (**126**) (**127**)

Scheme 16

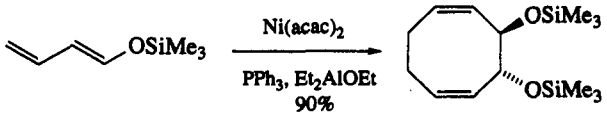
The nickel-mediated [4 + 4] cycloaddition strategy has also provided a concise and stereocontrolled route into the sequiterpene lactone (+)-asteriscanolide (**128**).[130] The basic features of this approach are outlined in Scheme 17. The critical [4 + 4] cycloaddition step occurred under standard conditions to give the key intermediate in 67% yield. Clearly, the intramolecular version of the nickel-catalyzed diene cyclodimerization has been established as a powerful and highly-selective protocol for the synthesis of cyclooctane ring systems and should find extensive application to natural product synthesis.



(**128**)

Scheme 17

The corresponding intermolecular nickel-catalyzed [4 + 4] cyclodimerization has not proven to be a useful synthetic tool, due primarily to low selectivities with unsymmetrical dienes and the general inefficiency of the reaction with dienes more complex than butadiene.[131,132] Several exceptions to this generalization do exist, however, as exemplified by the regio- and stereo-selective cyclodimerization of 1-trimethylsilyloxybutadiene in equation (6).[133,134] The presence of a substituent at the terminus of the diene is critical to the success of this reaction. However, 1,4-disubstitution on the diene completely suppresses the reaction. Methyl sorbate, for example, is recovered intact when exposed to the *in situ* generated Ni^0 catalyst used in these reactions. These few examples notwithstanding, it is clear that the intramolecular version of this coupling holds the most promise as a general synthetic method.



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5.3
[3 + 2] and [5 + 2] Arene–Alkene Photocycloadditions

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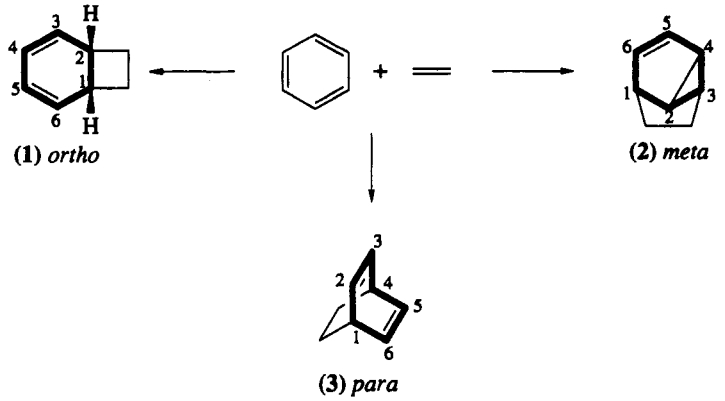
5.3.1 INTRODUCTION

Arene–alkene cycloadditions (Scheme 1) are among the most theoretically intriguing and synthetically promising recent discoveries in organic chemistry, providing particularly efficient synthetic access to a range of natural and non-natural compounds from simple, readily available precursors.[1] Reflecting their enormous versatility and their consequent designation in this series as higher order cycloadditions, these reactions have the unique capability of producing from three- to nine-membered rings through [2C + 2C], [3C + 2C], [4C + 2C], [5C + 2C], [6C + 2C], [4C + 3C], [4C + 4C] and [5C + 4C] conjunctions of arenes with various π-systems. In this chapter, an overview of this fascinating class of reactions will be



(1) *ortho* (2) *meta*

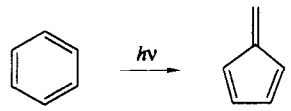
(3) *para*

Scheme 1

presented. In accord with the goals and focus of this series, emphasis will be placed on developments of the last decade and on the unique role of these reactions in organic synthesis. Primary attention will be given to the *meta* cycloaddition reaction due to its more extensive development and use in synthesis. As a consequence of the inexorable relationship between synthesis and mechanism, this treatment will start with a brief historical perspective and mechanistic analysis.

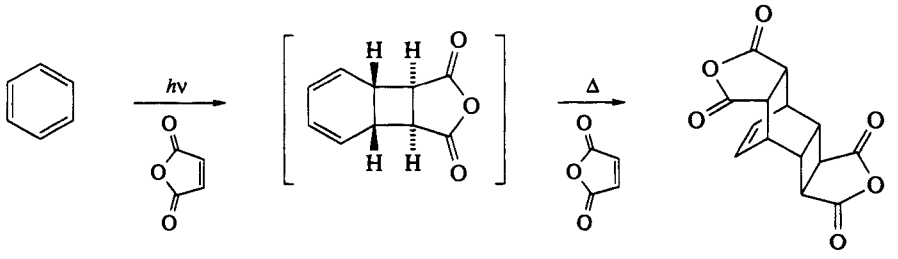
5.3.2 HISTORICAL PERSPECTIVE

The genesis of contemporary arene–alkene photochemistry is marked in large measure by the 1957 publication of Bryce-Smith and Blair[2] in which irradiation of benzene is reported to give fulvene (equation 1). Serving to dispel the long-held view that benzene and its derivatives are photochemically inert, this finding did much to attract further interest to this unexplored field, leading in turn to the discovery of new rearrangement processes[3] and eventually the arene–alkene cycloadditions.



(1)

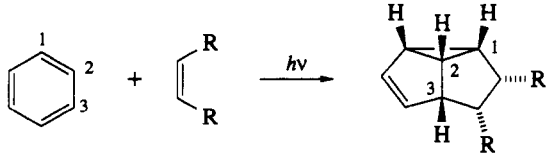
Of particular note in these early studies is the work of Bryce-Smith and Angus,[4] in which an attempt was made to trap the fulvene produced during the irradiation of benzene by conducting the reaction in the presence of a powerful dienophile, maleic anhydride. Instead of the expected Diels–Alder cycloadduct of fulvene, this reaction (equation 2) was found to yield a novel 2:1 adduct (**5**), which was subsequently shown[5] to form through initial photocycloaddition of maleic anhydride to the 1,2- or *ortho*-related positions of benzene, giving cycloadduct (**4**), which then provides (**5**) through a Diels–Alder cycloaddition. Analogous results were subsequently reported for the photo-mediated reactions of other dienophiles with benzene.[6] Contemporaneous work in the Büchi group[7] demonstrated that benzene derivatives are also capable of cycloaddition to alkenes. These seminal contributions, along with later reports from these and other investigators, served to illustrate the generality of the 1,2- or *ortho*-cycloaddition reaction and seeded the field for an even richer harvest.



(2)

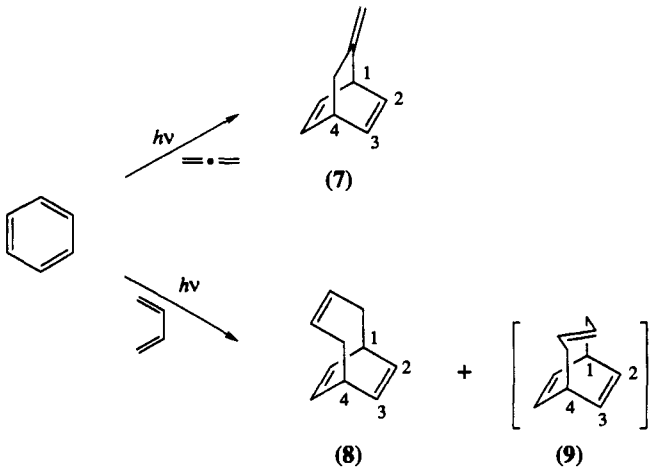
(4) (5)

Stimulated by these early discoveries, interest in the photochemistry of other arene–alkene systems grew rapidly, leading in 1966 to the co-discovery by Wilzbach and Kaplan[8] and by Bryce-Smith, Gilbert and Orger[9] of a second type of cycloaddition, involving bonding of an alkene to the 1,3- or *meta*-related positions of an arene (equation 3). Shortly thereafter, the first examples of a third type of cycloaddition were reported,[10] involving bonding of dienes and allenes to the 1,4- or *para*-related positions of the original arene ring (equation 4).



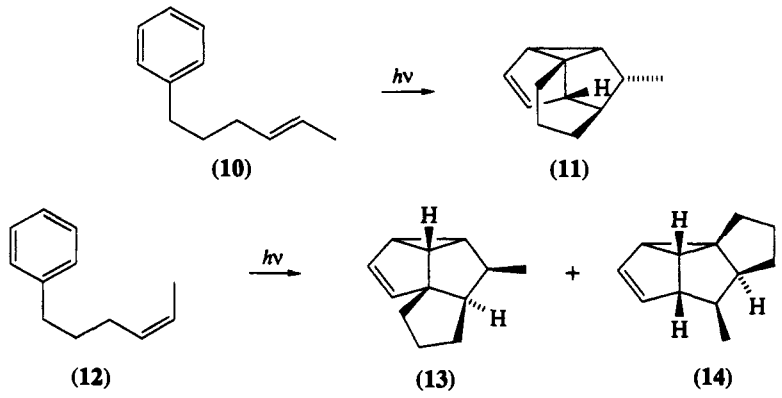
(3)

(6)



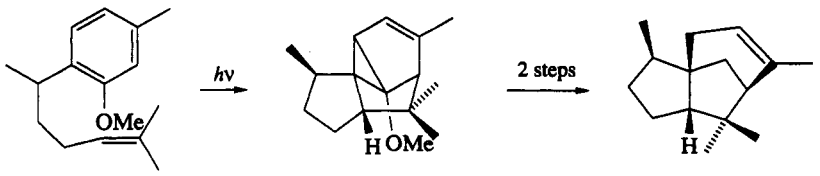
(4)

Following this exciting period of rapid discovery, investigations of arene–alkene cycloadditions focused more heavily on their scope and mechanism(s). Bryce-Smith and Longuet-Higgins[1f,11] were the first to present a theoretical treatment, providing an orbital symmetry analysis of the three types of cycloaddition. In connection with the possible role of charge transfer in these reactions, a mnemonic was introduced later by Bryce-Smith and Gilbert[12] for predicting the type of reaction an arene–alkene pair will undergo, based on the difference in their ionization potentials. In 1969, Morrison and Ferree[13] reported the first examples of an intramolecular arene–alkene cycloaddition (equation 5), discovered in the course of their exciting studies on bichromophoric compounds. Subsequent studies by the groups of Morrison,[1h] Srinivasan[14] and Yang[10c] implicated an exciplex intermediate in the cycloaddition process. More recently, Mattay and coworkers[1m–p] have provided direct spectroscopic evidence supporting such an intermediate, at least for some arene–alkene cycloadditions. Further studies in the 1970s, particularly by the Reading group and by Srinivasan and coworkers, served to test and refine previous mechanistic proposals, thereby substantially extending the generality of these reactions.[1a–f]



(5)

In 1981, Wender and Howbert[15] reported the first application of an arene–alkene cycloaddition in complex molecule synthesis. Heralding the spectacular synthetic efficacy offered by these reactions, this report provided a general protocol for the use of the *meta* cycloaddition in total synthesis, demonstrating its merit in a four-step total synthesis of (±)-cedrene (**17**; equation 6). In 1982, Houk[16] developed a significant extension of earlier mechanistic analyses based on a frontier molecular orbital treatment. Providing through calculations a better description of the energies of interacting orbitals than that derived from ionization potential differences alone, this treatment added a much-needed enhancement of predictive capability to the rapidly growing field. Efforts by the Sheridan group[17] on another aspect of these cycloadditions served for the first time to provide much needed information on the intermediacy of a diradical species in the latter stage of the *meta* cycloaddition. Concurrent experimental studies, highlighted in particular by the contributions of the Cornelisse group,[18] suggested that in the early stages of this process considerable charge transfer occurs between the arene and alkene. In recent years the Cornelisse[19] and Mattay[1m–p] groups have independently and collaboratively provided a rather impressive and appealing



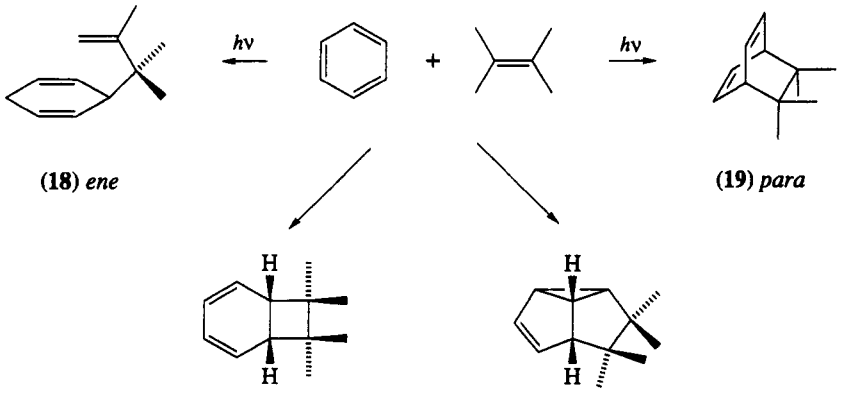
(6)

(15) (16) (17) Cedrene

general mechanistic treatment of the arene–alkene cycloadditions. Thus in a period of three decades the chemical community has witnessed the evolution of a new class of reactions, from an admittedly 'strange process'[1e] to one which is becoming better understood mechanistically and which has proven to be exceedingly effective for complex molecule synthesis.[1i,j,r]

5.3.3 MECHANISTIC CONSIDERATIONS

When an arene is irradiated in the presence of an alkene a number of processes can take place, including exciplex formation, excitation transfer, isomerization, addition, and cycloaddition. Of these, the pathways involving covalent association of the arene and alkene can lead to ene addition products as well as *ortho*, *meta* and *para* cycloadducts (equation 7).



(7)

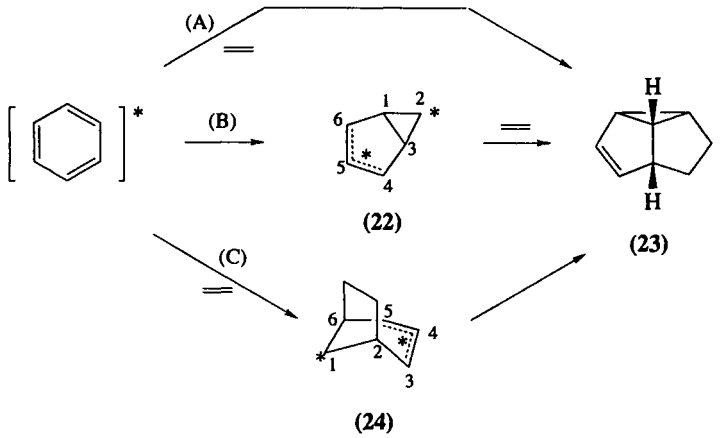
(18) *ene* (19) *para*

(20) *ortho* (21) *meta*

As noted above, Bryce-Smith and Longuet-Higgins[11,20] were the first to provide a theoretical treatment of these reactions. Using orbital symmetry arguments, they proposed that *ortho* and *para* cycloadditions of alkenes to benzene (and by analogy other arenes) are forbidden from the $^1B_{2u}$ (S_1) state, unless charge transfer is involved. *Meta* cycloadditions are considered to be allowed from this state with or without charge transfer. In a sequel to this contribution, which elaborated the charge transfer aspect of this analysis, attention was drawn to the relationship of the ionization potential difference (ΔI.P.) between the arene and alkene and the relative quantum efficiencies for their *meta* and *ortho* cycloadditions.[12] It was noted that reactions of benzene (I.P. = 9.24 eV) with alkenes having I.P.'s between 8.6 and 9.6 eV proceed generally with *meta*-mode selectivity. In contrast, when the ΔI.P. difference between the arene and alkene is greater than 0.6 eV, a situation which would favor charge transfer, *ortho* cycloaddition is preferred. While exceptions to these 'rules' have been noted,[1m–p] this analysis provided a much-needed organization of the field and the basis for further theoretical developments. As revealed in these subsequent studies, the main limitation of the ionization potential analysis rests on the fact that it is based solely on the energies of filled orbitals. The energies of unoccupied orbitals, derivable from electron affinity data, are not included even though they would figure in charge transfer interactions. These limitations were subsequently addressed by other workers and in a particularly effective fashion by Mattay.[1m–p]

While the orbital symmetry analysis of the arene–alkene cycloadditions addresses their 'allowedness', it does not specify a sequence for bond formation. It was recognized, however, that these cycloadditions could proceed stepwise and that in the specific case of the *meta* cycloaddition, three temporally distinct pathways are possible (Scheme 2): (a) a fully concerted path (A) where all bonds are formed simulta-

neously; (b) cyclization of the arene (B) to a prefulvene species (**22**), followed by addition of the alkene to carbons 2 and 4 (or 6) of this intermediate; and (c) complexation of the alkene to the excited arene (exciplex formation) or excitation of a ground-state complex, followed by bonding of the alkene to the *meta*-related carbons of the arene, and subsequent cyclopropane formation (C). Of these possibilities, the concerted process (A) has received little attention, in part because the extensive bond reorganization and nuclear motion is considered to be unlikely. This pathway also does not allow a simple rationalization of the regioselectivity observed in the cycloaddition. The prefulvene mechanism (B), on the other hand, was strongly favored in some early and even more recent discussions.[1f] Support for this mechanism was not unreasonably encouraged by the observation that while irradiation of arenes alone gives fulvenes, a *meta* cycloadduct is obtained when the same reaction is conducted in the presence of an alkene. Both results are in accord with the intermediacy of a prefulvene (**22**). However, as additional information on this reaction was obtained, it became increasingly apparent that its selectivity, particularly regioselectivity, could not be explained by a prefulvene intermediate. Deuterium labelling studies also revealed that bond formation between the arene and alkene occurs much in advance of cyclopropane bond formation,[18] which is opposite to what would be expected for a prefulvene mechanism. Finally, while not emphasized in these earlier discussions, it is also apparent that the addition of an alkene to a prefulvene would require bond formation to the sterically less-accessible concave face of the prefulvene.

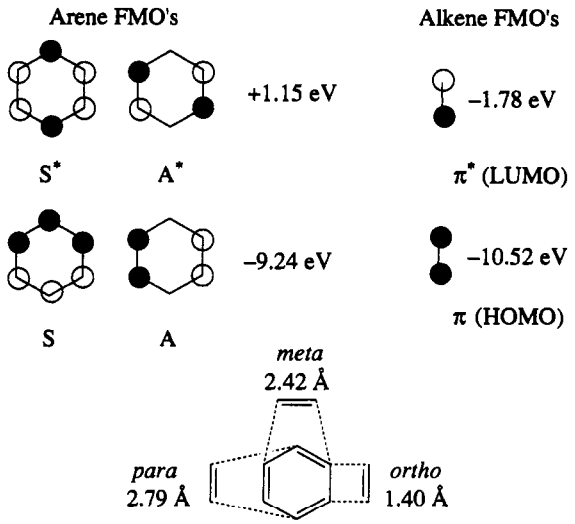


Scheme 2

Support for the third mechanism, the exciplex pathway (C), came initially from the studies of Morrison[1h] and of Srinivasan.[14] Morrison was able to show that quenching of the intramolecular cycloaddition of 6-phenyl-2-hexene is only about one-half as efficient as fluorescence quenching for this substrate, a result consistent with a short-lived, unquenchable cycloaddition precursor. While less direct, the stereoselectivities observed by Srinivasan[14,21] in studies on anisole derivatives are also interpretable in terms of an exciplex intermediate. Extensive studies by Cornelisse and coworkers[18,22] on substituent effects also suggest that the arene is already polarized at the stage when bond formation to the alkene begins, as would be expected for an exciplex involving charge transfer. More recently, Mattay[1m–p] has reported the observation of long-wavelength emission attributable to an exciplex and additionally has found that quenching of this emission and of product formation have identical rate constants.

In 1982, Houk[16] provided a frontier molecular orbital analysis for rationalizing the partitioning between *ortho*, *meta* and *para* modes of cycloaddition. In this treatment the HOMO and LUMO energies of the alkene were explicitly considered along with the energies of the singly occupied molecular orbitals (SOMO) of the excited arene. For the simple case of benzene and ethylene the relevant electronic configurations and their energies are given in Scheme 3. The actual orbitals for benzene are combinations of these; the lowest excited singlet is $^1B_{2u}$ (SA*–AS*). Consideration of the symmetry-determined mixing of these frontier molecular orbitals indicates that the ethylene HOMO can mix with the benzene S orbital to stabilize a *meta* cycloaddition and with the benzene A orbital to stabilize an *ortho* cycloaddition. Alkene interaction with A* is possible for both *ortho* and *meta* modes of cycloaddition.

Interactions leading to *para* cycloaddition (S + ethylene LUMO) are only weakly stabilized. *Para* cycloadditions are also disfavored by the distance-determined (2.79 Å) poor overlap between interacting orbitals of the arene with those of the alkene. From this analysis it is predicted that an *ortho* mode of cycloaddition will be favored for an arene AS* transition while *ortho* but preferentially *meta* cycloaddition will be stabilized in the SA* transition. In addition to symmetry considerations, the effectiveness of the



Scheme 3

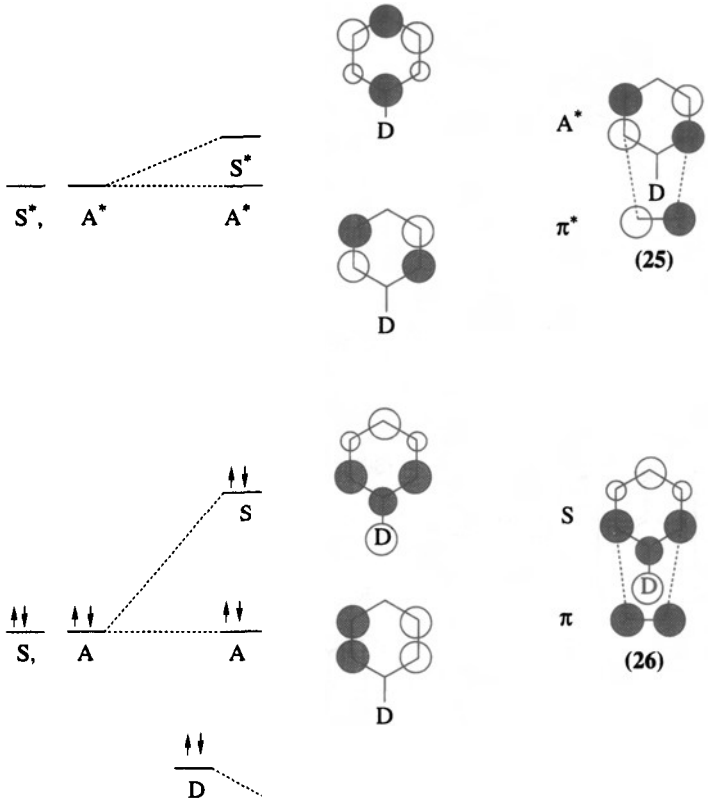
indicated mixings are also related to the relative energies of the interacting orbitals. In order to obtain these energies, calculations at the STO-3G level (GAUSSIAN 82 program) were performed for the case of benzene and ethylene, fixed in parallel planes and separated by 2.5 Å (*i.e.* in a reasonable approximation of the exciplex).[23] The results indicate that the *meta* approach is favored slightly over the *ortho* approach (−1.32 *vs.* −1.25 eV, respectively), in agreement with experimental observations.[24]

In the case of donor-substituted arenes, this FMO analysis indicates that *meta* cycloaddition is favored over the *ortho* mode due to the preferential stabilization of the SA* transition (Scheme 4). This mode selectivity is indeed observed in numerous cycloadditions involving simple alkenes and alkoxy- or alkyl-substituted arenes.[1q] However, as the difference in energy between interacting orbitals is increased due to substituent effects, charge transfer becomes more important. In such cases, both *ortho* and *meta* modes of cycloaddition are possible but the former is usually preferred on the basis of its better orbital overlap.

FMO analysis further indicates that the magnitude of the coefficients of the interacting orbitals determines the regioselectivity of a cycloaddition. Thus for *meta* cycloadditions the increased size of the *ortho* coefficients relative to the *meta* in the S orbital of the arene leads to the expectation that the alkene will add across the donor group, *i.e.* to positions 2 and 6 or *ortho* and *ortho'* related to the donor-bearing atom (**25**, **26**; Scheme 4). The regioselectivity of the *ortho* and *para* cycloadditions can also be deduced through a similar analysis of orbital coefficients. Finally, the *exo*/*endo* selectivities of the *meta* and *ortho* cycloadditions are also rationalized in the FMO treatment by secondary orbital interactions. The *endo* selectivity observed in many *meta* cycloadditions is thus attributed to stabilizing secondary orbital interactions arising from mixing of the S and A* arene orbitals with the HOMO and LUMO orbitals of the alkene. The frequently observed *exo* selectivity of *ortho* cycloadditions is similarly treated by interaction between the arene S orbital and the alkene HOMO.

Recognizing the limitations of previous treatments, Mattay[1m–p] recently reported an analysis of arene–alkene cycloadditions which is noteworthy in its capacity to accommodate the observed polarization and steric effects and data supporting an exciplex intermediate. In this treatment, an empirical 'rule', derived from a correlation of reaction selectivity and the degree of excited state charge transfer,[25] is used to predict reaction mode selectivity for a wide range of arene–alkene reactions. The degree of excited-state charge transfer is estimated in this analysis from the free enthalpy of electron transfer (ΔG_{ET}), which in turn is calculated, using the Rehm–Weller equation (equation 8),[26] from the oxidation potential of the donor (D), the reduction potential of the acceptor (A), and the excitation energy of the reactant excited state. When ΔG_{ET} is negative or nearly zero, addition is expected to predominate over cycloaddition, as is indeed observed in the reactions of certain electron-rich alkenes with excited-state arenes. When ΔG_{ET} is positive, cycloaddition is expected, with *ortho* cycloaddition favored for values up to approximately 1.4–1.6 eV and *meta* cycloaddition is favored for more positive values.[19]

In 1987, Cornelisse and coworkers[19] reported a semi-empirical calculation for the *meta* cycloaddition of benzene with ethylene, which impressively consolidates many experimental aspects of this reaction and fits well with the Mattay analysis. This calculation, performed at the CNDO/S and MNDO levels, supports an exciplex mechanism with charge polarization, in accord with Mattay's treatment and a related mechanism developed earlier in the Cornelisse laboratories.[22] According to this mechanism (equa-



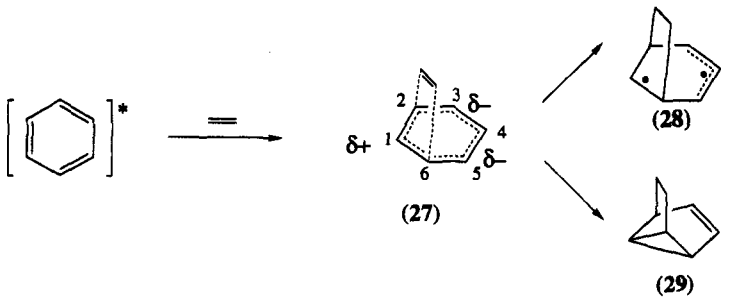
Scheme 4

$$\Delta G_{ET} = F\left[E^{Ox}_{1/2}(D) - E^{Red}_{1/2}(A)\right] - \Delta E_{excit} + \frac{e^2N}{4\pi\varepsilon_0 a}\left[\frac{1}{\varepsilon} - \frac{2}{37.5}\right] \quad (8)$$

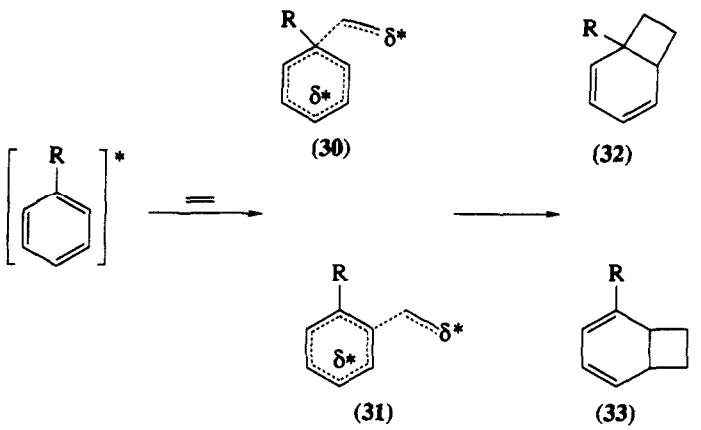
where $E^{Ox}_{1/2}(D)$ and $E^{Red}_{1/2}(A)$ = oxidation (reduction) potential of the donor (acceptor) molecule in acetonitrile; E_{excit} = excitation energy; F = 96490 Coulomb;

tion 9a), bonding between the arene and alkene precedes cyclopropane bond formation and occurs with appreciable polarization (see **27**) in the early stage of the reaction. As will be discussed shortly, this polarization effect allows one to rationalize the regio and *exo/endo* stereoselectivities of the *meta* cycloaddition. Importantly, the calculations further indicate that as the reaction proceeds, dipolar character dissipates and the system evolves along the reaction coordinate toward the cycloadduct (**29**) directly or through a nonpolar diradical (**28**) which then undergoes cyclopropane formation to provide the cycloadduct. Such a polarization–depolarization pathway explains the solvent and the deuterium-isotope effects associated with the reaction. It also can be used to rationalize the regiochemistry for at least the *meta* cycloaddition, since association of the arene and alkene would be expected to proceed in a fashion in which charge is stabilized by the arene substituents. This treatment also accommodates the intermediacy of a diradical species which has been implicated by several studies. Of particular note on this point are the impressive investigations of the Sheridan group (equation 10),[17] in which irradiation of either diazoalkene (**34**) or (**36**) is found to give the same product ratio as that observed in the direct irradiation of *m*-xylene (**37**) with cyclopentene. That such diradical species have never been observed in *meta* cycloadditions can be attributed to the large energy difference (22.9 kcal mol^{-1}), but the small energy barrier (7.5 kcal mol^{-1}) between the diradical and the cycloadduct.

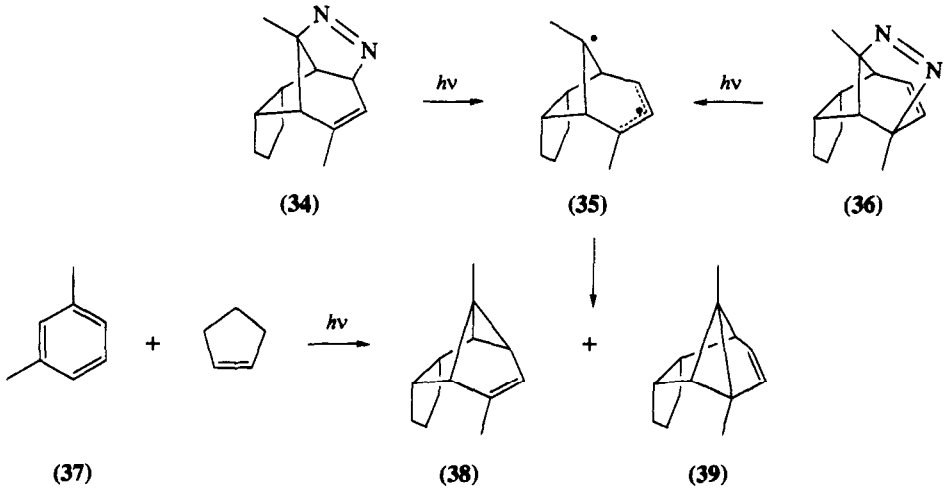
In 1987, Mattay[1m] provided a rather comprehensive analysis of regioselectivity and *exo/endo* selectivity based on his previously developed charge transfer treatment and on a mechanistic treatment similar to that proposed by Cornelisse. This work incorporates many findings of earlier studies.[1] According to this treatment, these reactions are proposed to proceed through an exciplex which is polarized in proportion



(9a)



(9b)

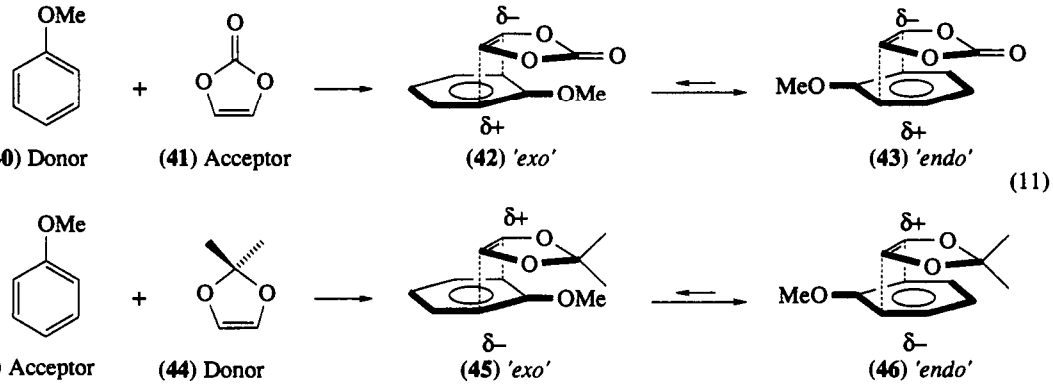


(10)

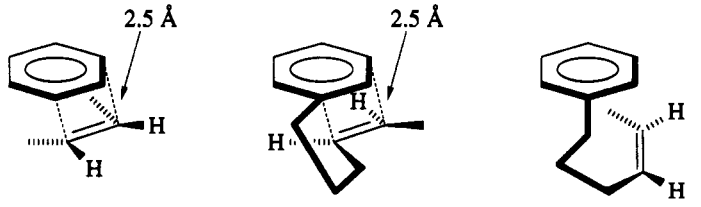
to the degree of charge transfer between the donor and the acceptor. Evolution of this species along the *meta* cycloaddition path occurs with polarization within the arene subunit (**27**; equation 9a) in advance of σ-bond formation, in accord with calculations[19] and experimental evidence.[18] As discussed in previous studies by Cornelisse, bond formation between the arene and alkene then proceeds in a fashion which maximizes charge stabilization by substituents on the arene ring in the early stage of the reaction (equation 9a). Consequently, donor groups at C-1 in (**27**) direct alkene bonding to positions C-2 and C-6 of the arene subunit since such groups would stabilize partial positive charge developing at C-1 in the early stage of the cycloaddition process. Conversely, acceptor groups at C-3 (or C-5 as numbered in **27**) would direct alkene bonding to positions C-2 and C-6 of the arene since such groups would stabilize partial negative charge build-up in the C-3—C-4—C-5 allyl subunit in the early stage of the reaction. This analysis is supported by experimental results: for alkoxy- and alkyl-substituted arenes, alkene addition occurs preferentially to positions C-2 and C-6 relative to the C-1 donor, while for acceptor-substituted arenes, such as trifluoromethylbenzene or cyanobenzene, alkene addition is preferentially directed to positions C-2 and C-6 relative to the C-3 acceptor group (as numbered in **27**).[18] Furthermore, for arenes bearing two substituents, addition is preferentially directed by the stronger donor or acceptor. The regio-

selectivity observed in *ortho* cycloadditions, while generally lower, is explained in a similar fashion involving species (**30**) and/or (**31**) (equation 9b), depending on the charge stabilization provided by R.

Exo/endo selectivity can also be rationalized on the basis of this treatment. An interesting example is provided by the *meta* cycloadditions of anisole with vinylene carbonate (**41**) and dioxole (**44**) (equation 11). Reactions of (**41**) give an *exo/endo* cycloadduct ratio of 0.5, while for the latter alkene a reversed preference is found, *i.e. exo/endo* = 3.2. In contrast to what would be expected on the basis of steric effects alone, a larger arene substituent, trimethylsilyloxy, gives even greater *exo* selectivity (9.3). This behavior can be explained if allowance is made for charge transfer. Thus polarization arising during the cycloaddition with (**41**) would electrostatically stabilize the *endo* addition mode (**43**) and destabilize the *exo* mode (**42**), the latter due to charge repulsion between the vinylene carbonate subunit and the alkoxy group of the arene. On the other hand, the more electron-rich dioxole (**44**) can serve as a donor in the cycloaddition, in which case charge repulsion is minimized along with steric effects in the *exo* orientation (**45**).



While the aforementioned electronic effects provide the basis for understanding many aspects of reaction selectivity, a complete analysis must also include orbital alignment and steric effects since in many cases these factors are dominant. For example, while most intermolecular *meta* cycloadditions involving alkyl- or alkoxy-substituted arenes and simple alkenes proceed with *endo* selectivity, the intramolecular *meta* cycloadditions generally give high, if not complete, *exo* selectivity.[1r] This difference in selectivity has been rationalized in numerous studies by Wender's group on the basis of steric effects associated with the formation and reaction of an exciplex. In this analysis (Scheme 5),[15] the plane of the alkene and that of the excited-state arene are oriented in a parallel fashion and separated by a distance of approximately 2.5 Å, in reasonable agreement with previous studies on exciplex systems[23] and the more recent calculations[16,19] noted above. The intermolecular reaction would then involve exciplex (**47**), in which an *endo* orientation is preferred due to secondary orbital interactions and, depending on substitution, electrostatic effects. In the corresponding intramolecular exciplexes, the favorable orbital alignment for *meta* cycloaddition is preserved only if an *exo* orientation (**48**) is adopted, as the *endo* exciplex (**49**) is poorly aligned. Moreover, *meta* cycloaddition proceeding *via* (**49**) would lead to the formation of a pro-



(**47**) Intermolecular exciplex model (*endo* orientation) Favored

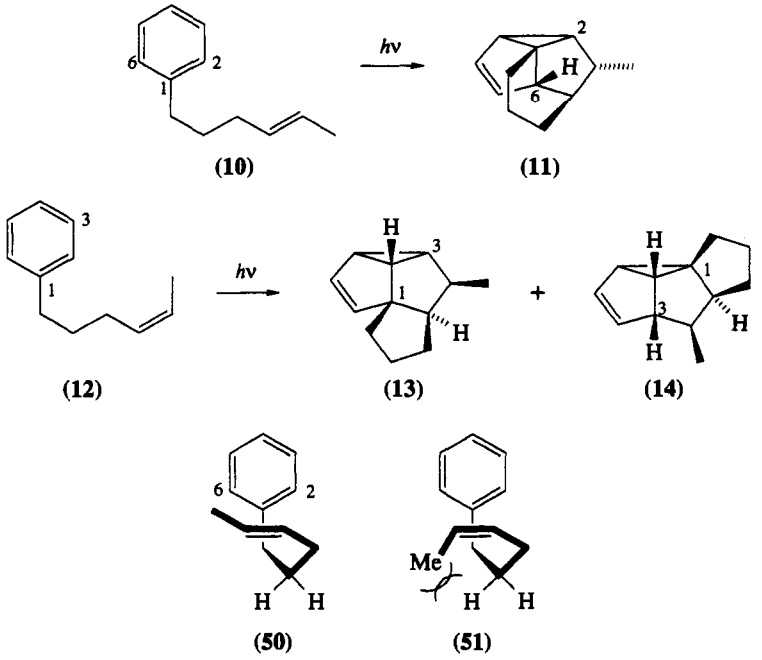
(**48**) Intramolecular exciplex model (*exo* orientation) Favored

(**49**) Intramolecular exciplex model (*endo* orientation) Disfavored

Scheme 5

duct with a highly strained *trans*-fused bicyclo[3.3.0]octane subunit. In contrast, the corresponding *exo* cycloaddition process proceeds to a less-strained *cis*-fused bicyclo[3.3.0]octane product.

Steric effects on reaction selectivity are also interpretable in terms of this exciplex model. For example (Scheme 6), the cycloaddition of (*E*)-6-phenyl-2-hexene (**10**) proceeds as expected through exciplex (**50**) with addition of the alkene subunit to positions C-2 and C-6 of the C-1 donor-substituted arene.[1h] In contrast, irradiation of the (*Z*)-isomer (**12**) occurs with addition to positions C-1 and C-3 to give cycloadducts (**13**) and (**14**). This contrasting behavior provided an important starting point for studies in Wender's group, as it indicated that the seemingly abnormal behavior of the (*Z*)-isomer is simply a result of destabilizing nonbonded interactions which would arise in exciplex (**51**) if addition were to occur across the donor (alkyl) group. This interpretation was tested and figured significantly in several studies in total synthesis, as will be described below. Since this effect arises in intramolecular cycloadditions involving alkenes bearing a substituent which is (*Z*) related to the tether connecting the alkene and arene, it is commonly referred to as the (*Z*)-alkene effect.



(**10**) (**11**) (**12**) (**13**) (**14**) (**50**) (**51**)

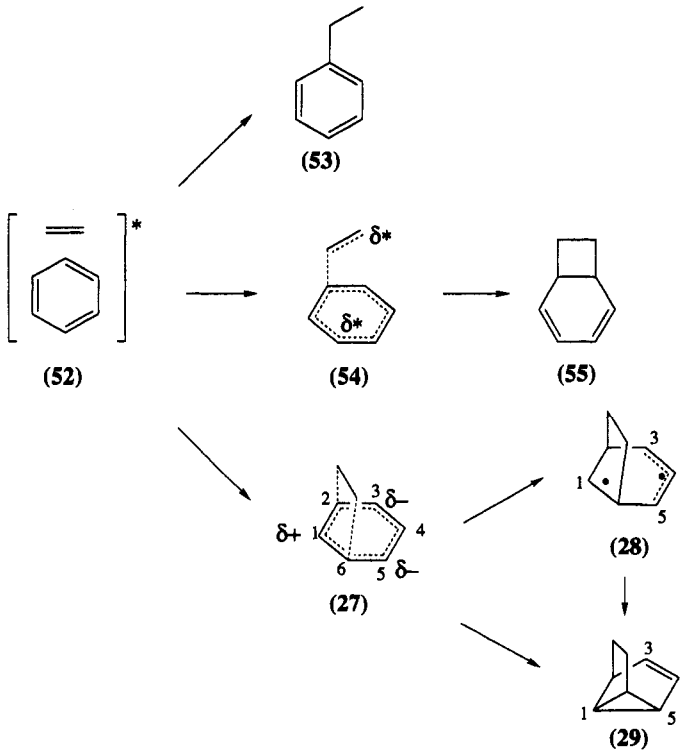
Scheme 6

Finally, steric effects have been observed to play a significant role in controlling the diastereoselectivity of the arene–alkene cycloadditions. Elaboration of this aspect of the reaction again rests on an exciplex model and will be provided in the context of synthetic applications where it has been most frequently encountered.

5.3.4 SUMMARY OF MECHANISM AND REACTION SELECTIVITY

The pathway depicted in Scheme 7 represents a consolidation of some of the more recent contributions noted above and is provided along with the following summary as a guideline for the implementation of this class of reactions in synthesis. Based on existing information, irradiation of an arene in the presence of an alkene appears to be a singlet process leading to an exciplex intermediate (**52**). The overall course (mode) of any ensuing photochemistry can then be predicted on the basis of this proposed intermediate. Based on the aforementioned charge transfer analysis, this species will be polarized in proportion to the donor and acceptor abilities of the arene and alkene. When charge transfer is highly favored (*i.e.* when ΔG_{ET} for electron transfer is negative), substitution or ene reactions are expected (**52** to **53**). When charge transfer is relatively weaker, cycloaddition occurs, with *ortho*-mode selectivity (**54**) for $0<\Delta G_{ET}<$ 1.4–1.6 and with *meta*-mode selectivity (**27**) for $\Delta G_{ET} >$ 1.4–1.6. *Para* cycloadditions are possible but disfavored by poor orbital overlap and primarily restricted to reactions of arenes with allenes, dienes and extended arenes.[27] Owing to the limited study of *para* cycloadditions, further generalization is at present

inappropriate. Mode selectivity for *ortho* and *para* cycloadditions can also be rationalized on the basis of FMO analysis, although limitations have been noted.

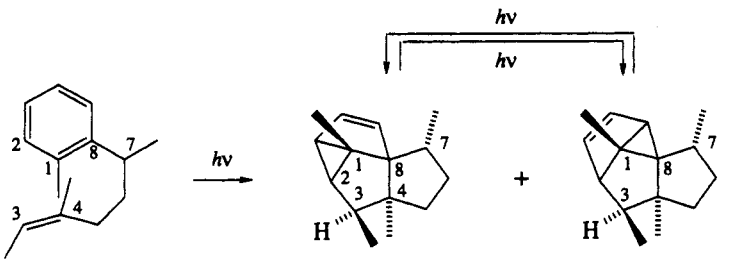


Scheme 7

In the next stage of the cycloaddition process, the weakly polarized exciplex is thought to evolve to polarized species (**54**) and/or (**27**), putatively involved in the *ortho* and *meta* cycloadditions, respectively. These species can be used to predict reaction regioselectivity. In the *ortho* mode of cycloaddition, regioselectivity is influenced by the degree of electron transfer and therefore the extent of polarization of (**54**), as well as the stabilizing effect of arene substituents and steric factors. Consequently, *ortho* addition to positions C-1 and C-2 of a C-1-substituted arene is preferred when ΔG_{ET} of electron transfer is low (*i.e.* approximately zero) and when the arene substituent at C-1 is charge stabilizing. When electron transfer is less likely, the regioselectivity of the cycloaddition is low. In the *meta* mode of cycloaddition, regioselectivity can be similarly predicted on the basis of the effectiveness of substituents in stabilizing charge in species (**27**). Thus bond formation to positions C-2 and C-6 of the arene would be favored when a donor group is at C-1, where it could stabilize positive charge, and/or when acceptor groups are at C-3 and/or C-5 where they could stabilize negative charge. As bond formation progresses, steric effects on regioselectivity become more pronounced and occasionally override these electronic directing effects. For example, the *meta* cycloaddition of cyclooctene to toluene proceeds with essentially exclusive addition of the alkene to positions C-2 and C-6 of the arene, as would be expected for a C-1 donor-substituted arene.[28] However, when the arene methyl group is replaced by a sterically more-demanding *t*-butyl group, alkene addition to positions C-3 and C-5 is favored.[29] Similarly, as noted for the dramatically contrasting behavior of (*E*)- and (*Z*)-6-phenyl-2-hexenes (Scheme 6), steric and orbital alignment effects imposed by the intramolecularity of certain cycloadditions can override electronic effects.

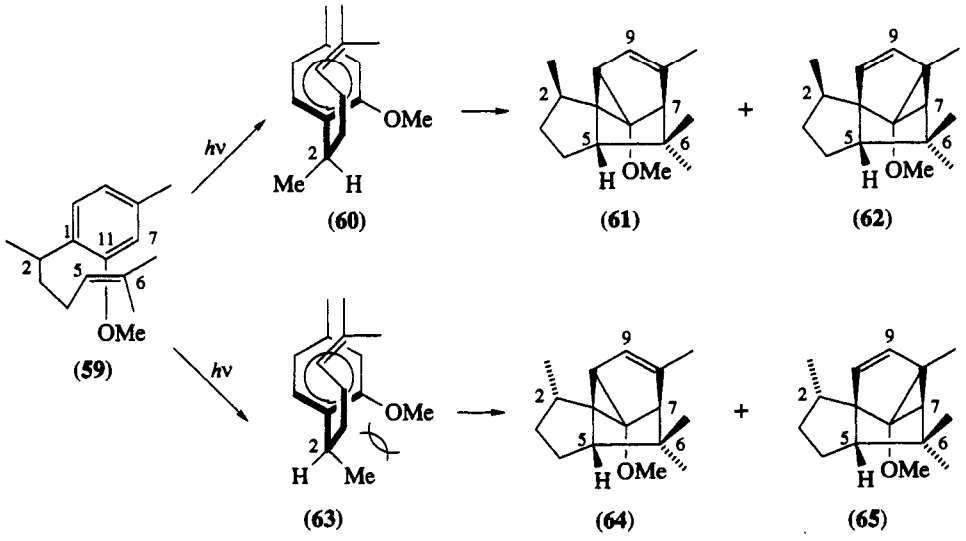
The next selectivity issue, *exo*/*endo* preferences, can be predicted for both the *ortho* and *meta* modes of cycloaddition on the basis of secondary orbital interactions (FMO treatment) and by electrostatic considerations involving polarized species (**54**) and (**27**). In general, intermolecular reactions with simple alkenes proceed with *endo* selectivity. Heteroatom-substituted or polarized alkenes (equation 11) give *exo*/*endo* mixtures, whose composition can be explained by electrostatic considerations. Intramolecular cycloadditions of simple alkenes and arenes joined by a three-atom tether generally proceed with high *exo* selectivity due in part to orbital alignment effects. In all cases, alkene geometry is preserved, except for sterically encumbered alkenes, in which case excitation transfer from the arene to the alkene can occur.

As alkene bonding progresses in the *meta* cycloaddition, calculations[19] and experimental evidence[17,18] suggest that dipolar character dissipates, resulting in one scenario in the direct formation of cycloadduct (**29**) or in another in the intermediacy of diradical species (**28**) (Scheme 7). For the latter, closure to the cycloadduct(s) would then proceed with bond formation between C-1 and C-3 and/or C-5. Factors contributing to the selectivity of this closure have not been fully investigated and indeed they are frequently obscured by the fact that many *meta* cycloadducts can be photoisomerized. For example, irradiation of arene-alkene (**56**) (equation 12) gives two cycloadducts (**57**) and (**58**) in a ratio of 1:4.5, respectively, at short reaction times whereas prolonged irradiation produces a 1:2.6 mixture.[30] Either isomer can be photoequilibrated. While caution is thus required, it would appear on the basis of many studies that the final closure favors formation of the less-strained cycloadduct. Cycloadduct (**58**) is thus favored over (**57**) because the alkyl groups at C-1 and C-8 are less sterically congested in the former as a result of its longer C-1—C-8 (cyclopropane) bond. Electronic factors are also expected to play a role in the final closure due to the differing interactions of substituents attached to normal *versus* cyclopropane bonds. Examples of this selectivity will be presented in the next section.



(**56**) (**57**) (**58**) (12)

The final major selectivity issue associated with the arene–alkene cycloadditions pertains to the influence of preexisting stereogenic centers on the course of the reaction. This selectivity has been rationalized by Wender's group in numerous studies on the basis of the aforementioned exciplex model for *meta* cycloaddition, from which steric interactions can be determined for all possible cycloadditions. For example, arene-alkene (**59**) (equation 13) could in principle produce cycloadducts (**61**) and (**62**) with a β-oriented C-2 methyl group and/or (**64**) and (**65**) with an α-oriented C-2 methyl group. Examination of the exciplex (**63**) leading to the latter pair, however, clearly reveals a destabilizing nonbonded interaction involving the benzylic methyl group and the methoxy group of the arene. Formation of the diastereomerically related exciplex (**60**) is thus favored, in agreement with the observed highly selective, if not exclusive, formation of cycloadducts (**61**) and (**62**).[15]



(**59**) (**60**) (**61**) (**62**) (13)

(**63**) (**64**) (**65**)

5.3.5 GENERAL SYNTHESIS DESIGN CONSIDERATIONS

Organic synthesis has evolved rapidly and impressively since its genesis in the nineteenth century, with each generation defining an ever-more demanding set of goals. As empiricism gave way to mechanistic understanding, a foundation was laid for the realization of greater control over reaction selectivity and thereby the advent of complex molecule synthesis. The past three decades have witnessed impressive successes in the synthesis of complex structures. Indeed, the problems posed by many synthetic targets are now 'solved' at a practical level. However, for the majority of synthetic problems, solutions either do not exist or are not practical. In general, few solutions approach the ideal, wherein the target is prepared from readily available starting materials in one step which proceeds in 100% yield and which is operationally safe and simple and ecologically acceptable. Obviously, this is a rather demanding but not unrealistic objective. While it is unlikely to be commonly realized, attempts to achieve this level of sophistication are of great importance as they are likely to produce fundamentally new and practical solutions which will clearly have a profound impact on the ways in which total synthesis will be used in the future.

The relationship of the arene–alkene cycloadditions and other strategy level reactions of this calibre to this goal of simplifying complex molecule synthesis can be appreciated from an analysis of a typical synthesis. Generally, a total synthesis proceeds from simple starting materials to a complex target. While 'simple' and 'complex' are frequently intuitive or at best qualitative descriptors of molecules, it is possible to determine more quantitatively these relative attributes of structure through the use of simple graph theory.[31] In essence, the atoms and bonds of a molecule can be related to the points and lines of a graph. The relative complexity of a graph (molecule) is therefore a function of the number of points (atoms) in the graph (molecule) and of the nature and number of their connections (bonds). It necessarily and objectively follows from this consideration that the average complexity increase per step in a synthesis determines the total number of steps needed to produce the target (complexity level), provided that the increase is relevant to the target. From a chemical viewpoint, this is equivalent to stating that the average number of target bonds formed per step necessarily determines the number of steps needed to complete a synthesis. Consequently, the incorporation of reactions like the arene–alkene *meta* cycloaddition, the Diels–Alder cycloaddition, or polyene cyclizations into a synthetic plan will generally produce a greater increase in average complexity per step in the synthetic sequence, thereby leading to a shorter synthesis. The ramifications of these considerations will become apparent as this analysis turns to synthetic applications.

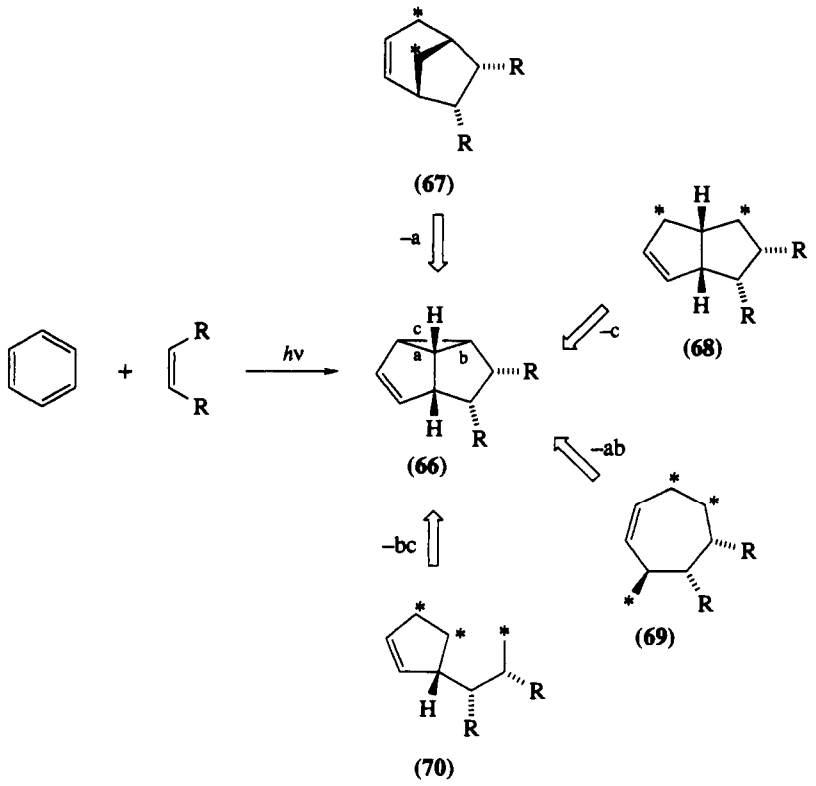
From another viewpoint, the value of the arene–alkene *meta* cycloaddition arises from its capacity to produce a cycloadduct (**66**; equation 14) with three new rings and up to six new stereocenters, an impressive feat even when compared with the highly regarded Diels–Alder cycloaddition. Moreover, the cycloadduct can be used in the synthesis of a variety of commonly encountered structural types including cyclopentanes, cycloheptanes, bicyclo[3.2.1]octanes and bicyclo[3.3.0]octanes. While frequently overlooked in some discussions of reaction classification, the overall processes leading to cycloheptanes, bicyclo[3.2.1]octanes and bicyclo[3.3.0]octanes are clearly classifiable as [5C + 2C], [3C + 2C] and [3C + 2C] cycloadditions, respectively. Examples of these types will be given in the following section.

While providing less of a complexity increase than the *meta* cycloaddition, the *ortho* and *para* modes of cycloaddition (equation 15) nevertheless offer a significant increase, not unlike that attending the Diels–Alder reaction. In both, a new ring and up to four contiguous stereocenters are formed. From a synthetic view, the *ortho* cycloaddition offers access to four- and six-membered rings, bicyclo[4.2.0]octanes, and eight-membered rings, the last through cleavage of the ring fusion bond. These processes are formally examples of [2C + 2C] and [6C + 2C] cycloadditions. The *para* cycloaddition also affords access to six-membered rings as well as bicyclo[2.2.2]octanes through a [4C + 2C] connection. *Para* cycloadditions involving dienes or a second arene additionally provide access to eight-membered rings through a [4C + 4C] cycloaddition.

5.3.6 SYNTHETIC APPLICATIONS

With the above synthetic considerations as a backdrop, the use of the arene–alkene cycloaddition in complex molecule total synthesis can now be examined. The emphasis here will be on the *meta* cycloaddition process since it has received the most study. It will become apparent, however, that even this reaction has received relatively little attention in synthesis in spite of its enormous potential. This situation is likely to change rapidly as recent theoretical and synthetic advances are assimilated.

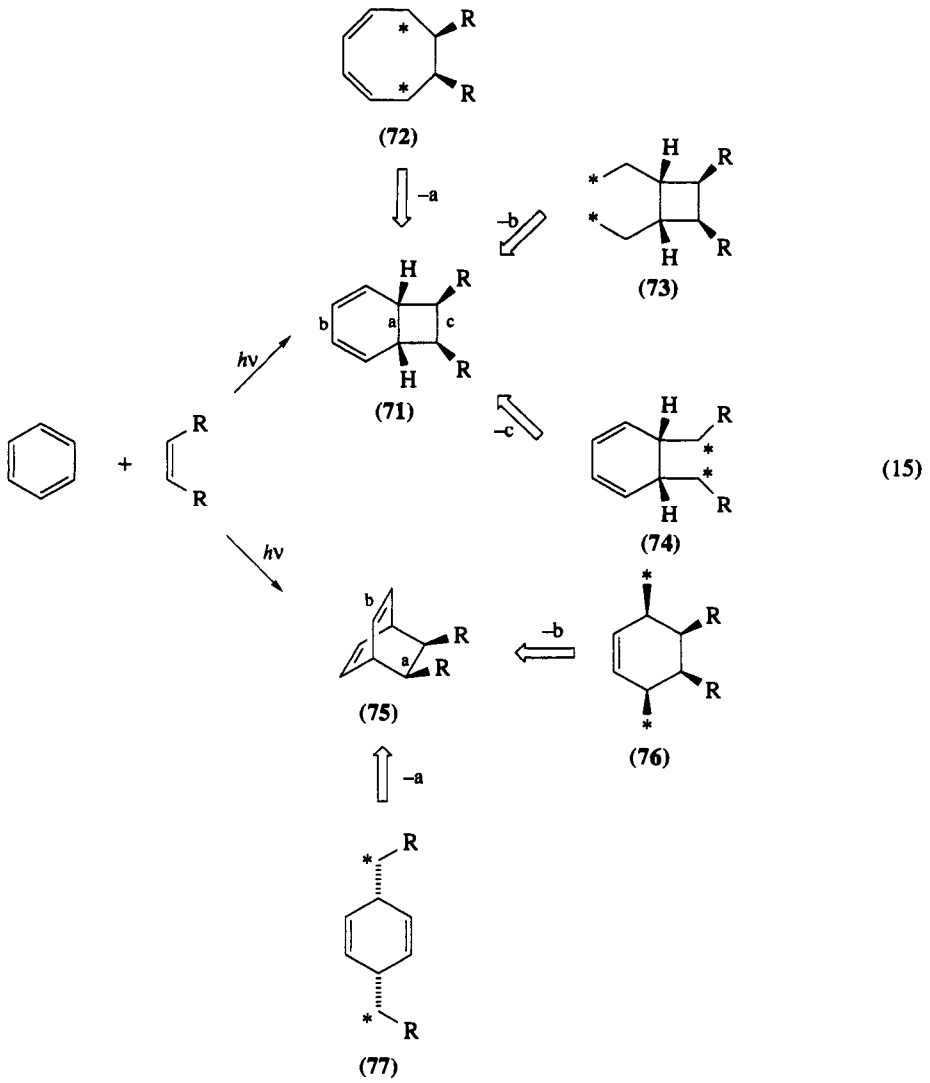
The first example of the application of the arene–alkene *meta* cycloaddition in complex molecule synthesis was the total synthesis of the sesquiterpene cedrene (**82**; Scheme 8).[15] This target was selected for



(14)

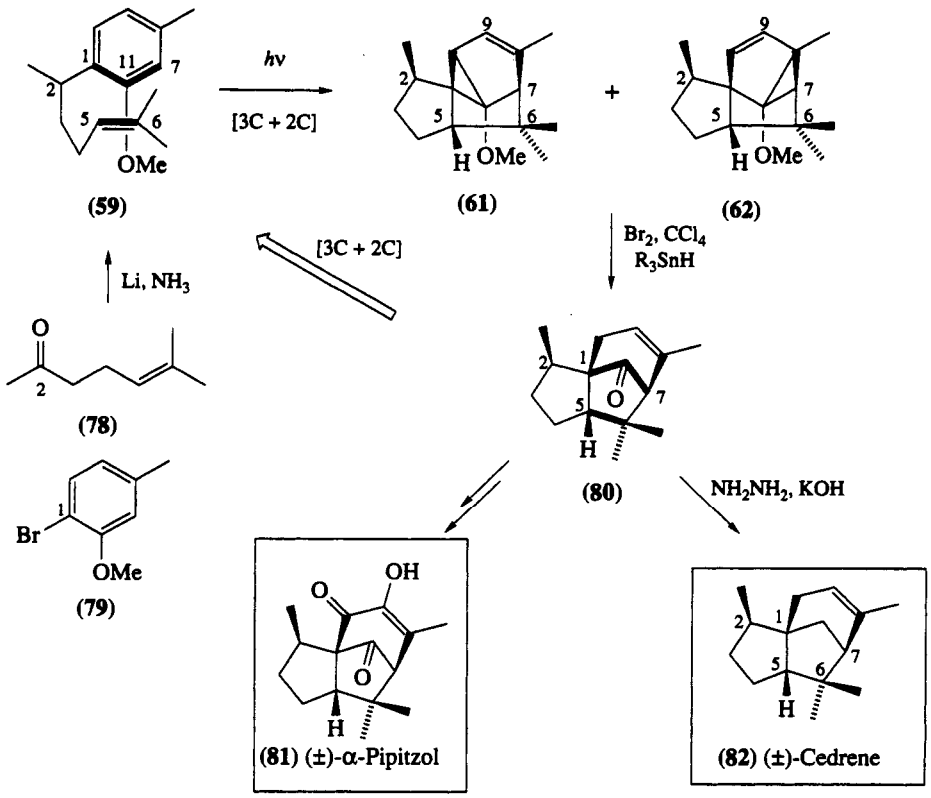
study because it offered the opportunity to investigate several issues of crucial importance to the broader implementation of this reaction in synthesis, including mode, regio and *exo*/*endo* selectivity and, for the first time, stereoinduction. From a retrosynthetic analysis, it is seen that the bicyclo[3.2.1]octane subunit of cedrene could arise from a [3C + 2C] cycloaddition, allowing for the connection of carbons 1 with 5 and 7 with 6, respectively. This connectivity is exactly that which would arise from the *meta* cycloaddition of arene-alkene (**59**). While not required in the product, the oxidation (methoxy group) at C-11 in this precursor was expected, for reasons discussed above, to control regioselectivity and to simplify the task of transforming the cycloadduct into the desired target.

That arene-alkene (**59**) would give the desired cycloadducts rested on several assumptions which can now be presented in terms of the previous discussion. Thus, with respect to mode selectivity, it is seen that the substitution of the arene and alkene in (**59**) is that which would be expected on the basis of FMO and charge transfer treatments to lead to a *meta*-selective process. This is further supported by earlier studies showing that alkyl-substituted anisoles give *meta* cycloadducts with simple alkenes.[21] While these studies also indicate that *ortho*-substituted anisoles give low yields of cycloadducts, the intramolecularity of the proposed route to cedrene would favor the cycloaddition. The regioselectivity of the key step in the cedrene synthesis (**59** to **61** and **62**) is predictable from two considerations: a methoxy group is known to be a stronger director (donor) than an alkyl group in intermolecular *meta* cycloadditions[21] and should therefore be the dominant director in (**59**), and *meta* addition across the C-1 alkyl group would be disfavored by the (*Z*)-alkene effect (Scheme 9), *i.e.* by nonbonded interactions of the type which were previously invoked to explain the contrasting regioselectivities observed in the cyclizations of (*E*)- and (*Z*)-6-phenyl-2-hexenes. With regard to *exo*/*endo* selectivity, cycloaddition of (**59**) should favor *exo* addition (**84** > **85**) since such a process allows for better orbital overlap in the precursor and for the formation of a less-strained cycloadduct (with a local *cis*-fused bicyclo[3.3.0]octane subunit). The influence of the benzylic stereogenic center on the stereochemical course of the reaction can be predicted from a consideration of the remaining exciplex possibilities, (**86**) and (**87**). A nonbonded interaction between the benzylic methyl group and the methoxy group of the arene would destabilize exciplex (**87**), thereby favoring formation of cycloadducts (**61**) and (**62**) *via* the alternative exciplex (**86**). Molecular mechanics calculations place the steric energy difference between these exciplexes at approximately 1.5 kcal mol^{-1}. Finally, since the regioselectivity of cyclopropane formation could not be predicted at the time of this analysis, the synthesis design allowed for the use of both possible cycloadducts as cedrene precursors. This analysis set the stage for the experimental evaluation of its underlying assumptions.

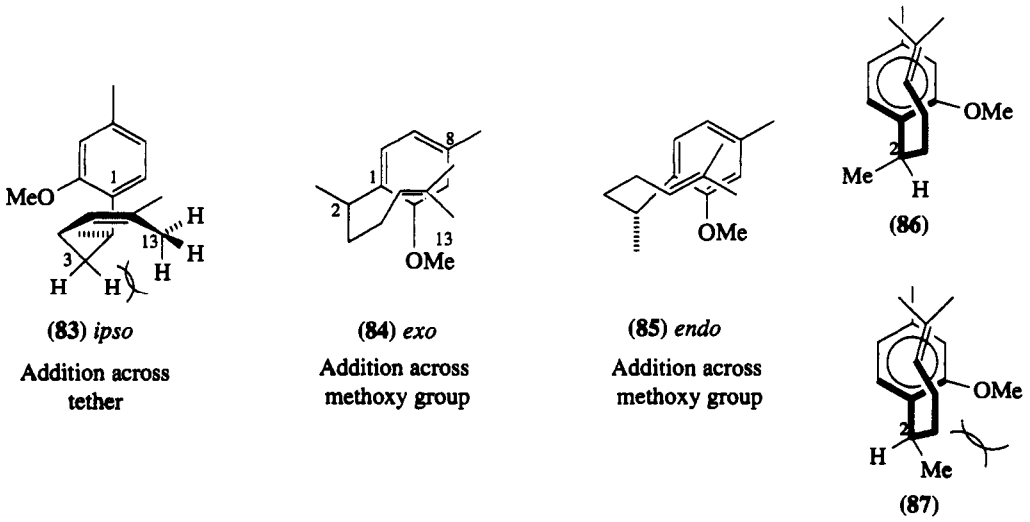


The design of many syntheses evolves from an analysis of the suitability of certain strategy level reactions for solving target-related problems, as exemplified in the preceding paragraph. The overall efficacy of a design is also, however, a function of how easily the starting materials for key steps can be made and how readily the products of these steps can be converted to the desired target. Arene–alkene cycloadditions fare rather well when judged by these criteria. Typically, the cycloaddition precursors are readily prepared through a variety of processes which allow coupling of an arene to an alkene, a notable example being the reductive condensation procedure developed by the Hall group.[32] According to this procedure (Scheme 8) the starting material for the key step in the cedrene synthesis was prepared by treating bromoanisole (**79**) with excess lithium metal (high sodium content) to provide an aryllithium intermediate which was then treated with commercially available ketone (**78**). Addition of ammonia to this reaction mixture resulted in reduction of the initial addition product and the formation of arene-alkene (**59**) in high yield.

In accord with the above analysis and its underlying assumptions, irradiation of arene-alkene (**59**; Scheme 8) results in the highly selective formation of cycloadducts (**61**) and (**62**) (70% yield), differing only by the regiochemical sense of cyclopropane formation. The isomeric nature of these cycloadducts is demonstrated by their photointerconversion and by their subsequent conversion to cedrene. Cleavage of the cycloadducts to cedrenone (**80**) is accomplished directly with acid. However, a brominative cleavage is more reproducible, giving bromocedrenone as an intermediate which is readily reduced with tri-*n*-butyltin hydride to afford (**80**). The selectivity of these cleavages is thought to be governed by formation of a cyclopropylcarbinyl cation (or its equivalent) at C-9 and by the stabilization provided by the methoxy group during the cleavage of the proximate cyclopropane bond. Subsequent deoxygenation of C-11 pro-



Scheme 8

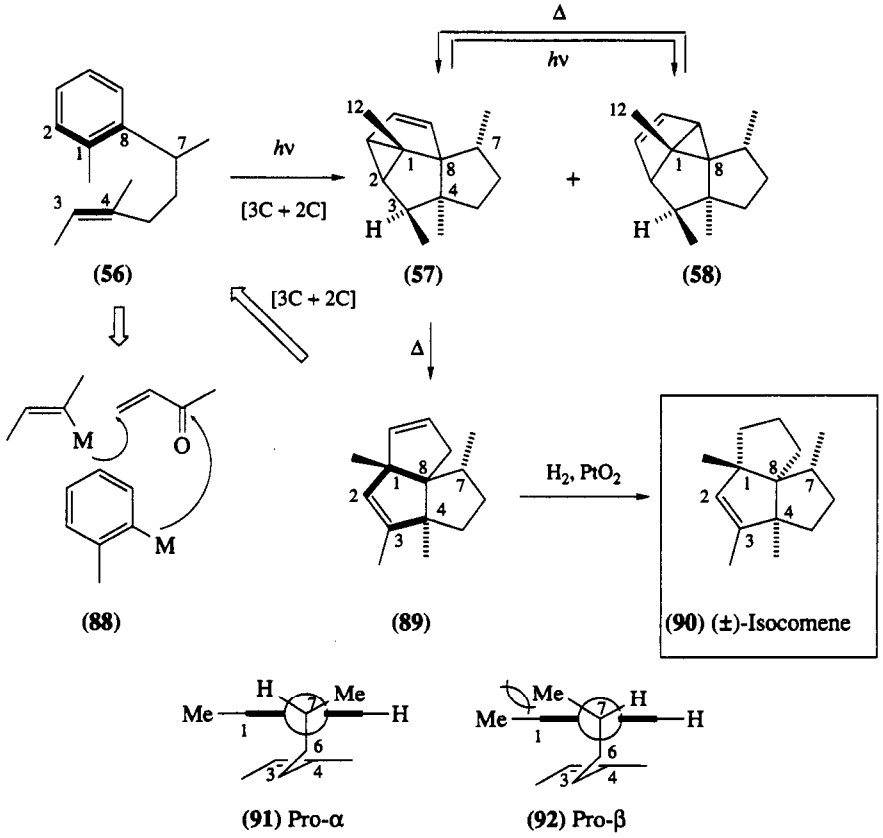


Scheme 9

vides cedrene (**82**) in a total of four steps from commercially available starting materials. The effectiveness of this synthesis, when compared with other syntheses of this molecule, is a predictable consequence of the aforementioned relationship of reaction complexity to brevity of synthesis design. Cycloadducts (**61**) and (**62**) have also been used in a comparably efficient synthesis of α-pipitzol (**81**), a more highly oxidized member of the cedrene family.

The synthesis of cedrene served to establish a firm foundation for the implementation of the *meta* cycloaddition in complex molecule synthesis and allowed also for a comparison of the effectiveness of an arene–alkene based strategy with the many impressive approaches to this well-known target. On the other hand, the next application of the *meta* cycloaddition was directed at isocomene (**90**; Scheme 10),[30] a relatively new structural motif but one which has been found with increasing frequency in new natural

products of biological interest. The retrosynthetic analysis of isocomene derives from the recognition that its ring system is composed of two bicyclo[3.3.0]octanes, either representing a substructure of a *meta* cycloadduct. While a synthesis could thus be fashioned around either subunit, the sequence selected for study allowed for an evaluation of the stereochemical fate of the alkene subunit as well as a further examination of synthetic issues tested up to that point only in the cedrene synthesis. The success of this sequence rests in part on the expectation that the target could be derived from the partial hydrogenation of diene (**89**), which in turn could be obtained from cycloadduct (**57**) *via* a sigmatropic 1,5-H shift. The effectiveness of this strategy for selectively cleaving this cycloadduct is completely dependent on the configuration of C-3, since as required by mechanistic considerations and supported in work on simple cycloadducts reported by Srinivasan,[33] only an α-oriented hydrogen at C-3 could participate in the required rearrangement. The stereogenesis of C-3 occurs during the cycloaddition and can be controlled only if the geometry of the starting alkene is retained during the course of the reaction. Previous studies of inter-[34] and intra-molecular[1h] cycloadditions involving simple disubstituted alkenes support such an expectation, but the fate of more sterically encumbered alkenes was uncertain since loss of stereochemistry could occur through a sterically less-demanding excitation transfer process.



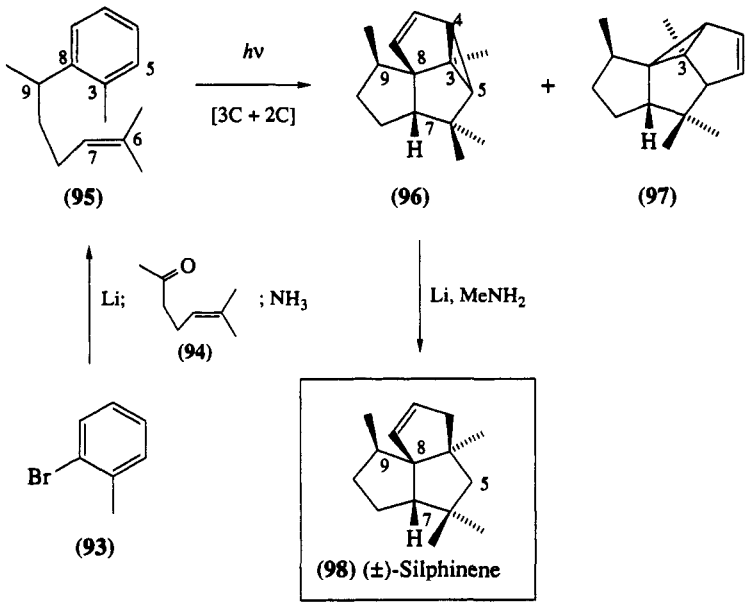
Scheme 10

Along with the above issues, the design for the synthesis of isocomene incorporated a further test bearing on the interplay of steric and electronic effects. Specifically, the *meta* cycloaddition of arene-alkene (**56**) would be expected to proceed regio-randomly with alkene addition directed equally well by the C-1 methyl (donor) and the C-8 alkyl (donor) groups, based on electronic considerations alone. However, if the previously discussed (Z)-alkene effect were to be manifested in the cycloaddition, the reaction would be expected to proceed in only the desired regiochemical sense. Resolution of the remaining issues of selectivity draw heavily on the cedrene work, leading to the expectation of an *exo*-selective addition based on orbital overlap considerations and of high stereoinduction favoring the pro-α exciplex (**91**) due to steric destabilization which would inhibit formation of the pro-β exciplex (**92**). This analysis proved to be in agreement with the experimental results, as irradiation of arene-alkene (**56**) gives cycloadducts (**57**) and (**58**) (1:2.5) in 72% yield, each ostensibly arising from exciplex (**91**). In connection with a caveat

made earlier, it is important to note that at shorter irradiation times these cycloadducts are produced in a 1:4.5 ratio and each cycloadduct can be photoisomerized to the other, suggesting that caution be exercized in evaluating literature data which does not discriminate between kinetic and photo-equilibrated mixtures.

The conversion of the cycloadducts (**57**) and (**58**) to isocomene proceeds according to plan. Thermolysis of the former provides diene (**89**), which is also obtained from cycloadduct (**58**), presumably *via* a 1,3-alkyl shift which produces (**57**) as an intermediate. Partial hydrogenation of diene (**89**) affords isocomene in six steps from commercially available starting materials. The brevity of this approach to such angularly-fused triquinanes is a further manifestation of the synthetic benefit arising from the complexity increase associated with the *meta* cycloaddition.

Perhaps the best example of the efficacy of the arene–alkene cycloaddition in the synthesis of angularly fused tricyclopentanoids is seen in the three-step total synthesis of silphinene (**98**; Scheme 11).[35] As in isocomene, the key to this synthesis is again based on the recognition that the bicyclo[3.3.0]octane subunit of the target could be derived through the [3C + 2C] connectivity established in a *meta* cycloaddition. Silphinene (**98**) is thus related to cycloadduct (**96**), which in turn is the cyclization product of arene-alkene (**95**). As discussed above, this arene-alkene would be expected to undergo *meta* cycloaddition across the C-3 methyl group, since addition across the C-8 alkyl group would be disfavored by the aforementioned (*Z*)-alkene effect. Furthermore, *exo* addition would be favored over *endo* on the basis of orbital overlap considerations. Finally, stereoinduction should be high, comparable with that obtained in the isocomene synthesis, since the basis for control remains relatively unchanged.

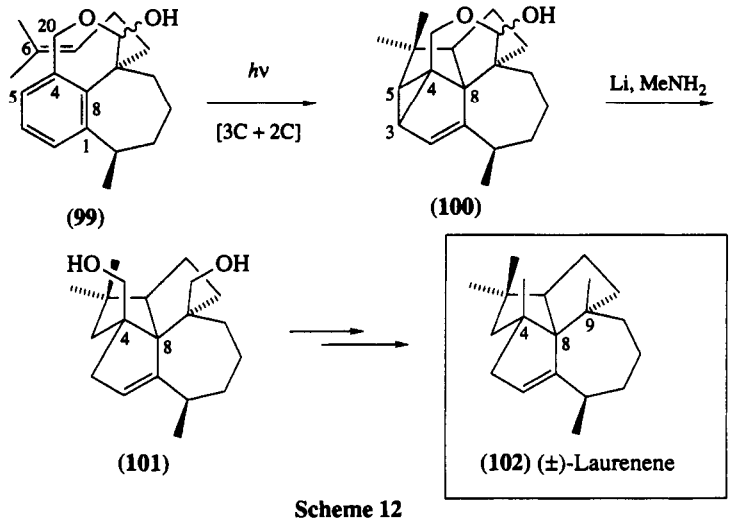


Scheme 11

The key precursor in the silphinene synthesis, arene-alkene (**95**), is obtained in one step from commercial materials and provides, in accord with the above analysis, cycloadducts (**96**) and (**97**) (1:1) in 70% yield. Mode, regio-, *exo*/*endo*- and stereo-selectivity are essentially complete. Transformation of cycloadduct (**96**) to silphinene involves reduction with lithium in methylamine, which proceeds with formation of the alkene radical anion and subsequent rupture of the better aligned cyclopropane bond (C-4—C-5 > C-3—C-4). Requiring only three steps from commercial materials, this synthesis dramatically illustrates how complexity can be rapidly built up through strategies based on the *meta* cycloaddition.

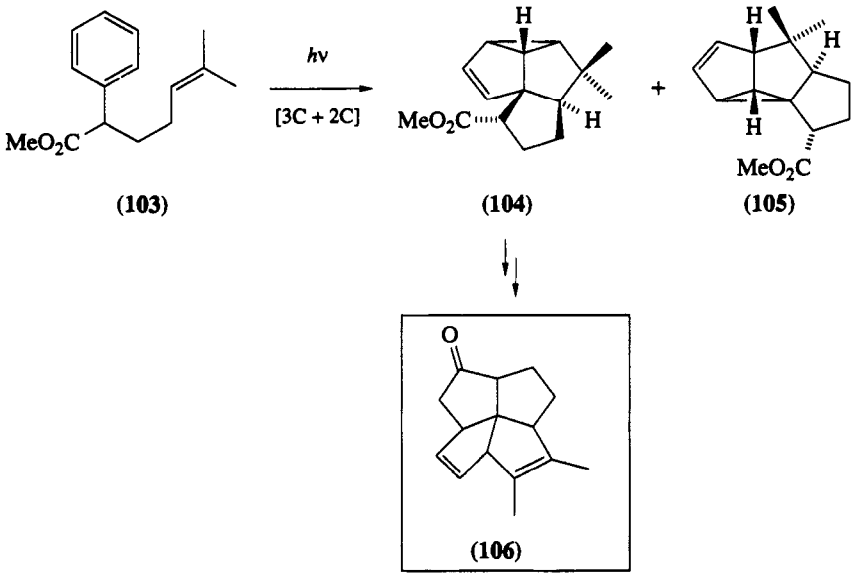
The successful elaboration of isocomene and silphinene provides the basis for the general application of the arene–alkene *meta* cycloaddition to targets incorporating an angularly fused tricyclopentanoid ring system. A further and significant illustration of the exquisite effectiveness of this process for this structural class is seen in the synthesis of laurenene (**102**; Scheme 12),[36] the first naturally occurring rosettane. As determined by other contemporaneous efforts, the synthesis of laurenene can require in excess of 30 steps, but as few as 13 steps when derived through the *meta* cycloaddition. The key to simplifying this structure centers again around the recognition of the relationship between its bicyclo[3.3.0]octane subunits and the structure of a *meta* cycloadduct. For reasons relating to the execution of this plan, the

specific *meta* cycloadduct which figures in this effort is (**100**), which is seen to be a product derivable from arene-alkene (**99**). The expectation that (**100**) should be the major or exclusive cycloadduct follows largely from the silphinene synthesis. Thus the (*Z*)-alkene effect precludes *meta* addition across C-8 while addition across C-1 would incur greater steric interaction with the cycloheptyl ring than would be expected for addition across C-4 involving the hydropyranyl ring. In accord with this analysis, irradiation of (**99**) does indeed give cycloadduct (**100**) in 51% yield. Significantly, unlike many other types of cycloaddition, *meta* cycloaddition proceeds efficiently even when three contiguous quaternary centers are developed. Furthermore, only one vinylcyclopropane isomer is produced. As previously discussed, the factors determining this (cyclopropane formation) selectivity are not generally understood, although strain minimization appears to be important. Thus cycloadduct (**100**) is calculated to be less strained than its vinylcyclopropane isomer by some 5 kcal mol^{-1}.[37] Completion of the laurenene synthesis from the cycloadduct exploits the cyclopropane bond cleavage employed in the silphinene synthesis, allowing for the conversion of (**100**) to diol (**101**). Reduction of this diol gives laurenene (**102**), in 13 steps overall.



Scheme 12

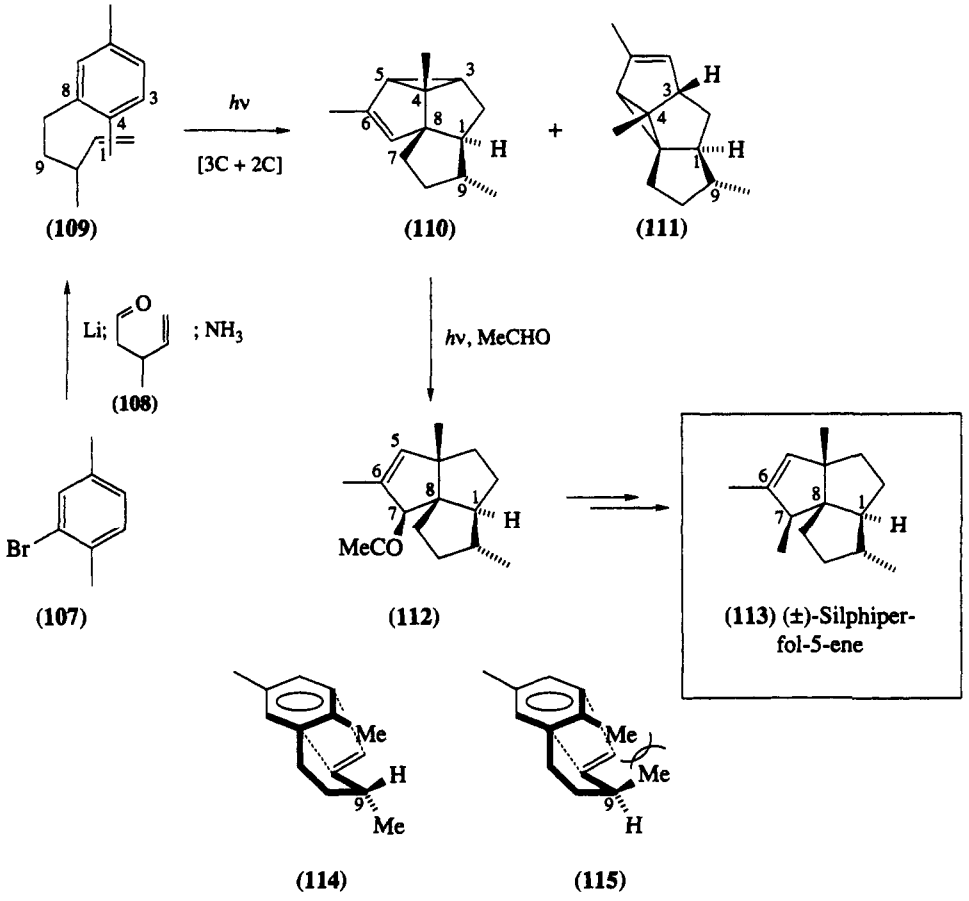
A novel strategy for rosettane synthesis is also seen in the work of Keese and coworkers.[37] As illustrated in Scheme 13, the tricyclopentanoid subunit of the rosettane target (**106**) is assembled through a *meta* cycloaddition, after which the fourth target ring is elaborated through conventional cyclization



Scheme 13

techniques. The regioselectivity of the *meta* cycloaddition process can be attributed to the aforementioned (Z)-alkene effect, which would disfavor addition across what is otherwise a donor (alkyl)substituted center. The diastereoselectivity of this cycloaddition is that expected from steric considerations, as the larger benzylic substituent (ester > H) emerges on the sterically less-encumbered face of the local bicyclo[3.3.0]octane subunit of the products (**104** and **105**).

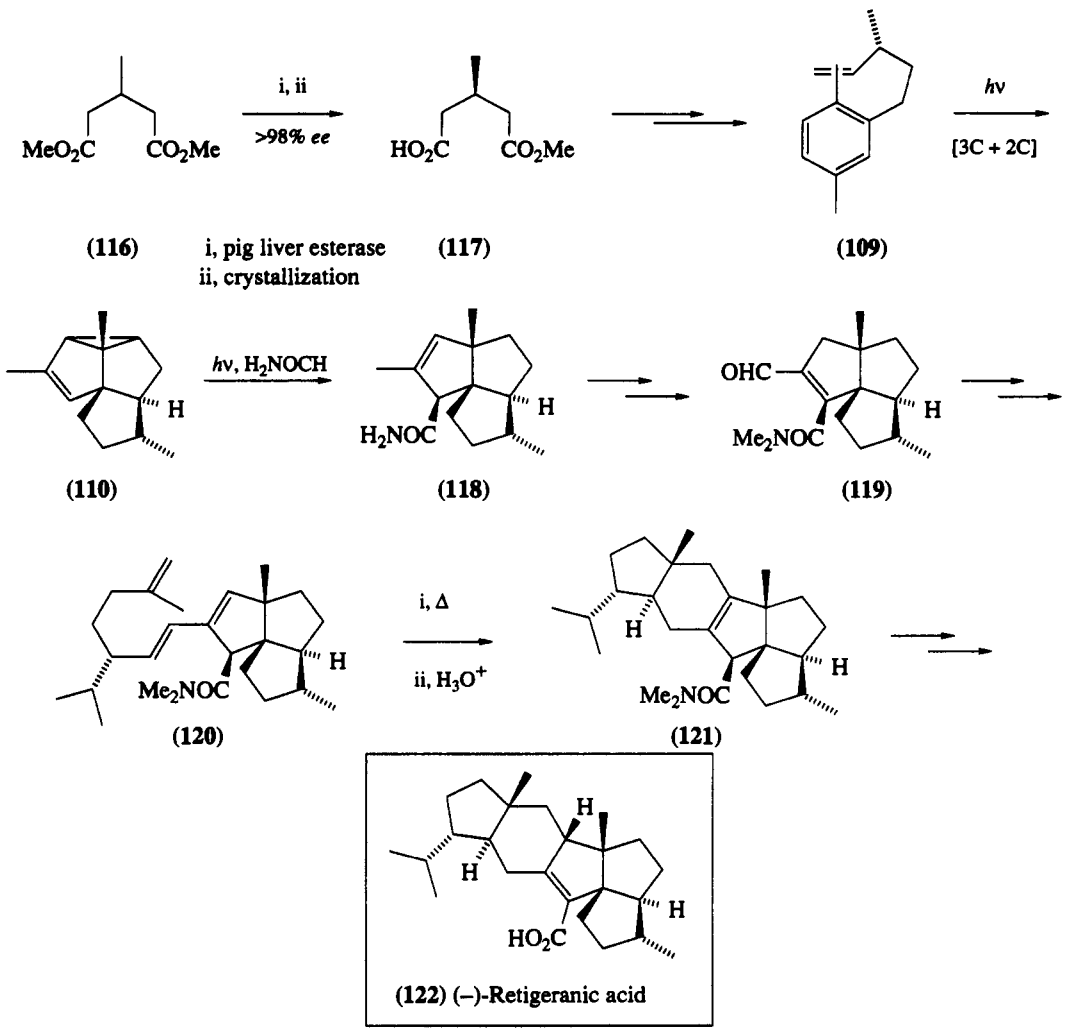
A further example of the arene–alkene *meta* cycloaddition in angularly fused tricyclopentanoid synthesis is seen in the syntheses of the silphiperfolenes, which were designed, in part, to evaluate the influence of an allylic stereogenic center on the cycloaddition and thereby to extend the aforementioned exciplex model.[38] For these syntheses, illustrated here in the case of silphiperfol-5-ene (**113**; Scheme 14), it was expected that the target would arise through cyclopropane cleavage of cycloadduct (**110**), which in turn would be derived from arene-alkene (**109**). The cycloaddition was expected to proceed through exciplex (**114**), as formation of the diastereomeric exciplex (**115**) would be destabilized by the indicated methyl–methyl interaction. In practice, irradiation of (**109**) produces cycloadducts (**110**) and (**111**), each arising from addition across the C-4 methyl group. Isomers arising from addition across the C-8 alkyl group are also presumably formed. With respect to the key issue in this study and in accord with the exciplex model, allylic stereoinduction (*i.e.* by the C-9 stereogenic center) appears to be complete. A further finding of this study is a new cyclopropane cleavage reaction which involves addition of an acetyl radical to the convex face of the C-6—C-7 double bond of cycloadduct (**110**), thereby controlling C-7 stereochemistry and producing a C-6 radical which then induces rupture of the adjacent C-3—C-5 bond. C-4—C-5 cleavage is disfavored due to the poor orbital alignment of this bond with the C-6 radical center.



Scheme 14

The strategy explored in the syntheses of the siphiperfolenes has more recently proven effective in the asymmetric total synthesis of (–)-retigeranic acid (**122**),[39] as illustrated in Scheme 15.

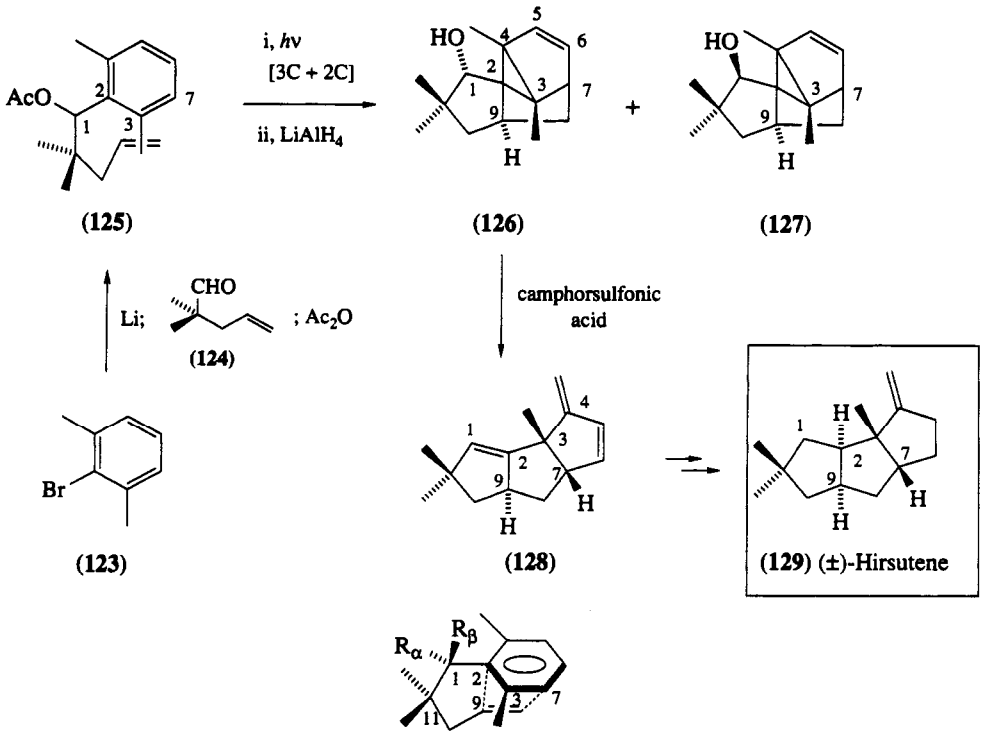
Another major tricyclopentanoid structural motif, the tricyclo[6.3.0.$0^{2,6}$]undecane skeleton of the so-called linearly fused triquinanes, is also readily accessed by using the *meta* cycloaddition process, as



Scheme 15

exemplified in the syntheses of hirsutene (**129**; Scheme 16)[40] and coriolin (**135**; Scheme 17).[41] Examination of the *cis-anti-cis* ring fusion stereochemistry of hirsutene reveals that it is concealed within a cycloadduct (*e.g.* **126**) arising from a *meta* cycloaddition of a 5-aryl-1-pentene (*e.g.* **125**). An important feature of this cycloaddition is that its *exo/endo* selectivity as the target requires the hydrogen at C-9 in the cycloadduct to be *anti* to the hydrogen at C-7 as well as to the C-3 methyl group (see exciplex **130**). Stereochemistry arising at C-2 after cleavage of (**126**) can be expected to favor formation of the less-strained *cis*-fused ring system relative to the corresponding *trans*-fused bicyclo[3.3.0]octane. In the specific case of hirsutene, this stereochemistry was expected to arise through hydrogenation of a protected form of triene (**128**). The formation of this triene in turn illustrates another method available for the deconvolution of *meta* cycloadducts, specifically that in which a leaving group (at C-1 in **126**) external to the cycloadduct core is used to trigger opening of the cyclopropane system. While two cyclopropane bonds could participate in such a process, C-2—C-4 cleavage is expected to be favored over C-2—C-3 cleavage since the former would proceed with formation of a tertiary allylic carbonium ion. Given the role of the C-1 leaving group, the configuration of C-1 is not necessarily significant. However, the stereochemistry arising in the cycloaddition of (**125**) would reveal new information about the intrinsic stereo preference of a benzylic group, since in contrast to previous studies this group is flanked in (**125**) by equivalent *ortho* substituents. A further feature of interest in this study is the regioselectivity of the cycloaddition, since arene-alkene (**125**) possesses neither a dominant director group nor a (*Z*)-alkene. However, models do indicate that addition across the C-2 alkyl group would result in the development of a more congested (strained) cycloadduct than that arising from addition across the C-3 methyl group. Of

course, these arguments are based on an expectation that cycloaddition will be *meta selective, which is* not unreasonable given the substitution of the arene and alkene subunits.

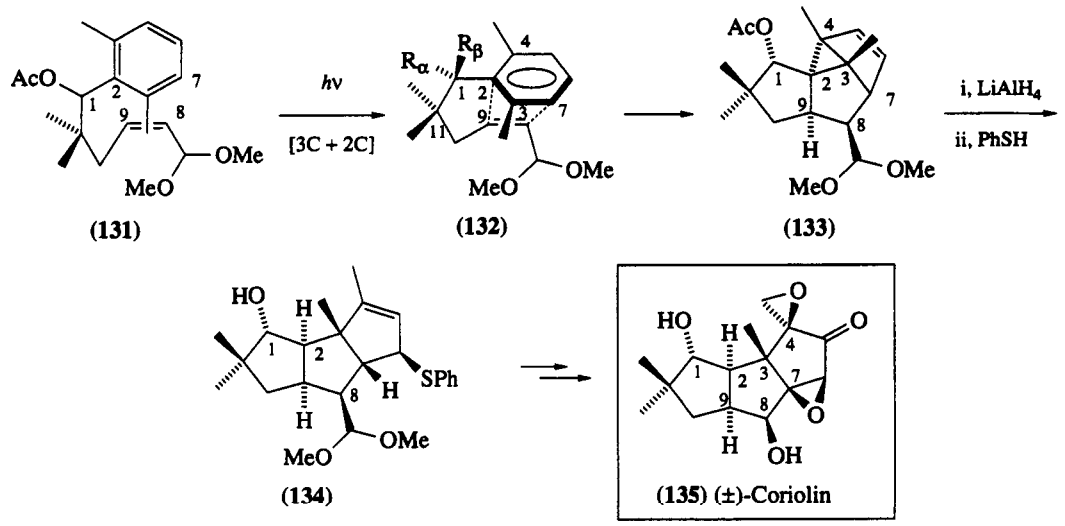


Scheme 16

The arene-alkene (**125**) required in the synthesis of hirsutene is easily prepared through the condensation of the aryllithium derived from (**123**) with aldehyde (**124**) and quenching of the addition product with acetic anhydride. Photolysis of (**125**) is followed by the reductive removal of the acetate group, which provides products (**126**) and (**127**) (3:1, respectively) in 33% yield along with minor amounts (7% and 2%) of the vinylcyclopropane isomers corresponding to the angularly fused cycloadducts. The preference for the α-acetoxy epimer in this cycloaddition is attributable to product development control, since in this epimer the acetoxy group is on the sterically less-congested face of the local bicyclo[3.3.0]octane subunit. This result is also in accord with the aforementioned work reported by Keese.[37] As discussed previously, solvolysis of (**126**) affords triene (**128**) which upon selective reduction provides hirsutene (**129**).

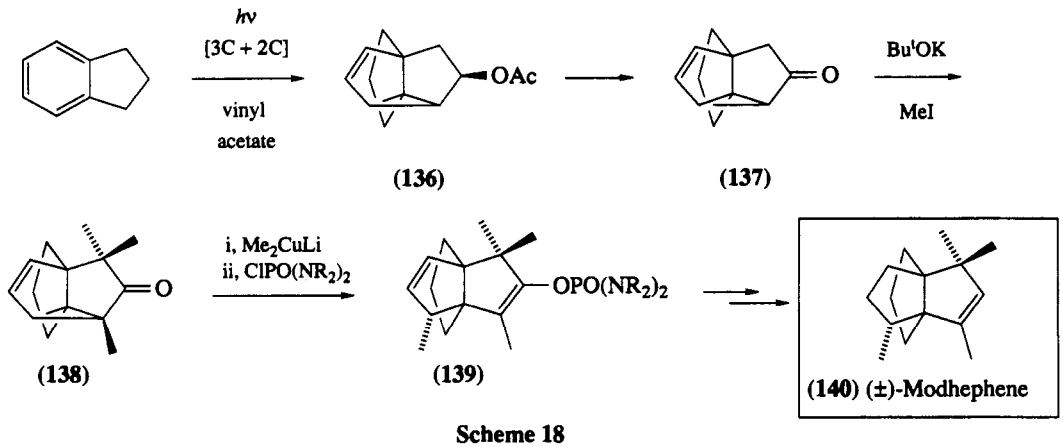
Drawing heavily on the 'model' studies with hirsutene, the synthesis of coriolin (**135**; Scheme 17) requires that provision be made for the additional oxygenation of the target and that an alternative cycloadduct cleavage method be employed. The key cycloaddition step involves the irradiation of arene-alkene (**131**) which gives the desired cycloadduct (**133**), albeit in low yield (15%), presumably due to enhanced steric congestion arising from the positioning of the bulky acetal group in the vicinity of the three developing, contiguous quaternary centers (C-2, C-3 and C-4). This congestion is further reflected in the fact that, in this reaction, starting material undergoes (*E*)–(*Z*) isomerization. However, the (*Z*)-isomer reacts preferentially to give the desired product. While otherwise problematic, the steric effects operating in this cycloaddition work to increase stereoselectivity since the benzylic (C-1) acetoxy group is now more strongly directed to the less-congested α-face than is found in the cyclization of arene-alkene (**125**). The completion of this synthesis involves a novel method for cycloadduct cleavage (**133** to **134**) in which the addition of a thiophenoxy radical leads to the formation of a cyclopropylcarbinyl radical, triggering homolytic rupture of the better aligned (C-2—C-4 > C-3—C-4) cyclopropane bond and generation of a C-2 radical. Hydrogen abstraction by this radical proceeds with the formation of the thermodynamically preferred *cis*-fused product (**134**), from which coriolin is derived.

A third general, structural motif of the tricyclopentanoids, the propellane system, is exemplified by modhephene (**140**; Scheme 18).[42] Retrosynthetically, the core ring system of modhephene is seen to be



Scheme 17

related to *meta* cycloadduct (**136**), which in turn is derivable from the intermolecular *meta* cycloaddition of vinyl acetate to indane. The formation of this cycloadduct would be favored by the directing influence of the donor (alkyl) group and by charge transfer, which would stabilize the *endo* exciplex. While not the only reaction product, cycloadduct (**136**) is indeed the major cycloadduct obtained in this process. Subsequent conversion of (**136**) to modhephene involves a novel permethylation of a fluxional enolate derived from (**137**) and a potentially general cleavage process based on the 'conjugate addition' of dimethylcopper lithium to vinylcyclopropyl ketone (**138**).

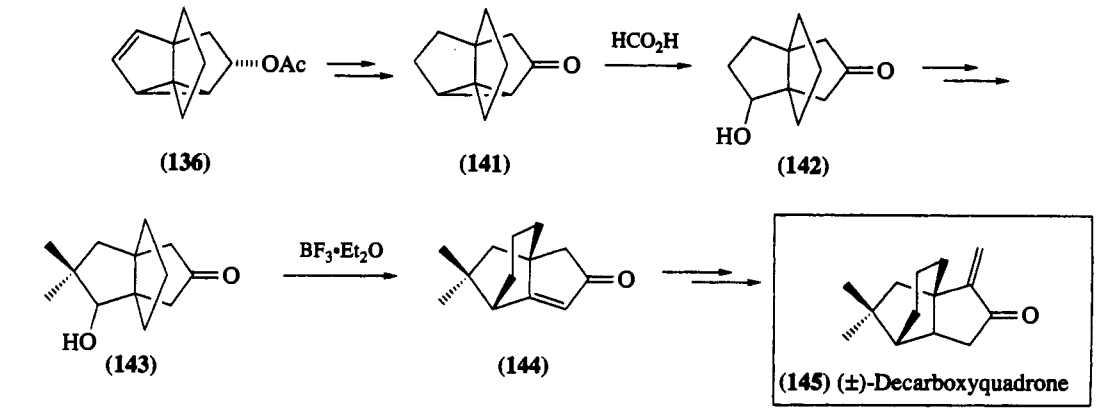


Scheme 18

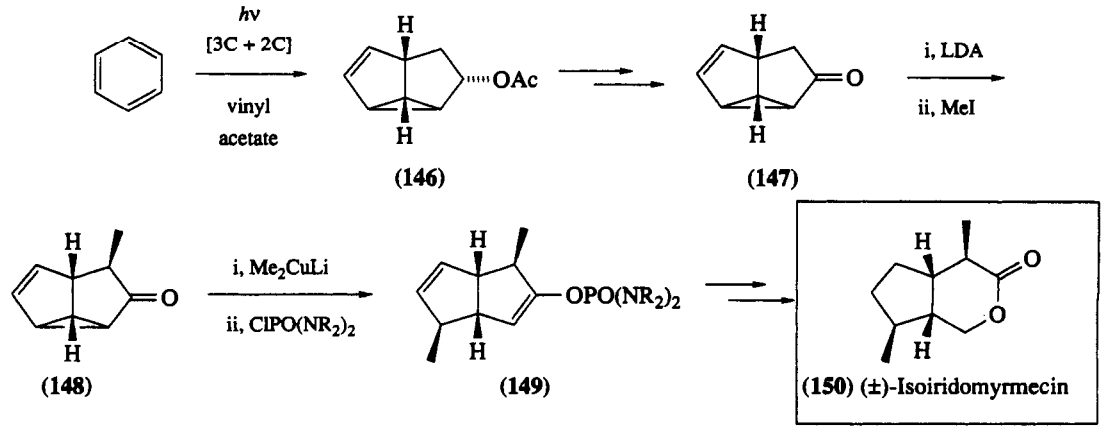
The cycloadduct of indane and vinyl acetate (**136**) has also figured in a clever synthesis of decarboxyquadrone (**145**; Scheme 19) reported by Mehta.[43] For this target the cycloadduct is reduced and solvolyzed to provide alcohol (**142**). Dimethylation and rearrangement provides the required tricyclic subunit of the target.

An analogous cycloaddition involving benzene and vinyl acetate (Scheme 20) also provides rapid access to simple bicyclo[3.3.0]octanes, which have many synthetic uses as illustrated in part by their value in a straightforward synthesis of isoiridomyrmecin (**150**).

A final example of a [3C + 2C] connection based on the *meta* cycloaddition merits special mention as it demonstrates a new regioselectivity for the process, which in turn provides access to a new structural class. In the preceding studies of the intramolecular process, regioselectivity is controlled by a strong director group at a position *ortho* to the alkene tether and/or by the (*Z*)-alkene effect. As illustrated in a study directed at the synthesis of a quadrone analog, namely dedimethylquadrone (**156**; Scheme 21),[44] the absence of these control elements in arene-alkene (**151**) leads to the formation of cycloadduct (**152**) arising from addition across the tether as well as cycloadducts (**153**) and (**154**) from addition across the

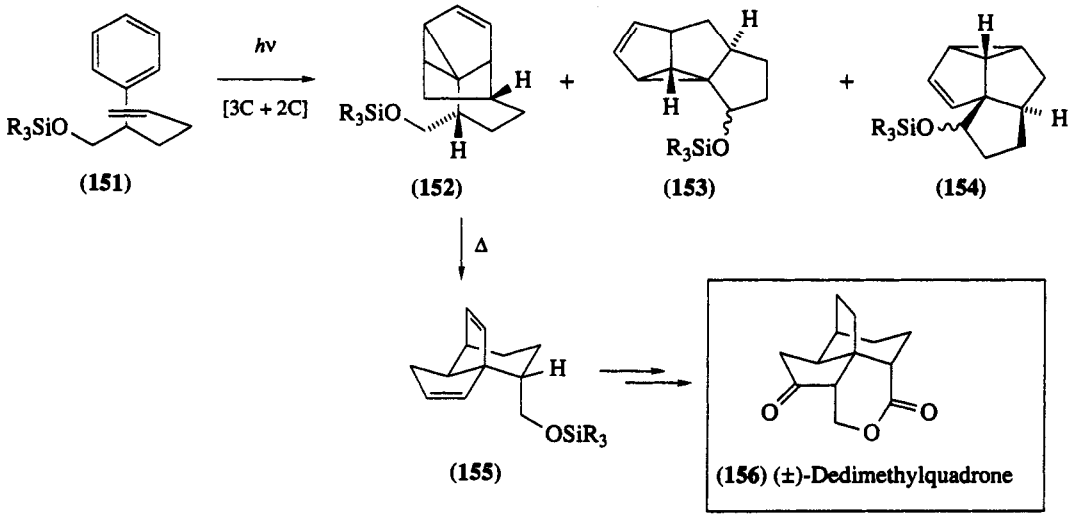


Scheme 19



Scheme 20

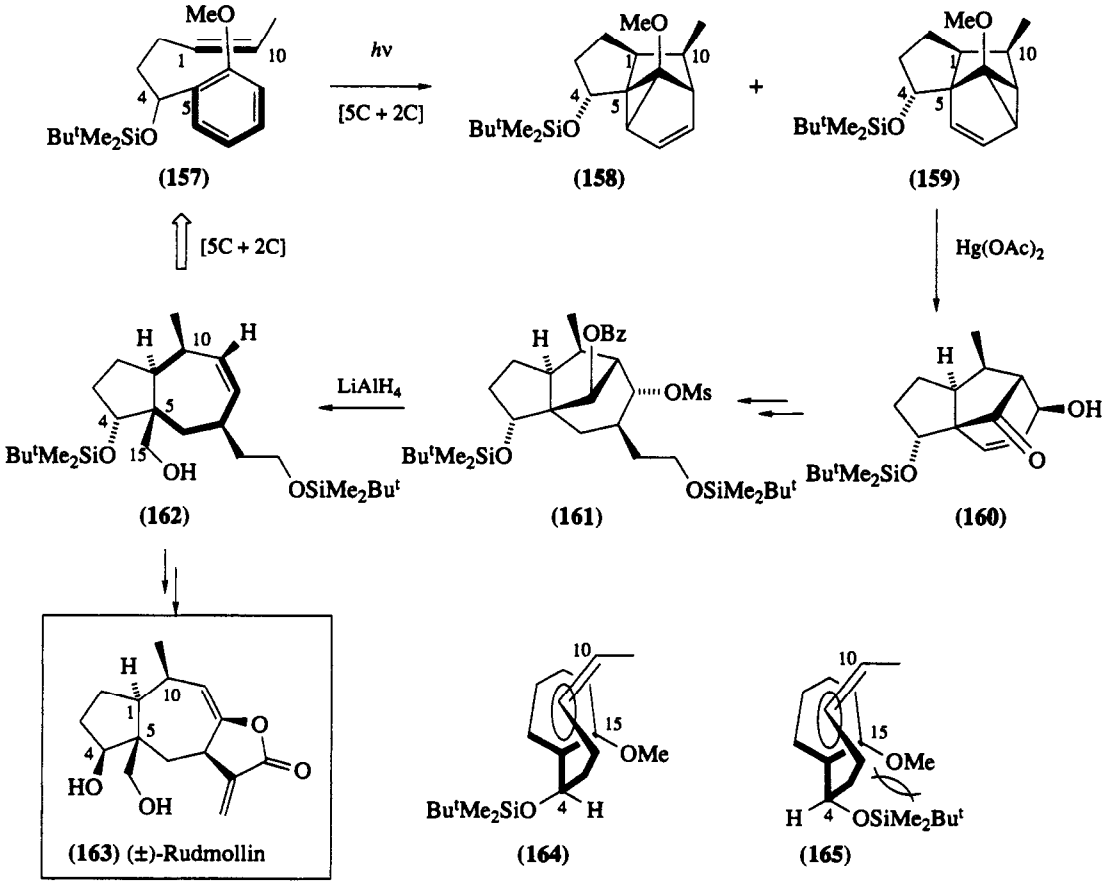
unactivated *ortho* position (5.8:1:1.1, respectively). This result reflects the intrinsic regiochemical preference for the intramolecular *meta* cycloaddition. Another noteworthy point of this study is the exclusive formation of one vinylcyclopropane isomer (**152**), corresponding to addition across the tether. This finding is in accord with the previous discussion regarding the influence of strain on the final cyclopropane



Scheme 21

closure, as the vinylcyclopropane isomer of (**152**) would possess a highly strained *trans*-fused bicyclo[4.1.0]heptane subunit. This study also provides another example of the effectiveness of the homosigmatropic 1,5-hydrogen shift, as thermolysis of cycloadduct (**152**) furnishes diene (**155**), which possesses the tricyclic core of quadrone.

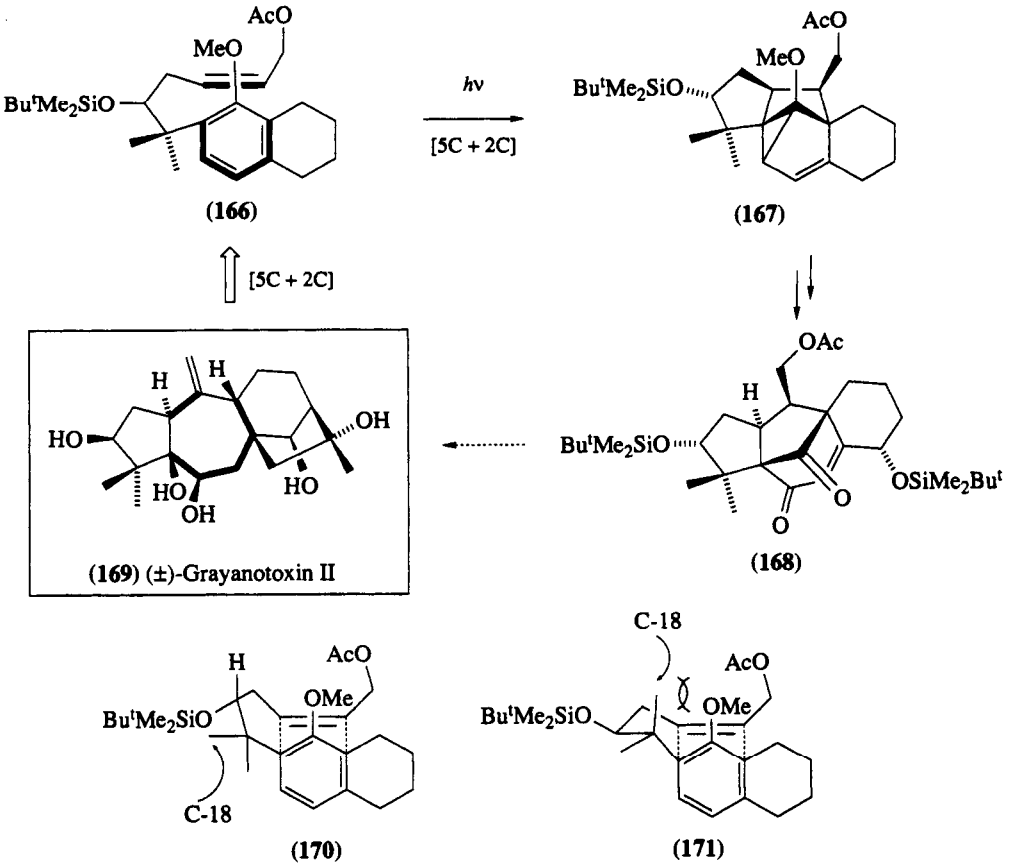
In all of the aforementioned studies, an arene–alkene *meta* cycloaddition is used to establish a five-membered ring through a [3C + 2C] connection. The obvious value of this process in five-membered ring synthesis can be readily extended to a [5C + 2C] approach to the synthesis of seven-membered rings through modification of the cycloadduct cleavage procedure. For example, rudmollin (**163**; Scheme 22), a pseudoguaiane with antileukemic activity, possesses the bicyclo[5.3.0]decane subunit of cycloadducts (**158**) and (**159**), which in turn are related to arene-alkene (**157**) by a *meta* cycloaddition reaction. The selectivity of the cycloaddition follows directly from previous considerations. Thus the arene and alkene substituents should favor a *meta* mode of addition, directed by the stronger donor (methoxy) and proceeding through the less-strained *exo* exciplex (**164**). Stereoinduction should be high and controlled by nonbonded interactions, which would destabilize exciplex (**165**), and by product development control, which favors positioning of the larger benzylic substituent on the less-encumbered cycloadduct face.



Scheme 22

Illustrative of the effectiveness of this [5C + 2C] approach to seven-membered rings, irradiation of arene-alkene (**157**) indeed affords two cycloadducts (**158**) and (**159**) (2:1) in 62% yield, each possessing a highly functionalized cycloheptanoid subunit.[45] At this point the key to the synthesis of rudmollin rests on the success of two bond cleavages. The first is accomplished by treatment of either or both cycloadducts with mercury(II) acetate. This reaction produces a common product (**160**). The next cleavage is based on mesylate (**161**), which is derived from ketone (**160**) and gives upon fragmentation bicyclo[5.3.0]decane (**162**), an immediate precursor to rudmollin (**163**). The control of stereochemistry at centers C-1, C-4, C-5 and C-10 in the key cycloaddition provides the basis for the general application of this strategy to guaiane and pseudoguaiane syntheses.

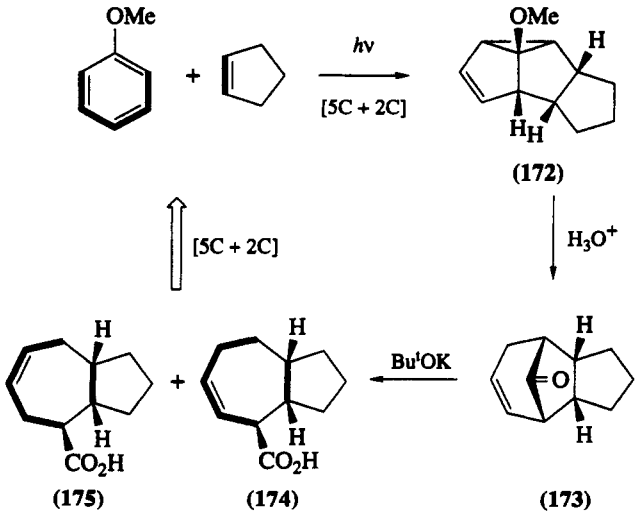
A further demonstration of the ring forming capabilities of the *meta* cycloaddition are seen in the investigation of its use for the synthesis of grayanotoxins, such as grayanotoxin II (**169**; Scheme 23).[46] Noteworthy in this effort is the use of a tetralin as an arene component. This study also involves the first examination of stereoinduction by a homobenzylic stereogenic center. Importantly, irradiation of arene-alkene (**166**) provides pentacycle (**167**) as the only detectable cycloadduct. Mode, regio- and *exo*- selectivity associated with this reaction are in accord with previous considerations, while stereoinduction can be rationalized from an examination of exciplexes (**170**) and (**171**). The latter would be expected to be destabilized by the indicated C-18 methyl/methoxy interaction, thereby favoring reaction *via* exciplex (**170**). The formation of only one vinylcyclopropane isomer is a predictable consequence of strain, which is minimized when the methoxy and C-18 methyl groups are on a cyclopropane bond rather than the shorter σ-bond of the isomer of (**167**). Overall, this transformation is a rather dramatic demonstration of the synthetic capabilities of the *meta* cycloaddition as it allows the one-step conversion of a simple bicyclic material to a pentacyclic product with seven stereogenic centers.



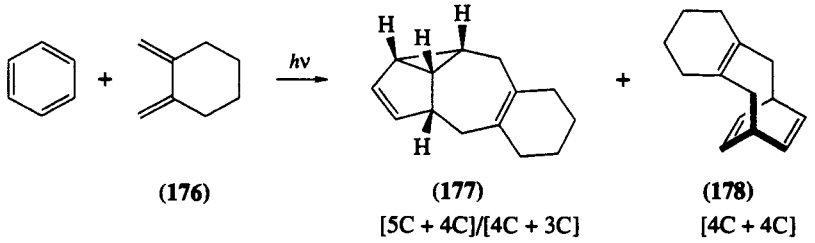
Scheme 23

Intermolecular *meta* cycloadditions provide yet another option for the facile [5C + 2C] construction of seven-membered rings, as illustrated in Srinivasan's pioneering studies (Scheme 24).[47] The availability of simple arenes and alkenes and of numerous methods as discussed above for the modification of *meta* cycloadducts makes this a particularly effective stategy for cycloheptanoid synthesis.

In contrast to the major developments in the use of [3C + 2C] and [5C + 2C] cycloadditions based on the arene–alkene *meta* cycloaddition, relatively less is known about the use of the *meta* cycloaddition as a means to achieve [3C + 4C] and [5C + 4C] connections. Nevertheless, these processes have great potential, provided that the factors determining their selectivity could be elucidated. For example, benzene and diene (**176**) (equation 16) undergo cycloaddition to furnish a [3C + 4C] (or [5C + 4C]) cycloadduct (**177**) and a [4C + 4C] cycloadduct (**178**).[48] Cleavage of the former adduct as in the aforementioned cases would provide access to seven- or nine-membered rings. While most dienes react with arenes to give [4C + 4C] cycloadducts, the range of dienes and arenes studied thus far is too limited to rule out the development of [3C + 4C] and [5C + 4C] cycloadditions as useful synthetic processes.



Scheme 24



(16)

In summary, this chapter has highlighted the mechanistic and synthetic advances which have been realized in studies on arene–alkene cycloadditions, primarily during the past decade. Much is now understood but far more remains to be done. Critical tests of the leading mechanisms are necessary to establish their generality. It would also be highly desirable to determine how the available mechanistic insight might be put to practical use in, say, increasing the yield of inefficient cycloadditions. Many simple additions, for example, proceed in only 60–70% yield. Another major but as yet unexplored aspect of these cycloadditions relates to control of absolute stereochemistry. Given the sophistication of mechanistic models, such studies could be very valuable, from both mechanistic and synthetic considerations.[49] A further area of great importance pertains to the development of the *ortho* and *para* modes of cycloaddition as methods for complex molecule synthesis. Given the ways in which such cycloadducts can be formed and manipulated, the synthetic potential of these processes is vast. The past decade has witnessed an exciting and significant surge of research on the arene–alkene cycloadditions. It is clear that these reactions will continue to be a highly significant subject for future mechanistic and synthetic research.

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49. Studies related to this point are under way at Stanford University.

6.1
Cyclobutene Ring Opening Reactions

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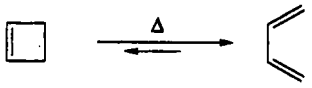
6.1.1 INTRODUCTION

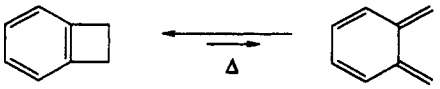
Cyclobutenes and 1,3-butadienes can be interconverted by either thermal or photochemical means. The thermal conversion of a number of simple cyclobutenes to the corresponding 1,3-dienes was first noted in the early 1950s.[1] Typically, simple cyclobutenes are thermodynamically less stable than the open-chain dienes due to the considerable ring strain. For the parent pair, cyclobutene → 1,3-butadiene (equation 1), the energy difference is 28.5 kcal mol^{-1}.[2] In contrast, the 1,3-diene isomer is generally considerably less stable than the ring form when the double bond of the ring is part of an aromatic system, for example in benzocyclobutene, since ring opening in this case results in loss of aromaticity (equation 2).

The generality of the thermal ring opening of cyclobutenes and the ease with which it often takes place has made this reaction an important route to 1,3-dienes of defined structure. More important however is the *in situ* generation of reactive 1,3-dienes, especially short-lived dienes such as *o*-quinodimethane (**1**) or vinylketene (**2**) (equation 3). *o*-Quinodimethanes typically undergo subsequent [4 + 2] cycloaddition or ene reactions. In contrast, both [2 + 2] and [4 + 2] cycloadditions have been observed for the vinylketenes. In addition, both species partake in six-electron electrocyclic reactions if an additional vinyl or aryl group is present. Such tandem sequences represent powerful strategies for the synthesis of complex target molecules.

This chapter is restricted to a short, but by no means complete, review of key synthetic routes to cyclobutenes, benzocyclobutenes and cyclobutenones and a generally qualitative discussion of the way in which substituents control both the ease of ring opening and the stereochemistry of the products obtained. The reader should thus be in position to make useful predictions. Finally we have included pertinent synthetic applications which illustrate in useful and often very imaginative ways the value of the

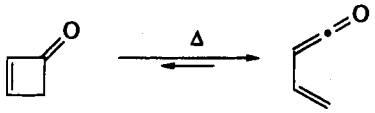


(1)



(1)

(2)



(2)

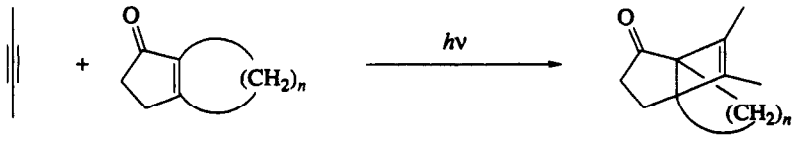
(3)

thermal cyclobutene ring opening reaction in organic synthesis. The photochemical ring opening of cyclobutenes is rarely useful in a synthetic strategy and will not, except for one or two examples, be addressed in this review.

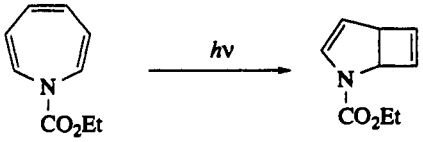
6.1.2 PREPARATION OF CYCLOBUTENES

A summary of most of the available routes to cyclobutenes and cyclobutenones is given in equations (4)–(7). These approaches can be divided into two major strategies. (a) Cycloaddition between an alkyne and an alkene to give directly a cyclobutene. In the case where the alkene partner is a ketene, cyclobutenones are obtained (see Section 6.1.5). (b) Introduction of a double bond into a preformed cyclobutane derivative, typically *via* an elimination reaction.

Owing to space restrictions only a few general comments will be made concerning these methods. The photochemical [2 + 2] cycloaddition utilizes simple alkynes (acetylene and mono- or di-alkyl derivatives) and alkenes bearing at least one strongly electron-withdrawing group (equation 4a).[3] Yields are usually above 50%, often higher than 80%. Bicyclic cyclobutenes can be prepared by irradiation of cyclic or heterocyclic 1,3-dienes or 1,3,5-trienes, as exemplified by the photolysis of *N*-ethoxycarbonyl-1*H*-azepine (equation 4b).[3]



(4a)

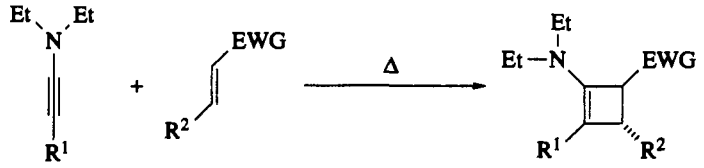


(4b)

Thermal [2 + 2] cycloadditions proceed to give cyclobutenes either when an alkyne bearing an electron-withdrawing group is reacted with an electron-rich alkene such as an enamine[4] or enol ether (equation 5), or when the alkyne substituted with an electron-donating group, such as dimethylamino, is heated with electron-poor alkenes (equation 6).[5] Good to excellent yields of cyclobutenes are generally obtained.

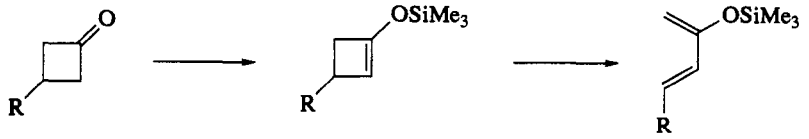
(5)

X = H, Y = OR; X = NR_2, Y = alkyl



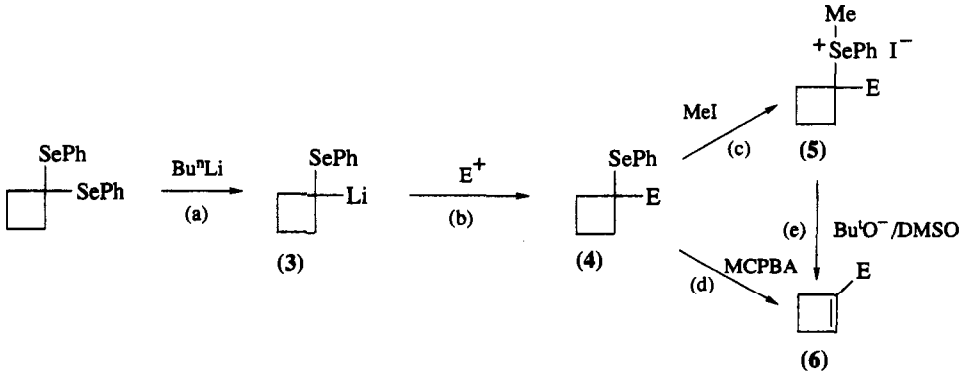
$R^1 = R^2$ = alkyl or aryl (6)

Intact cyclobutanes, especially cyclobutanones, can serve as obvious precursors to many cyclobutenes. For example, cyclobutanones have been converted to their silylated enol ethers by standard methodology.[6] Thermolysis of these intermediates gives rise to 1-alkoxysilyl-1,3-butadienes (equation 7).



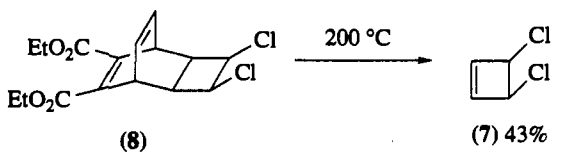
(7)

Halazy and Krief[7] have converted cyclobutanone into 1-lithio-1-selenophenylcyclobutane (**3**) by treating 1,1-diselenophenylcyclobutane with Bu^nLi. The lithio derivative can be trapped with a variety of electrophiles including alkyl halides, epoxides and aldehydes or ketones to yield the selenides (**4**). Unsaturation is introduced into the ring *via* a *cis* elimination from the *in situ* formed selenoxide or by β-elimination from the methylselenonium salt (**5**). Control of the regiochemistry in the elimination steps to give cyclobutenes rather than methylenecyclobutanes is possible. For example, the use of NaH or Bu^tO^- in DMF to affect the β-elimination of MeSePh from (**5**) leads only to the cyclobutenes (**6**) since under these strongly basic conditions alkylidenecyclobutanes are cleanly isomerized to 1-alkylcyclobutenes. The yields are typically in the range 70–90% in steps (a) and (b) and 60–65% for either (d) or (e) (Scheme 1).



Scheme 1

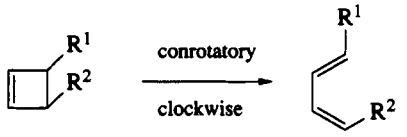
A number of less general routes to cyclobutenes have also been described. These include the ring enlargement of cyclopropyl substituted carbenes[8] and the acid-catalyzed ring enlargement of both 3-hydroxymethylcyclopropenones[9] and 3-acylcyclopropenones.[10] Finally, mention should be made of the large-scale preparation of *cis*-3,4-dichlorocyclobutene (**7**) *via* a retro Diels–Alder reaction of the cyclobutane (**8**), prepared in two steps from cyclooctatetraene.[11] 3,3-Dimethoxycyclobutene has also been prepared *via* a retro Diels–Alder reaction.[12]



(**8**) (**7**) 43%

6.1.3 RULES PERTAINING TO THE THERMAL CYCLOBUTENE RING OPENINGS

The thermally activated conversion of cyclobutenes to 1,3-butadienes is controlled by orbital symmetry. Woodward and Hoffman[13] and Fukui[14] described the allowed thermal process as conrotatory, *i.e.* one in which the substituents at C-3 and C-4 both move in the same direction, either in a clockwise (equation 8) or counter-clockwise fashion (equation 9). In the photochemical process the motion of the same substituents is in the opposite direction, resulting in the formation of either a *trans,trans* or a *cis,cis* 1,3-diene (equations 10 and 11).



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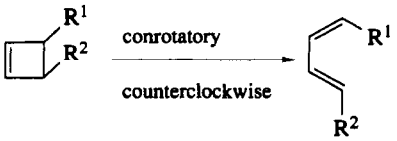

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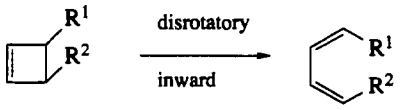

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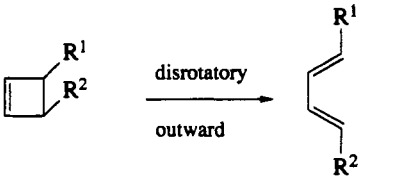


(11)

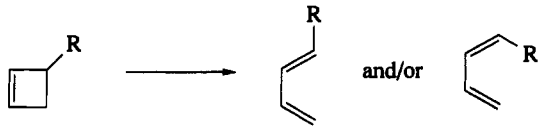
It has been demonstrated that the thermally allowed conrotatory process is 15 kcal mol^{-1} more favorable than the disrotatory mode.[15] It should be noted that the 'disallowed' process can be observed for molecules in which the allowed conrotatory process is structurally denied. Such a situation exists for the series of *cis*-[*n*.2.0] bicyclics when $n < 3$ since the monocycle formed upon ring opening cannot accomodate a *trans* double bond.[16] Ring opening in these molecules to yield the observed *cis,cis*-1,3-dienes could occur *via* the forbidden disrotatory mode, the allowed conrotatory mode followed by isomerization, or by a nonconcerted diradical process. Bicyclo[2.1.0]pent-2-ene converts to 1,3-cyclopentadiene at room temperature, bicyclo[2.2.0]hex-2-enes typically require temperatures above 150 °C for isomerization to 1,3-cyclohexadienes, while the corresponding bicycloheptenes are stable to nearly 400 °C. Lower temperatures (250 °C) are again found for the bicyclo[4.2.0]oct-7-enes, where a conrotatory ring opening to a *cis,trans*-1,3-cyclooctadiene becomes sterically feasible. These temperatures should be compared with the 175–180 °C range necessary to isomerize *cis*-3,4-dimethylcyclobutene to *cis,trans*-2,4-hexadiene.[17]

6.1.3.1 Substituent Effects on the Cyclobutene Ring Opening Reaction

A number of authors have recently reported detailed studies on the cyclobutene → 1,3-butadiene ring opening reaction in order to gain a better understanding of the many diverse results which have been compiled over the past 40 years. An excellent compilation of data, including various thermodynamic perameters, is available in the 1980 monograph by Marvell.[1]

In a lengthy theoretical paper, Rondan and Houk considered the available data, described *ab initio* calculations and discussed earlier explanations concerning the stereochemical aspects of the ring openings of substituted cyclobutenes.[18] These authors came to the following conclusions. The stereochemistry of the thermal electrocyclic conrotatory ring opening of 3- and 4-substituted cyclobutenes is controlled by

electronic effects. Electron-donating substituents prefer to rotate outward, with the preference increasing as the electron donor ability of the substituent increases. Conversely, powerful electron-withdrawing substituents were predicted to have the opposite effect and rotate inward (equation 12).

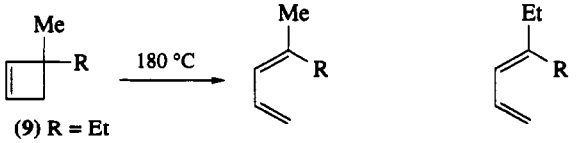


(12)

For the 3,3-disubstituted and *cis*-3,4-disubstituted cyclobutenes it was predicted that the stronger electron donor would rotate outwards while the weaker donor rotates inward. In the case of the *trans*-3,4-isomers, outward rotation of both substitutions would normally be expected; however, calculations have predicted that the in-in rotation is preferred for two *trans* 3,4-BH_2 substituents.[18]

The above generalizations should be sufficient to serve most of the needs of the synthetic chemist. Those interested in obtaining a more detailed understanding of the theoretical basis of the arguments are referred to the Rondan and Houk paper and the references therein.[18] Some examples which illustrate the application of these guidelines are shown below for 3,4-disubstituted cyclobutenes and benzocyclobutenes.

The thermolysis of 3,3-, 3,4-*cis*- and 3,4-*trans*-disubstituted cyclobutenes can provide useful comparisons of the propensity of two substituents to rotate either inward or outward. Frey and his colleagues[19] were amongst the first to note that the simple notion of the larger the substituent the greater the tendency for outward rotation, was incorrect. They showed that the activation energy for isomerization to the 1,3-diene was less for 3,3-diethylcyclobutene than for the 3,3-dimethyl analog and thereby inferred that an ethyl group rotates inward more readily than a methyl group. This conclusion was verified by the observation that 3-ethyl-3-methylcyclobutene (**9**) gave a 68:32 mixture of the dienes (**10**) and (**11**) when heated in the gas phase at 180 °C. In a subsequent study, Curry and Stevens[20] showed that the preferred inward rotation of the sterically larger group was also observed for 3-methyl-3-propylcyclobutene and the 3-methyl-3-isopropyl analog. Even in the competition between methyl and *t*-butyl, the bulky *t*-butyl group rotated inward to a surprisingly large (32%) extent. Replacement of the alkyl group by phenyl, substituted phenyl or cyclopropyl groups resulted in a mixture of products in which these groups rotated inward to the extent of 30–50%. These data are summarized in Table 1. Rationalization of the results in terms of extra stabilization of the transition state for an aryl group rotating inward, and destabilization of transition state relative to methyl when the alkyl group rotates outward, were put forward.[20] Some of these arguments were later questioned by Houk.[18]



(**9**) R = Et

(**10**) 68%

(**11**) 32%

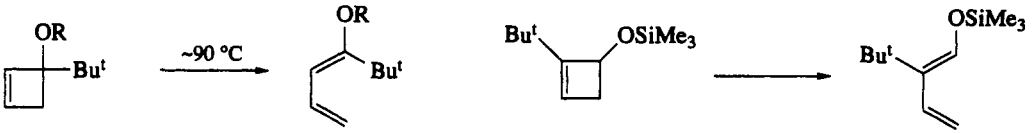
Table 1 Gas-phase Thermolysis of 3,3-Disubstituted Cyclobutenes (**9**)

R in (**9**)	*Diene* (**10**) (%)	*Diene* (**11**) (%)
Ethyl	68	32
Isopropyl	66	34
n-Propyl	62	38
t-Butyl	32	68
Cyclopropyl	43	57
Phenyl	30	70
4-Methoxyphenyl[a]	52	48
4-Cyanophenyl[a]	45	55

[a]At 161 °C.

Perhaps the most spectacular illustrations of the above 'rules' come from the Houk group. For example, these authors were able to show that heating 3-*t*-butyl-3-methoxycyclobutene (**12**), or the 3-trimethylsilyloxy analog (**13**) in C_6D_6 (90–95 °C) or $CDCl_3$ (reflux), respectively, afforded only the dienes

(14) and (15).[21] Clearly, the direction of rotation of the substituents is not dominated by the steric interactions encountered by the inward rotating substituent. Steric interactions encountered by the outward rotating substituent are also readily overcome if it is strongly electron donating, as shown by the clean conversion of (16) to (17).



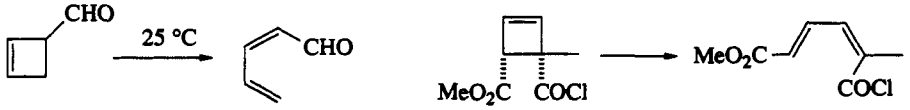
(12) R = Me
(13) R = $SiMe_3$

(14) R = Me
(15) R = $SiMe_3$

(16)

(17)

The preferred, predicted inward rotation of the strongly electron-withdrawing formyl group was also verified experimentally.[22] Thus cyclobutene-3-carbaldehyde (18) undergoes ring opening at room temperature with a half-life of about 50 h to give (*Z*)-2,4-pentadienal (19) accompanied by less than 2% of the (*E*)-isomer. The preference for inward rotation by the formyl group is thus greater than 2.7 kcal mol^{-1}. Based on these findings, a chlorocarbonyl group is expected to follow this trend. As predicted, the methyl ester (20) undergoes selective ring opening (at room temperature!) to give the diene (21). Less electrophilic carbonyl functions such as ketones and, even more so, carboxylic acids, esters and amides, show an increased tendency to rotate outward. Thus the ketoester (22) gave a 2:1 mixture of two (*E,Z*) products (23) and (24). The major product resulted from inward rotation of the keto and outward rotation of the ester group.[23]

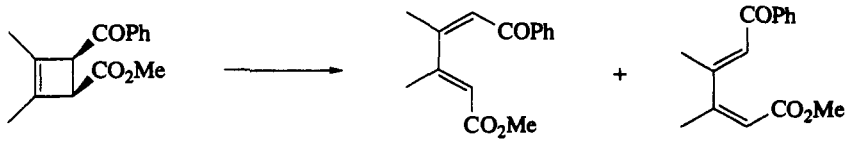


(18)

(19)

(20)

(21)

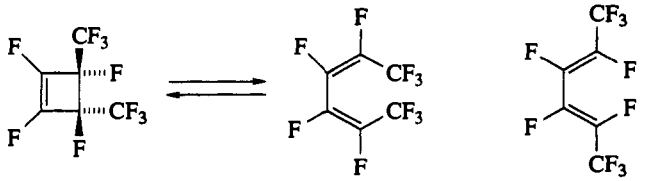


(22)

(23)

(24)

Halogen substiuents show a strong tendency for outward rotation.[24] The particularly strong tendency by fluorine to rotate outward has been demonstrated by the work of Dolbier *et al.*,[24a,b] who have shown that ring opening of the perfluorinated cyclobutene (25) gives (26) in which preference for outward rotation of the two *trans* 3,4-fluorine substituents forces the relatively large trifluoromethyl substituents to rotate inward. The activation energy for the ring opening of (25) to (26) is approximately 18 kcal mol^{-1} lower than that leading to (27). These results are consistent with the Rondan and Houk calculations which showed that strong *p*-electron donating substituents rotate preferentially outward.[18] Interestingly, in the perfluorinated series studied by Dolbier *et al.* the 1,3-dienes are generally less stable than the corresponding cyclobutenes, in contrast to most 1,3-diene–cyclobutene equilibria.



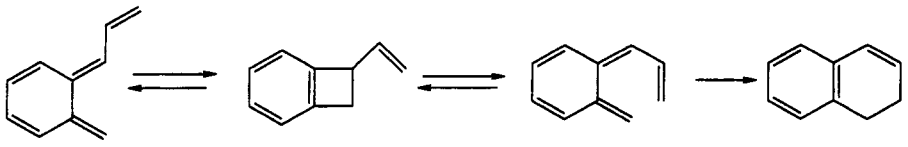
(25)

(26)

(27)

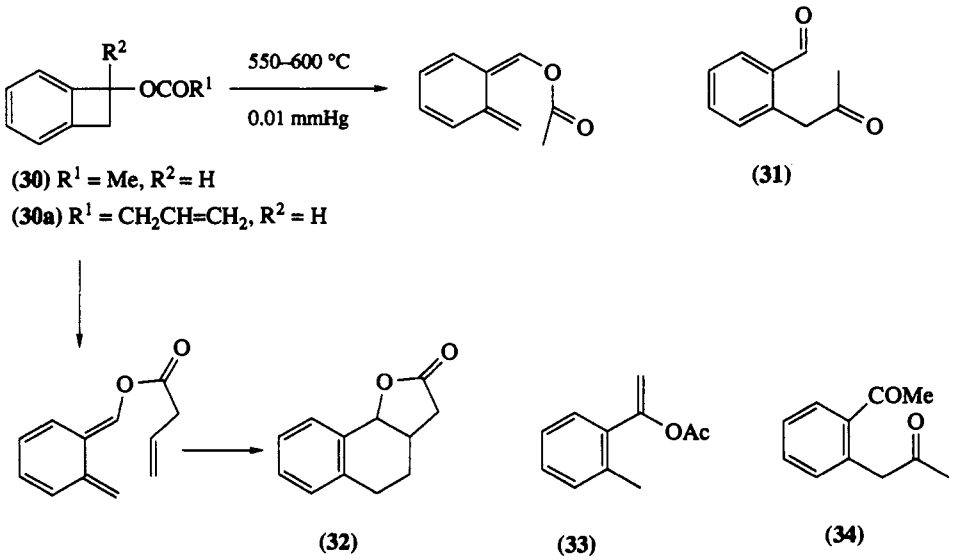
Inward rotation by substituents which normally prefer outward motion can be observed when the ring opening reaction is reversible, as in the case of benzocyclobutene → *o*-quinodimethane (equation 2), and the less favored isomer is further transformed by an irreversible reaction. For example, 1-vinylbenzocy-

clobutene (**28**) when heated in the absence of a dienophile yields 1,2-dihydronaphthalene *via* inward rotation of the vinyl group to give (**29**), followed by an electrocyclic ring closure.[25]



(**28**) (**29**)

Under flash vacuum thermolysis conditions (550–600 °C/0.01 mmHg), even an acetoxy group can be induced to rotate inward, as shown by the conversion of (**30**) to the ketoaldehyde (**31**).[26] The presence of a suitably placed dienophile, even the weak terminal vinyl group as in (**30a**), results only in the intramolecular Diels–Alder product (**32**), thereby demonstrating the large preference for outward motion by an acyloxy derivative.[26] Similar thermolysis of 1-acetoxy-1-methylbenzocyclobutene (**30**; $R^1 = R^2 = Me$) afforded a 96:4 mixture of the vinyl acetate (**33**) and the diketone (**34**); these products arise from outward and inward rotation of the acetoxy group, respectively (Scheme 2).

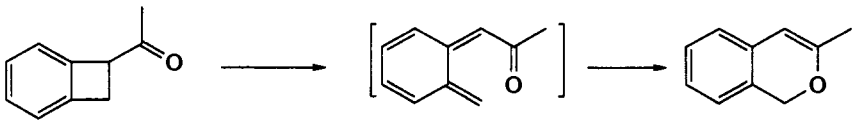


(**30**) R^1 = Me, R^2 = H
(**30a**) R^1 = $CH_2CH{=}CH_2$, R^2 = H

(**31**) (**32**) (**33**) (**34**)

Scheme 2

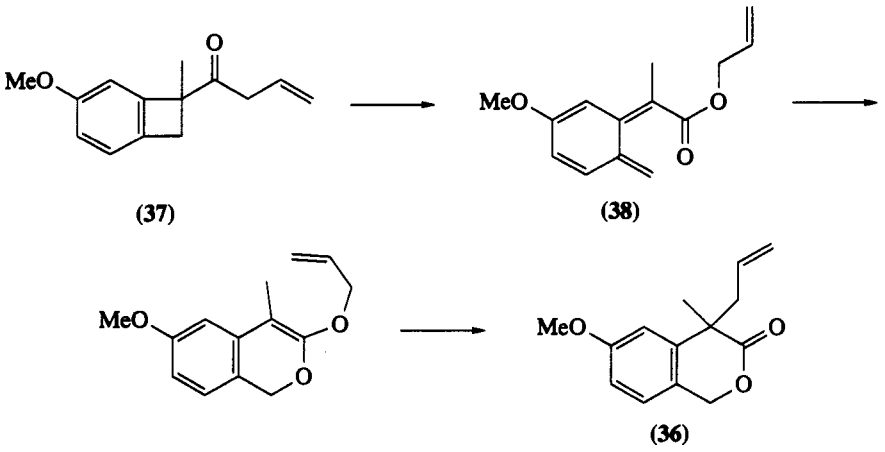
Based on the Houk predictions regarding cyclobutene-3-carbaldehyde,[18] the easy isomerization of 1-acetylbenzocyclobutene to the benzopyran (**35**),[27] which proceeds *via* inward rotation of the acetyl group and a subsequent cyclizations, is not surprising.



(**35**)

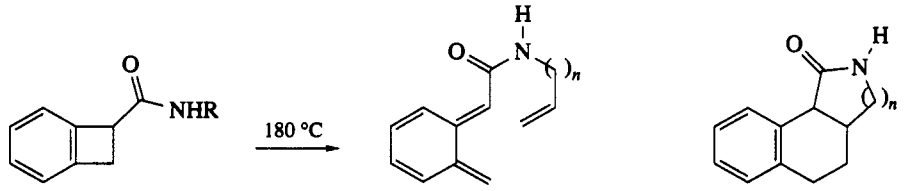
Fukumoto *et al.*[28] have taken advantage of the propensity for inward rotation of an acyl group to prepare the isochroman-3-one (**36**), an intermediate in their synthesis of geneserine, a constituent of the calabar bean. The conversion of the benzocyclobutene (**37**) to (**36**) proceeds *via* ring opening to the *o*-quinodimethane (**38**) followed by cyclization and a 3,3-sigmatropic rearrangement.

Oppolzer,[29] in a series of key papers in 1974, showed that the amide substituents in the benzocyclobutenes (**39**) can rotate outward to give the dienamides (**40**) as intermediates. Intramolecular trapping by the remote alkene groups afforded the tricyclic derivatives (**41**) in very good to excellent yields. This work clearly established the value of benzocyclobutenes in the preparation of complex polycyclic target



(37) (38) (36)

molecules. No evidence of inward rotation of the CONHR group, which could have resulted in a 3-amino substituted benzopyran, was reported.

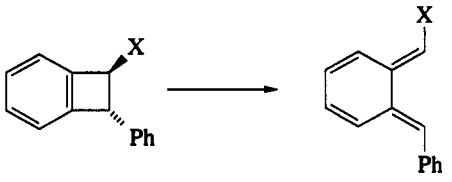


(39) (40) $n = 1, 2$ (41) $n = 1, 2$

From a synthetic point of view it is useful to know not only the direction of rotation of the substituents, *i.e.* the stereochemistry of the diene produced, but also the temperatures at which cyclobutenes open at synthetically useful rates. Much of the early work in this area has been done without the synthetic aspect in mind and some of the temperatures quoted below may be of value only for comparison purposes.

For the synthetic chemist the following should serve as useful guidelines. If an electron-donating substituent at the sp^3 carbons is able to rotate outward it lowers significantly the temperature required for cyclobutene ring opening. The stronger the electron-donating ability, especially *via* resonance effects, the lower the temperature for isomerizations.

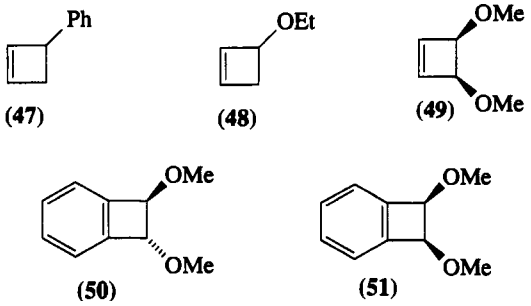
This conclusion is nicely illustrated by the series 1-phenylbenzocyclobutene (**42**), *trans*-acetoxy-2-phenylbenzocyclobutene (**43**) and the *trans*-1-methoxy (**44**) and *trans*-1-alkoxy (**45**) analogs. These compounds undergo synthetically useful rates of ring opening to the corresponding *o*-quinodimethanes at approximately 190–210 °C for (**42**),[30] 150–170 °C for (**43**),[31] 100 °C for (**44**)[32] and <0 °C for (**45**).[33] In each of the latter three cases, both substituents rotate outward.



Compound	*Reaction Temp.* (°C)
(**42**) X = H	>200
(**43**) X = OAc	150
(**44**) X = OR	80–110
(**45**) X = O^-	<0
(**46**) X = Ph	20

A similar trend can be found in the monocyclic series. As expected, the difference between cyclobutene itself and a 3-alkyl substituted cyclobutene is relatively minor. For 3-phenylcyclobutene (**47**) the extra stabilization of the transition state for either the in or out rotation is sufficient to lower the ring opening temperature to approximately 100 °C.[34a] An even more dramatic lowering to 30–50 °C is observed for the isomerization of (**48**) to (*E*)-1-methoxy-1,3-butadiene.[34b] The difference between (**48**) and *cis*-1,2-diethoxycyclobutene (**49**) can be ascribed to the fact that in (**49**) one of the methoxy groups is forced to undergo an unfavorable inward rotation. A similar differential exists for *cis*- and *trans*-1,2-di-

methoxybenzocyclobutenes (**50**) and (**51**). These compounds, together with others bearing representative substituents and the 'best estimate' of the temperature required for a reasonable rate of ring opening, are collected in Table 2; many further examples can be found in the Marvell monograph.[1] Further comments concerning reaction conditions, and propensity for outward or inward rotation during ring opening, will be made at appropriate places during the discussion of synthetic applications of the cyclobutene ring opening reactions.



(**47**) (**48**) (**49**) (**50**) (**51**)

Table 2 Ring Opening Temperatures of Representative Cyclobutenes

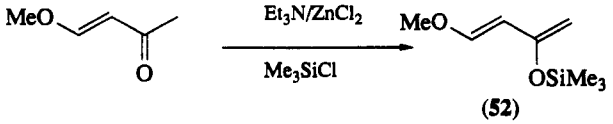
Compound	*Temp. (°C)*	*Ref.*
cis-3,4-Dimethylcyclobutene	175	1
Cyclobutene	150	1
3-Methylcyclobutene	150	1
cis-3,4-Dichlorocyclobutene	135–165	24c
cis-3,4-Di(methoxycarbonyl)cyclobutene	120	1
3-Phenylcyclobutene (**47**)	98	34a
trans-3,4-Dichlorocyclobutene	90	24c
cis-3,4-Dimethoxycyclobutene (**49**)	>80	38
cis-3,4-Bis(hydroxymethyl)cyclobutene	60–70	39
3-Ethoxycyclobutene (**48**)	30–50	34b
cis-3,4-Diphenylcyclobutene	27	1
3-Formylcyclobutene	25	22
3-Formyl-4-hydroxymethylcyclobutene	<0	39
trans-1,2-Dimethoxybenzocyclobutene (**50**)	80	115
cis-1,2-Dimethoxybenzocyclobutene (**51**)	>110	115
2,3-Dimethylcyclobutenone	120	82

6.1.4 SYNTHESIS *VIA* CYCLOBUTENES

6.1.4.1 Preparation of Reactive 1,3-Dienes

One of the more obvious synthetic uses of cyclobutenes which has already been mentioned is for the preparation of specifically substituted 1,3-dienes, often to be used in subsequent [4 + 2] cycloaddition reactions.

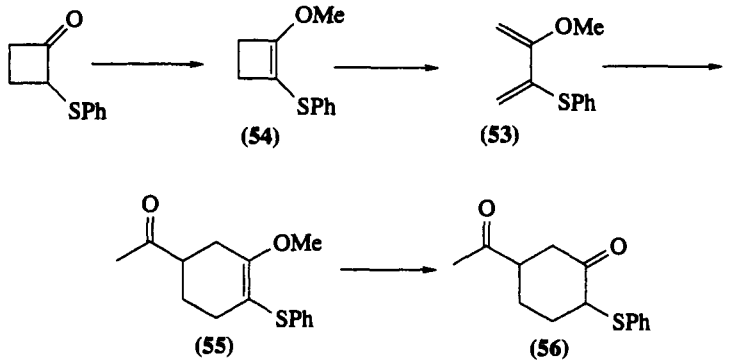
The synthetic value of highly oxygenated 1,3-dienes in both the Diels–Alder and hetero Diels–Alder reaction is evident from the outstanding work of the Danishefsky group.[35] They typically prepared such compounds, *e.g.* (**52**), by converting the appropriate ketone into its enol silyl ether.



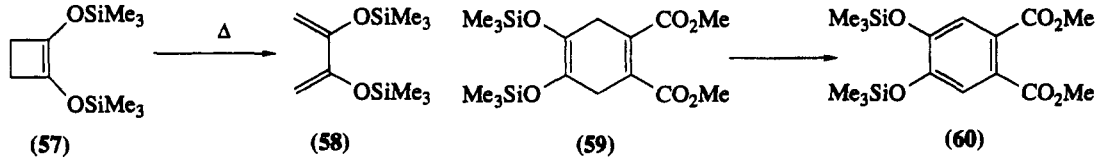
(**52**)

A number of authors have shown that, in addition to the above route, highly oxygenated 1,3-dienes can be prepared from the corresponding cyclobutene enol silyl ethers. For example, 2-methoxy-3-phenylthiobuta-1,3-diene (**53**) was obtained in essentially quantitative yield by rapid passage of a hexane solution of 1-methoxy-2-phenylthiocyclobut-1-ene (**54**) through a column containing glass helices at 340 °C.[36a]

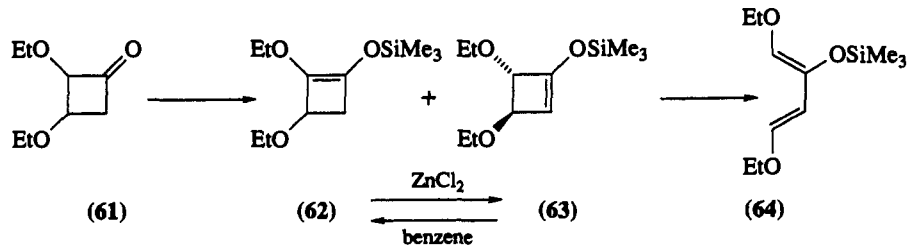
Diene (**53**) undergoes Diels–Alder reactions with unsymmetrical dienophiles such as methyl vinyl ketone to give preferentially the adduct (**55**). Further manipulations of (**55**), such as acid hydrolysis to an α-phenylthiocyclohexanone (**56**), were carried out.



2,3-Bis(trimethylsilyloxy)-1,3-butadiene (**58**) has been obtained from the cyclobutene (**57**) in 84% yield (6 h, 180 °C). This compound, as expected, reacted with dimethyl acetylenedicarboxylate to furnish adduct (**59**) in 82% yield after a 24 h reflux in toluene; oxidation yielded the substituted phthalate (**60**).[36b]

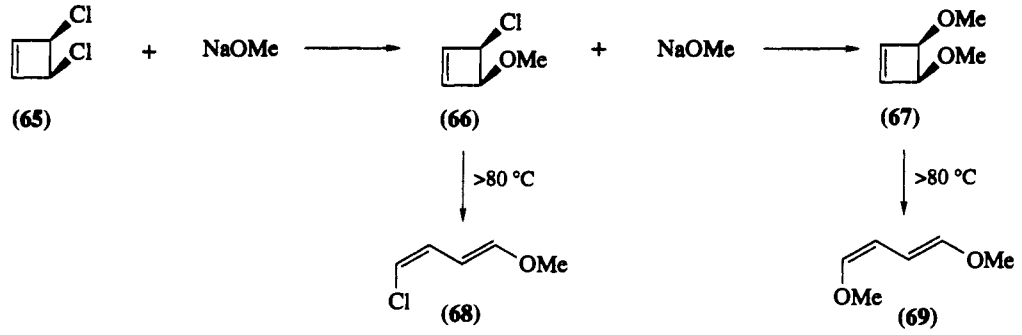


Aben and Scheeren[37] have described a rather general approach to even more highly oxygenated 1,3-dienes based on the reaction of vinyl ethers or ketene acetals with ethoxyketene generated *in situ* from ethoxyacetyl chloride and triethylamine. Thus the cyclobutanone (**61**), obtained in 80% yield from ethoxyvinyl ether and ethoxyketene, was converted into a mixture of enol silyl ethers (**62**) and (**63**) with Me_3SiCl and $ZnCl_2$ in benzene. Since the *trans*-3,4-diethoxy derivative (**63**) undergoes ring opening at considerably lower temperature (<25 °C), because of the preferred out-out rotation of both ethoxy groups, than the isomeric cyclobutene (**62**) (>80 °C), and since (**62**) and (**63**) are in equilibrium in benzene in the presence of $ZnCl_2$, essentially pure diene (**64**) can be obtained. The preparation of the ethoxy analog of the Danishefsky diene (**52**) in 85% yield from the thermolysis of 3-ethoxy-1-trimethylsiloxycyclobut-1-ene at 50 °C in MeCN was also described.

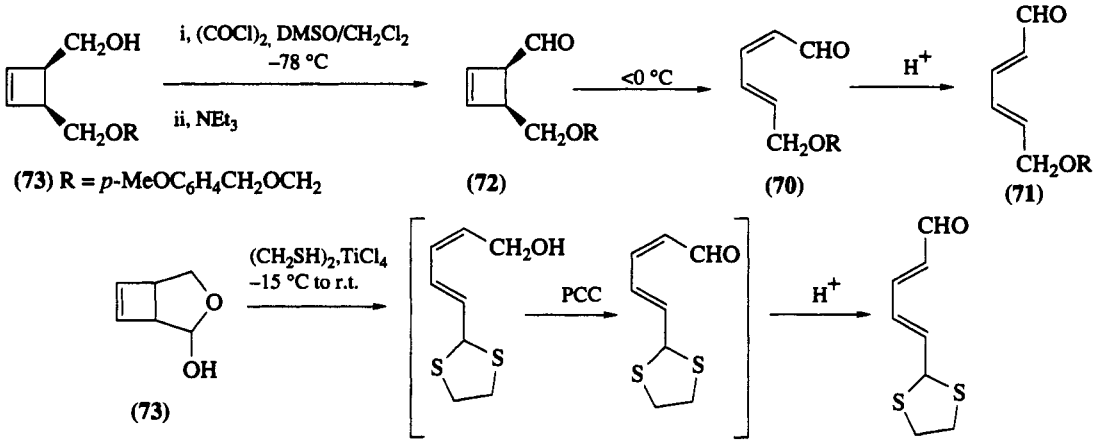


cis-3,4-Dichlorocyclobutene (**65**) reacts cleanly with 1 equivalent of NaOMe in MeOH *via* an S_N2' mechanism to yield *cis*-3-methoxy-4-chlorocyclobutene (**66**).[38] In the presence of excess methoxide the dimethoxy derivative (**67**) is obtained. When heated above 80 °C, both compounds undergo ring opening and furnish the (*E,Z*)-dienes (**68**) and (**69**), respectively.

The functionalized dienals (**70**) and (**71**), potentially of value as the C_5–C_{10} and C_7–C_{12} segments, respectively, in the synthesis of lipoxygenase derived metabolites of arachadonic acid, have been prepared in high purity as shown in Scheme 3.[39] The expected aldehyde (**72**) obtained by Swern oxidation of (**73**) underwent ring opening below room temperature to yield exclusively (**70**; 90%). Both the stereochemistry of the product which results from the electron-withdrawing formyl group preferentially rotating in-

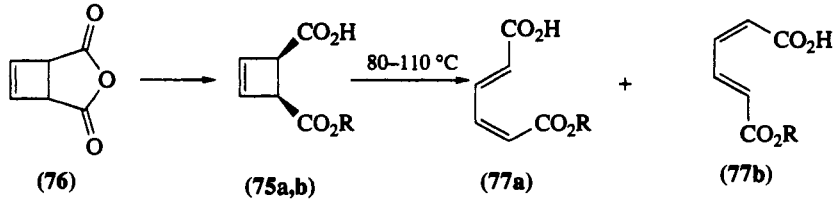


ward while the *p*-methoxybenzyloxymethyl group rotates outward, and the low activation energy for the ring opening, are predicted by the Rondan and Houk[18] calculations. Acid treatment of (**70**) caused isomerization to the thermodynamically more stable (**71**). The mono ethylenedithiol protected (*E,E*)-hexa-2,4-dienediol (**74**) was obtained when the hemiacetal (**73**) was reacted with 1,2-ethanedithiol/$TiCl_4$ at −15 °C followed by PCC oxidation. Presumably the initial ring opened product isomerized to (**74**) under the reaction conditions.



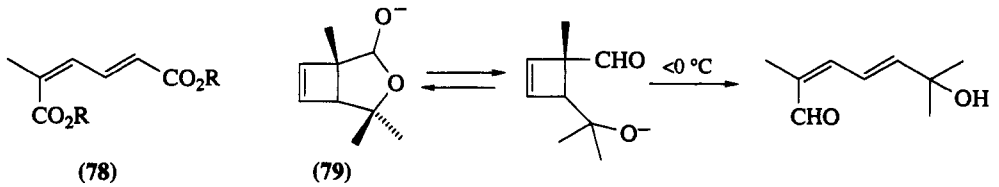
Scheme 3

Thermolysis of the half esters (**75a,b**) obtained upon reaction of the cyclobutene anhydride (**76**) with *n*-butanol or 2-trimethylsilylethanol and DMAP in DMSO at 110 °C gave approximately 1:1 mixtures of the dienoic acid esters (**77a,b**). Obviously there is no strong preference for outward (or inward) rotation of a carboxylic acid *vs.* a typical ester function. Interestingly, when the solvent was changed from DMSO to 1,2-dichloroethane a 3:1 ratio of (**77a**) to (**77b**) was formed. The variation in the isomer ratio can be rationalized by assuming that the effective size of the carboxylic acid group is larger in DMSO than in $ClCH_2CH_2Cl$ due to hydrogen bonding with the solvent and thus has a greater tendency to rotate outward in that solvent.[40] Alternatively, one could argue that in the presence of a hydrogen bond accepting solvent, the carboxylic acid function becomes more electron rich and thus shows a greater tendency to outward rotation compared with CO_2R.



a: R = Me; **b**: R = CH_2SiMe_3

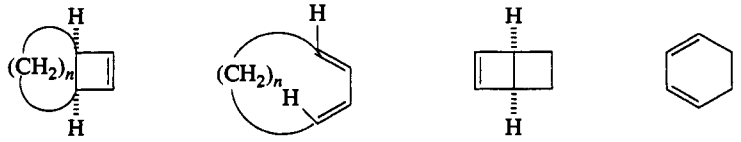
Replacement of C-3 or C-4 hydrogen by a methyl group in (**75**) leads to both a lowering of the temperature required for ring opening and stereospecific formation of the diene (**78**) due to the outward rotation of the methyl group.[41] The very dramatic lowering of the temperature for ring opening by an aldehyde substituent and its preference for inward rotation is illustrated by the inability to trap the hemiacetal-aldehyde (**79**), obtained upon DIBAL reduction of the corresponding lactone at –78 °C, with methoxymethylenetriphenylphosphorane.[42]



(**78**) (**79**)

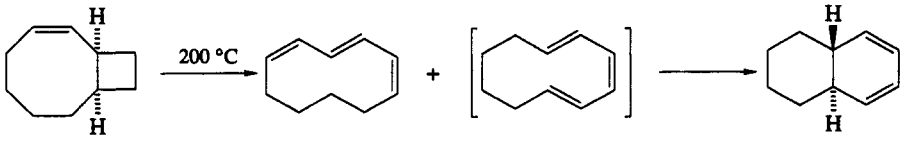
6.1.4.2 Two-carbon Ring Expansion *via* Cyclobutene Ring Openings

The possibility of a two-carbon ring enlargement *via* opening of a cyclobutene ring which is part of a bicyclo[*n*.2.0]alkene is shown schematically below. Assuming that the ring fusion is *cis* and that the number of atoms in the enlarged ring of the product is >8, the expected product should have both a *trans* and a *cis* double bond, *e.g.* (**80** → **81**).[43] Smaller ring final products cannot accommodate *trans* double bonds and thus cyclobutene ring openings producing, for example, (**82** → **83**) must occur either *via* a concerted symmetry forbidden[16,44] or a diradical pathway.[16] The ring expansion of bicyclobutenes such as (**80**; $n = 6$) occurs in the same temperature range, 160–200 °C, as found for most monocyclic *cis*-3,4-disubstituted cyclobutenes. Thus *cis*-bicyclo[6.2.0]cyclodec-2-ene is converted in 95% yield in 1 h at 200 °C to *cis,trans*-1,3-cyclodecadiene.[43]



(**80**) (**81**) (**82**) (**83**)

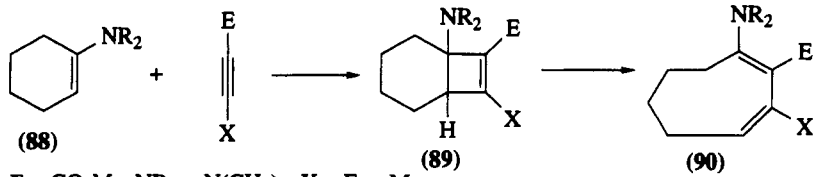
Dauben and Michno[45] studied the ring expansion of analogs such as (**84**). The double bond adjacent to the ring fusion reduced the thermolysis temperature to 140–160 °C. Typically similar amounts of the products (**85**) and (**86**) resulting from both the allowed modes of rotation of both substituents were observed. The *trans,cis,trans*-diene (**86**), formed by the inward rotation of the vinyl group, underwent a subsequent 6π-electrocyclic cyclization to the cyclohexadiene (**87**). The starting bicyclobutenes were prepared by ring expansion of the appropriate bicyclic cyclopropylmethylcarbenes.



(**84**) (**85**) (**86**) (**87**)

Bicyclobutenes which carry dialkylamino substituents at a bridgehead position have proved to be excellent synthetic intermediates. Such compounds are readily prepared by reaction of enamines of cyclic ketones (**88**) with alkynes bearing one or two electron-withdrawing groups, typically in apolar solvents such as ether. The presence of the strongly electron-donating dialkylamino group facilitates the ring opening such that it is sometimes difficult to isolate the bicyclobutene. The definitive work in this area has been carried out by Reinhoudt and coworkers.[46–49] Contrary to earlier studies, both experimental[50,51] and theoretical,[52] these authors have shown that ring opening of (**89**) occurs *via* the symmetry allowed conrotatory process when $n > 3$. As expected, the dialkylamino group rotates outward to yield the *trans,cis* ring-expanded diene (**90**).[46–48,53] This reaction is reversible in the case where $n = 3$.[46,47] Prolonged standing at room temperature typically converts (**90**) into the thermodynamically more stable

cis,trans-diene (**91**) *via* a 1,5-hydrogen shift. The isomeric *cis,cis*-dienes (**92**), which had previously been regarded as reaction products of enamines of cyclic ketones and DMAD, are a result of two consecutive 1,5-hydrogen shifts from (**90**) or, in some cases, simple isomerization of the strained *trans* double bond.[48] Compound (**91**) has reactivity which is comparable with that of (**88**) and thus a ring expansion sequence can be reiterated.[48]

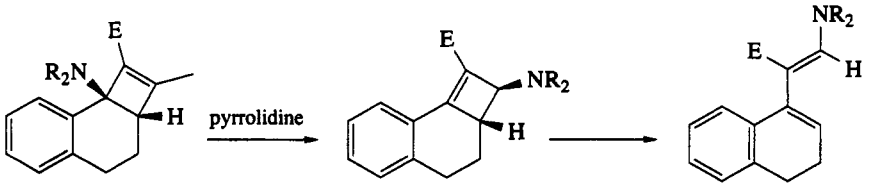


(**88**) (**89**) (**90**)

E = CO_2Me; NR_2 = $N(CH_2)_4$; X = E or Me

(**91**) (**92**)

Variations in the ring opening process with enamines derived from five- and six-membered ring ketones, such as tetralone (**93**), have been documented. When the bicyclic adduct (**94**) is warmed with pyrrolidine in chloroform, excellent yields of the diene (**96**) are obtained. This interesting transformation involves Michael addition of pyrrolidine to the cyclobutene (**94**) followed by elimination of the bridgehead pyrrolidine (S_N2') to generate a new cyclobutene (**95**) which undergoes a facile ring opening to (**96**).[46,49]

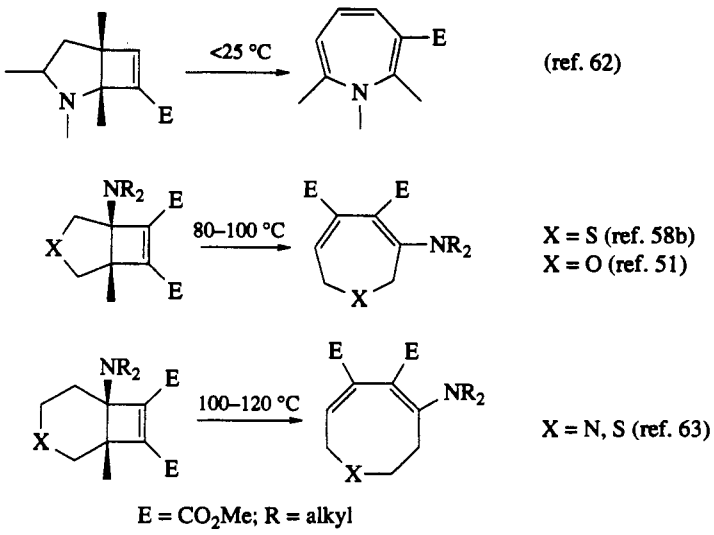


(**94**) E = CO_2Me; NR_2 = $N(CH_2)_4$ (**95**) (**96**)

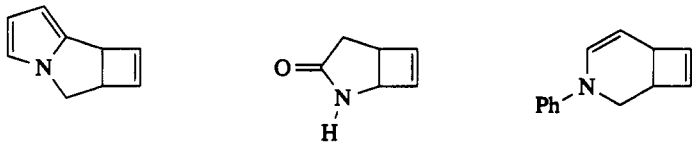
The enamine–acetylenedicarboxylate or ethyl propiolate ring expansion reaction has been used effectively in the synthesis of several natural products which contain medium or large rings, including steganone,[54] muxone,[55] velleral and related compounds.[56] The relevant sequence typically involves treatment of the appropriate enamine with DMAD or ethyl propiolate followed by hydrolysis of the ring expansion product with acid. The latter treatment regenerates the carbonyl group and causes decarboxylation of the carboxyl function α to the carbonyl group, eventually leading to a ring expanded enone. Five- and six-membered heterocyclic rings containing an electron-rich double bond react with DMAD, and also often with ethyl propiolate, to give [2 + 2] cycloaddition products. The initial addition products are usually isolable or verifiable spectroscopically, but generally they are converted directly into ring expanded heterocycles. A wide variety of heterocycles has been prepared by this route, including azepines from pyrroles,[57] 2,3-dihydroazepines from 2,3-dihydro-1*H*-pyrroles,[58] and 1,2-dihydroazocines from 1,2-dihydropyridines.[59] Indoles have been converted to 1*H*-benzo[*b*]azepines.[60] Replacement of the nitrogen in the above heterocycles by oxygen or sulfur is generally feasible and leads to acceptable results. An excellent review of the pioneering work in this area is available.[61] Several representative examples of such ring expansions are shown in Scheme 4.[51,58b,62,63]

The temperatures required for these expansions are typically below 100 °C if one or two electron-donating heteroatom substituents is attached to the bridgehead positions. Considerably higher temperatures are required in the absence of such substituents. For example, thermolysis of (**97**) requires 180–200 °C,[64] the amide (**98**) must be heated to over 450 °C in order to achieve ring expansion,[65] and the cyclobutene (**99**) is reported to be thermally stable.[66]

3,4-Dihydropyrans have been found to react with DMAD in refluxing xylene, affording useful yields of dihydrooxocines.[67] Ring expansion of the parent derivative (**100**) occurs only slowly at 180 °C in toluene but can be catalyzed with $EtAlCl_2$ (80%, 25 °C, toluene). The formation of (**101**) from 5-methyl-

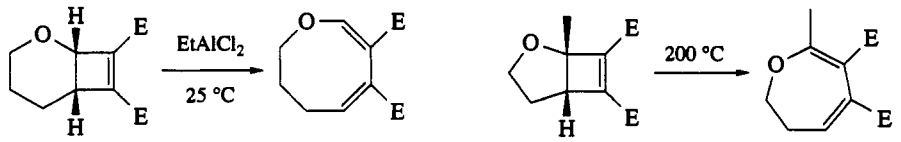


Scheme 4



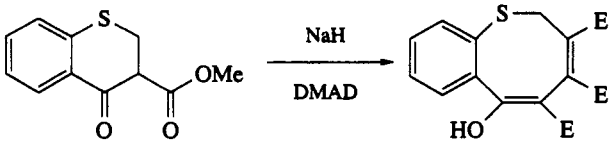
(97) (98) (99)

2,3-dihydrofurans and DMAD is favored in polar solvents such as DMF compared with toluene. Thermolysis of (**101**) to (**102**) requires 200 °C.



(**100**) E = CO_2Me (**101**) (**102**)

Reaction of DMAD with the enolates of keto esters results in a two-carbon ring expansion,[68,69] an example being the preparation of (**103a**) from (**103**). These latter results suggest a general sequence of ring expansions involving cyclic β-diketones, β-keto esters or β-keto sulfones and alkynes.

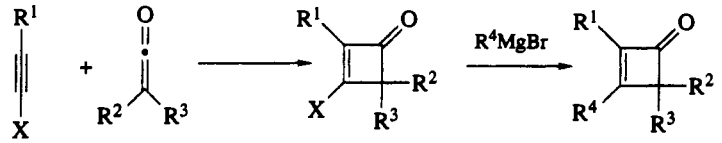


(**103**) (**103a**)

6.1.5 CYCLOBUTENONE RING OPENINGS

The ring opening of cyclobutenone derivatives leads to the formation of vinylketenes (equation 3). The potential of these compounds in the synthesis of complex molecules has been investigated in the 1980s by a number of research groups, most notably those of Moore, Liebeskind and Danheiser. An excellent review describing work in this area prior to 1986 is available.[70]

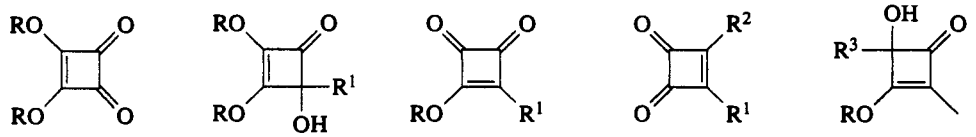
Cyclobutenones can be prepared by several routes including the reaction of ketenes, generally prepared *in situ* by dehydrohalogenation of acyl chlorides, with electron-rich alkynes such as alkoxyacetylenes,[71,72] alkylthioacetylenes[73] or ynamines.[71,74]



(104) (105)

X = OR, SR, NR_2; R^1, R^2, R^3 = H, alkyl, aryl; R^4 = alkyl, aryl

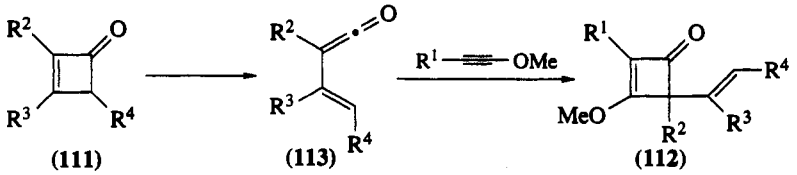
Typically, reaction of (**104**) with Grignard reagents leads to replacement of X by an alkyl or aryl substituent and gives rise to (**105**). Such reactions appear to occur *via* a Michael addition to (**104**) followed by elimination of the alkoxide;[72] 1,2-addition followed by loss of H_2O and hydrolysis of the intermediate enol ether leads to the same result. Dialkyl squarates (**106**) have recently become a favorite starting material for the preparation of a variety of substituted cyclobutenones, in particular those bearing one or more oxygen substituents. Liebeskind and coworkers have carefully reviewed both this and earlier approaches to cyclobutenones and concluded that diisopropyl squarate, a stable crystalline solid, offers the most versatility.[75] For example, reaction of (**106**; R = Pr^i) with alkyllithiums at –78 °C gives the 1,2-adducts (**107**), usually in >90% yield.[75,76] These substances are cleanly hydrolyzed to the enediones (**108**). The use of $LiAl(OBu^t)_3H$ in place of RLi affords the isopropyl ester of semisquaric acid (**108**; R^1 = H) in >60% overall yield.[75] Protection of the hydroxyl group in (**107**) as its TBDMS derivative and repetition of the alkylation–hydrolysis sequence affords differentially 3,4-disubstituted 1,2-cyclobut-3-enediones (**109**).[75] Reaction of (**108**) with aryl- or alkynyl-lithiums gives selective addition to the more reactive, nonvinylogous ester carbonyl group to yield (**110**).[77]



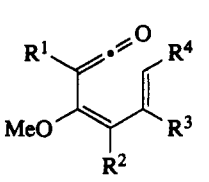
(106) (107) (108) (109) (110)

The synthetic value of the various cyclobutenones rests with their ready thermal opening to vinylketenes and subsequent reactions of these intermediates. Depending on the structure of the ketene generated, and the nature of any additional reagents present, a series of subsequent electrocyclic cyclizations, cycloadditions followed by further ring opening and again electrocyclic cyclizations can occur which lead to a marvellous variety of highly substituted phenols, resorcinols, quinones and annulated quinones, 2-alkylidene-1,3-cyclopentanediones and cycloocta-2,6-dien-1-ones.[70]

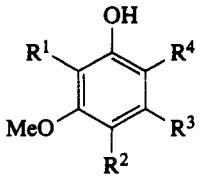
Those applications that make use of alkenyl derivatives such as (**112**) are particularly attractive since these compounds can themselves be generated from simpler cyclobutenenones.[78,79] Thus heating a cyclobutenone such as (**111**) above 80 °C results in a reversible electrocyclic cleavage to generate a vinylketene (**113**) which can combine with an electron-rich alkyne. Further electrocyclic cleavage of the vinylcyclobutenone (**112**) thus obtained furnishes a dienylketene (**114**) which undergoes a six-electron cyclization to afford, after tautomerization, a highly substituted phenol (**115**). This sequence provides an efficient, regiocontrolled route to a variety of selectively protected resorcinol and phloroglucinol derivatives and has been used to synthesize a number of natural products, including the antifungal derivative DB 2073 (**116**),[78a] grifolin (**117**),[78a] mycophenolic acid[78b] and khellinone.[79]



(111) (113) (112)



(114)



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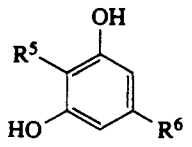
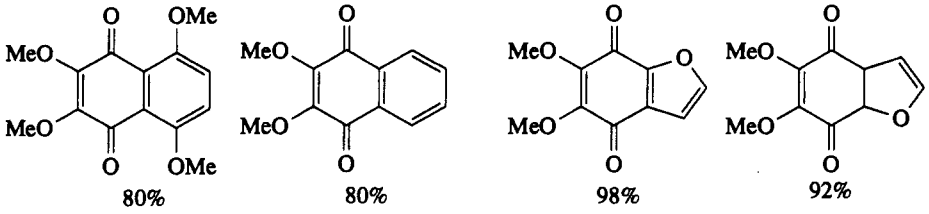


(116) $R^5 = C_6H_{13}$, $R^6 = Pr$

(117) R^5 = farnesyl, $R^6 = Me$

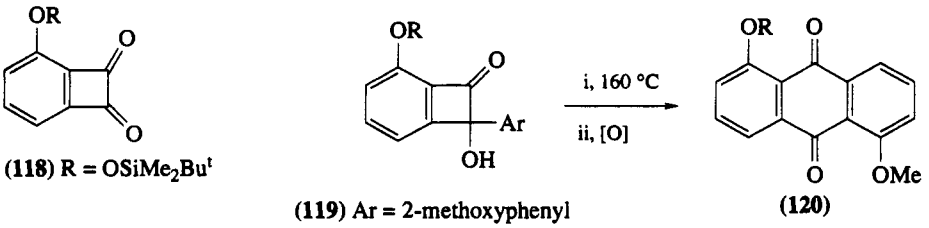
$R^1 = R^2 = R^3 = R^4 =$ H or alkyl

4-Aryl-4-hydroxycyclobut-2-enones rearrange upon heating in refluxing xylene (2 h) to hydroquinones which can be oxidized with Ag_2O, Ce^{IV}/SiO_2 or $FeCl_3/O_2$ to the corresponding quinones. A wide combination of substituents and heteroannulated rings have been prepared in excellent overall yield from the addition of lithio arenes to (**106**), (**108**) or (**109**) followed by thermolysis. Several examples are shown in Scheme 5. In these reactions the outward rotation of the hydroxyl group during the ring opening of intermediate (**110**) occurs, which places the aryl group in the ideal position for electrophilic attack on the carbonyl group of the ketene (or electrocyclization) necessary for cyclization.



Scheme 5

The same sequence when applied to benzocyclobutene-1,2-diones such as (**118**) afforded the adduct (**119**; 80%), which was rearranged upon heating at 160 °C and air oxidation to the anthraquinone (**120**).[77a]



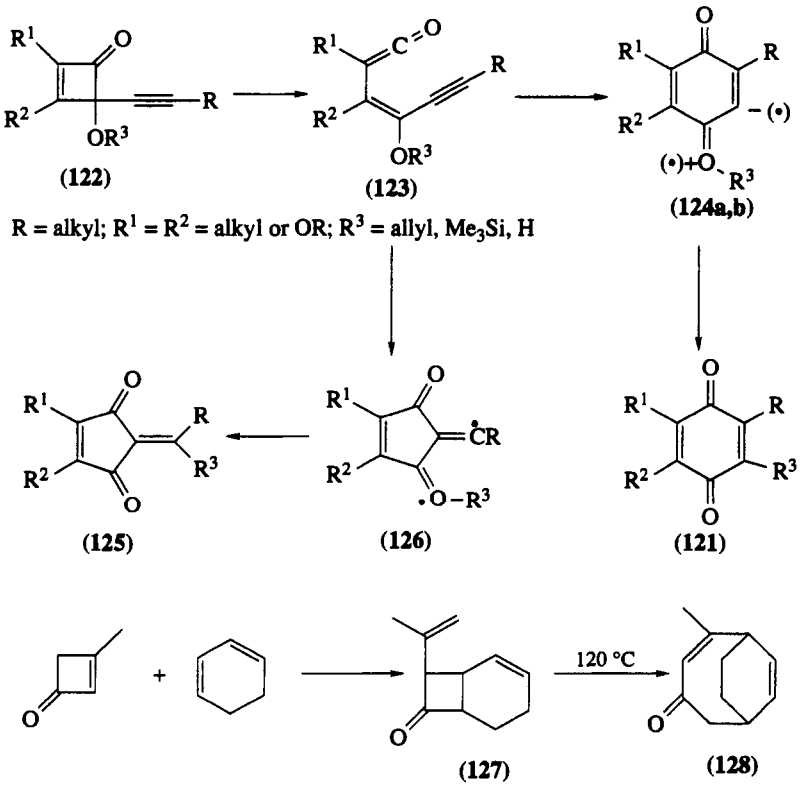
(118) R = $OSiMe_2Bu^t$

(119) Ar = 2-methoxyphenyl

(120)

Benzoquinones (**121**) also result from the thermolysis of 4-alkynylcyclobut-2-enones (**122**) in refluxing xylene.[80] This conversion proceeds *via* the alkynylketene (123), and possibly *via* the zwitterionic intermediate (**124a**) or the corresponding diradical (**124b**).[80c] The conversion of (**123**) to (**121**) is occasionally competitive with the formation of 2-alkylidenecyclopent-4-ene-1,3-diones (**125**), the result of an alternate alkyne–ketene cyclization. This latter route becomes the major pathway when R^1 = Ph, $SiMe_3$ or OEt in (**126**).[80c] Liebeskind and coworkers[81] have generalized the formation of (**125**) for a large variety of substituents by heating (**122**) with 10 mol % of $Pd(OCOCF_3)_2$ in THF at 60 °C for 1 h. All the above reactions have been applied to benzo analogs of (**122**), thus yielding naphthaquinones including nanaomycin A and deoxyfrenolicin.[80]

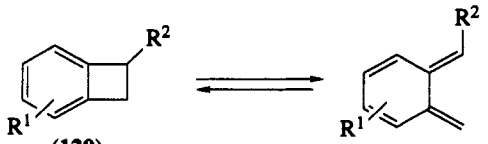
If the cyclobutene–vinylketene equilibrium is established in the presence of a 1,3-diene such as cyclopentadiene, cyclohexadiene or (*E*)-1,3-pentadiene, the ketene is trapped *via* a [4 + 2] cycloaddition reaction to furnish a 2,3-divinylcyclobutanone (**127**). When such reactions are carried out above 120 °C a further 3,3-sigmatropic rearrangement takes place to yield cyclooctadienones (**128**) in overall yields ranging from 30–90%. The intermediate divinylcyclobutanes can also be obtain by dehydrohalogenation of crotyl chloride in the presence of the dienes.[82]



(122) (123) (124a,b) (125) (126) (121) (127) (128)

6.1.6 BENZOCYCLOBUTENES AND DERIVATIVES

Benzocyclobutenes are one of a number of starting materials which can serve as precursors of *o*-quinodimethanes (**129** → **130**). This route to these reactive 1,3-dienes often has considerable advantage over others, despite the fact that occasionally temperatures in excess of 200 °C are required for ring opening, since no other reagents which might interfere with subsequent reactions of (**129**) are required. Thus remarkably clean and efficient transformations are often obtained.

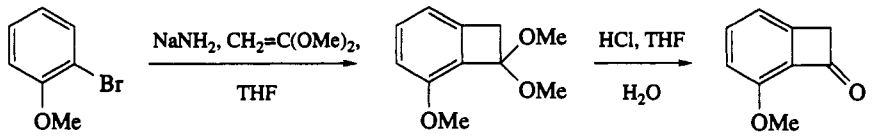


(**129**) (**130**)

The temperature required to set up the equilibrium between (**129**) and (**130**) is highly dependent upon R. Typical values are: R = O^-, 0 °C;[33] R = NR_2, 25–50 °C; R = OH, O-alkyl, 80–110 °C; R = O-acyl or NH-acyl, 110–140 °C; R = $CONHR^1$, COR^1, CO_2R^1, 150–180 °C; R = alkyl, phenyl, 180–210 °C; R = H, >210 °C.[83b] The value of *o*-quinodimethanes in organic synthesis rests with their outstanding reactivity as 1,3-dienes in both inter- and intra-molecular Diels–Alder reactions.[83] Even relatively unreactive dienophiles such as terminal vinyl groups and internal alkenes such as cyclopentene have been successfully combined with various derivatives of (**130**) either in an inter-[83b,85] or intra-molecular mode.[84] Imines[86] and aldehydes[83b,87] also react efficiently with (**130**), yielding dihydroquinolines and dihydrobenzopyrans, respectively. Nitriles[83b,87] and alkynes[83b,88] have also been employed as dienophiles. The vast potential of these intermediates for the synthesis of polycyclic compounds began to be realized in the 1970s, mainly due to the efforts of the research groups led by Oppolzer and Kametani. Only a limited number of examples illustrating the key role of benzocyclobutenes (and *o*-quinodimethanes) will be described. Excellent reviews covering the various years of development, including analysis of the relative regio- and stereo-chemistry observed in the cycloadditions reactions, are available.[83] Asymmetric induction in the intermolecular Diels–Alder reactions of (**130**) has also begun to be investigated.[83a,89]

A major initial limitation of the benzocyclobutene approach to *o*-quinodimethanes was the lack of efficient, large-scale syntheses for many specifically substituted derivatives. Fortunately, recent developments have removed much of this impediment. Conceptually, the synthesis of benzocyclobutenes from aromatic precursors can be envisaged in only a limited number of ways. These include [2 + 2] cycloadditions involving benzynes and alkenes, intramolecular cyclization on to a benzyne, cyclizations involving arene anions, and electrocyclic closure of *o*-quinodimethanes. Benzocyclobutene derivatives can also be prepared by aromatization of bicyclo[4.2.0]octanes. Detailed discussion of variations to these approaches can be found in the cited reviews.[83] The cobalt catalyzed co-oligomerization of 1,5-hexadiynes with alkynes, especially bis(trimethylsilyl)acetylene, has also been employed for the preparation of specifically substituted benzocyclobutenes.[90] In the latter case the cyclobutenes are often not isolated but converted directly to *o*-quinodimethanes and subsequent products.[90]

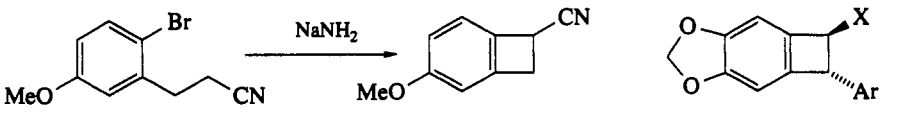
Stevens and Bisacchi[91] have carefully examined the trapping of benzynes, generated from a number of aryl bromides and sodium amide in THF, with 1,1-dimethylethylene and report procedures which afford 64–86% yields of 1,1-dimethoxycyclobutenes, *e.g.* (**131**). These compounds are hydrolyzed quantitatively to the corresponding benzocyclobutenones (**132**). Excellent regioselectivity was obtained with unsymmetrical benzynes derived from methoxy substituted bromobenzenes due to the polarized nature of the benzyne intermediate. Steric effects also influence regioselectivity: *o*-bromotoluene afforded a 3:1 mixture of 3-methyl- and 6-methyl-benzocyclobutene.



(**131**) 70% (**132**) ~100%

The diazotization of anthranilic acid, a classic route to benzyne, when carried out in the presence of vinyl acetate,[92] vinyl ethers[92] or 1,1-dichloroethylene gives the expected benzocyclobutenes in about 40% yield. Despite the rather moderate yields this method represents a convenient route to multigram quantities of the parent compounds, benzocyclobutenol and benzocyclobutenone. The latter is easily converted to benzocyclobutene-1,2-dione.[93] The diazotization sequence applied to 2-amino-3,6-dimethoxybenzoic acid and 1,1-dichloroethylene results in a 80% yield of 3,6-dimethoxycyclobuten-1-one.[94] Trapping of benzynes with other ethylene derivatives, and especially more substituted alkenes, has given generally poorer, variable results.[95]

The Kametani group has made considerable use of the intramolecular trapping of benzynes by pendant carbanion centers. The nitrile (**133**) is a key and versatile intermediate in many of the Kametani studies, including the preparation of optically pure estradiol.[83c,84,96] The ester of the benzocyclobutenecarboxylic acid (**134**) was prepared by a similar benzyne cyclization.[97] The acid (**134**) was converted *via* oxidative decarboxylation and HCl hydrolysis to the very labile *trans*-2-arylbenzocyclobutenol (**135**), which was used in the preparation of podophyllotoxin.[98]



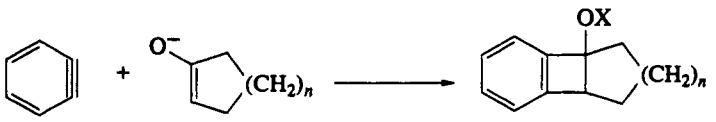
(**133**)

(**134**) X = CO_2H
(**135**) X = OH
Ar = 3,4,5-trimethoxyphenyl

Intermolecular benzyne–enolate cycloadditions have been studied in detail by Caubere *et al.*[99] Benzocyclobutenols (**136**) were obtained with enolates derived from five-, six- and seven-membered ring ketones. Larger ring enolates and acyclic enolates results in ring expanded ketones and *o*-disubstituted benzenes. The stability of the intermediate alkoxy anions (**137**) is rather high when $n < 3$ since the preferred outward rotation of the O^- group results in the formation of a *trans* double bond in a seven- or eight-membered ring. The preparation of analogs of (**136**) bearing additional functionality in the enolate ring has been described.[100]

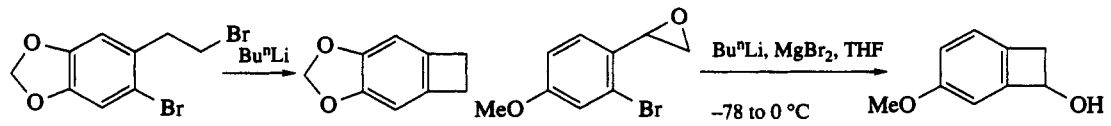
Intramolecular cyclizations *via* aryl anions have been used to prepare benzocyclobutenes (**138**) from *o*-bromo-β-phenethyl bromides[101] and benzocyclobutenols (**139**) from *o*-bromostyrene oxides.[102]

Flash vacuum thermolysis of *o*-methylbenzyl halides (**140**) at 500–600 °C gives benzocyclobutenes.[103,104] This reaction has recently been extended to the preparation of cyano and chloro sub-



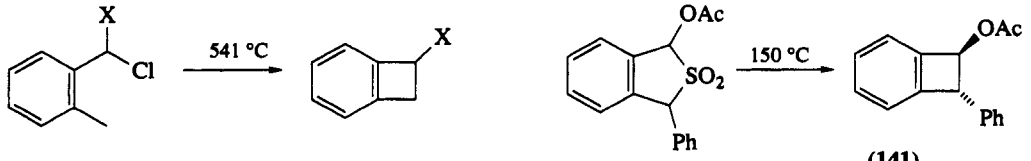
(136) X = OH

(137) X = O^-M^+



(138) (139)

stituted benzocyclobutenes.[105] Benzocyclobutene[106] and *trans*-2-phenyl-1-acetoxybenzocyclobutene (**141**)[107] have been obtained *via* thermolysis of the corresponding 2,5-dihydrobenzothiophene 2,2-dioxides. These reactions presumably occur by ring closure of thermally generated *o*-quinodimethane intermediates.



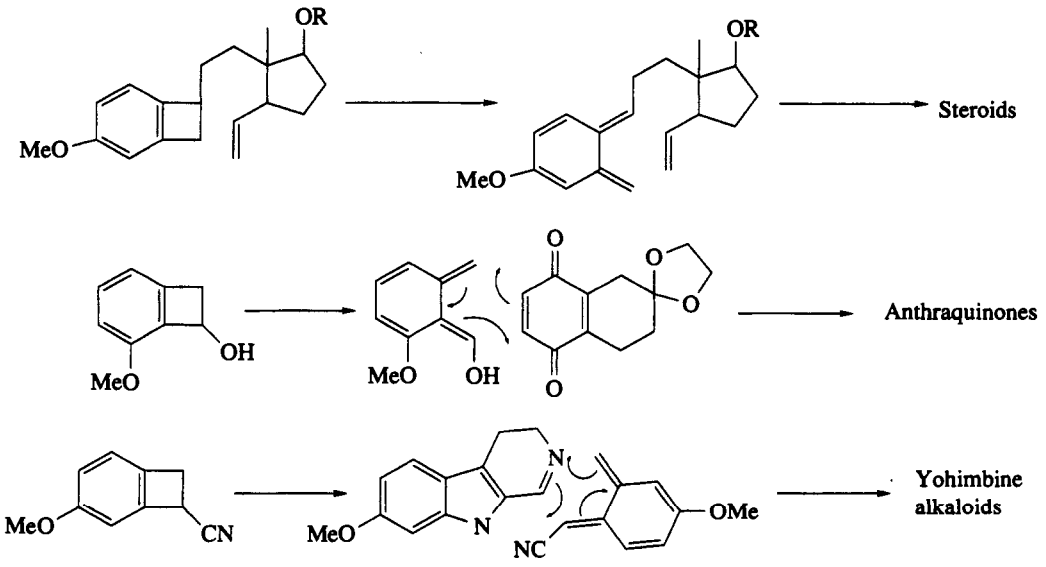
(140) X = H, Cl, CN (141)

The bicyclo[4.2.0]octane approach has proved valuable in particular situations. South and Liebeskind[93] have converted the adduct obtained from 3-methyl-1-trimethylsilyloxy-1,3-butadiene and 1,4-dichloro-3,3,4-trifluorocyclobutene into 3-hydroxy-5-methylbenzocyclobutene-1,2-dione in 72% yield.[93]

Target molecules which have six-membered rings fused to an aromatic nucleus are obvious candidates for synthesis *via* *o*-quinodimethane intermediates which are potentially accessible by benzocyclobutene ring openings. Early targets included a variety of steroids such as estrone, homoestrone, estradiol, various alkaloids, anthraquinones and anthracyclines. These applications in which the *o*-quinodimethane precursor is readily recognized have been often reviewed.[83] They are shown in a general scheme (Scheme 6). Application of *o*-quinodimethane intermediates generated from benzocyclobutenes to the synthesis of targets such di-[107] and tri-terpenes,[108] diterpene alkaloids,[109] morphinans[110] and norsteroids,[111] in which the aromatic ring has been substantially modified and thus the precursor is no longer readily apparent, have also been reported. Recently the use of alternate precursors to *o*-quinodimethanes especially the F^- catalyzed desilylation of *o*-substituted benzyltrimethylsilanes, has received considerable attention.[112]

The synthetic use of benzocyclobutenes bearing a single substituent on the cyclobutene ring is well established and quite predictable since one generally finds that most useful substituents prefer to rotate outward during the ring opening to give *o*-quinodimethanes having structure (**130**), which are reliably trapped as such by good external and even weak internal dienophiles. The fact that the benzocyclobutene ring opening is reversible, as shown for example by the racemization of optically active benzocyclobutenol,[113] does allow the possibility of observing products from the less favorable ring opening, especially in the absence of efficient dienophilic trapping reagents. Several such examples have been discussed (see Section 6.1.3.1).

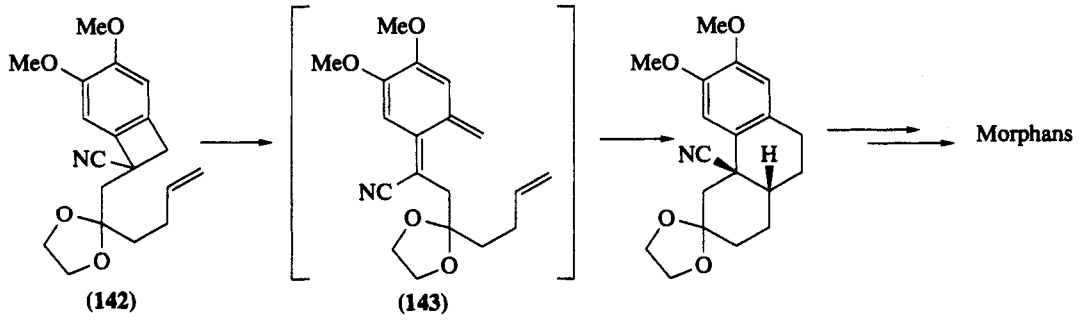
Synthetic applications involving 1,1- and 1,2-disubstituted benzocyclobutenes are more rare. Inward rotation of an alkyl group in the ring opening of 1,1-disubstituted benzocyclobutenes leads to an intermediate which is prone to 1,5-hydrogen shift.[114] Such a pathway is obviously detrimental to an application which requires trapping of the *o*-quinodimethane in the typical Diels–Alder format. The situation is particularly serious when one of the two groups is OR, due to the powerful tendency of the oxygen substituent for outward rotation. Benzocyclobutenol when heated alone is isomerized to 2-methylbenzaldehyde[115] either *via* a 1,5-hydrogen shift from a small amount of the isomer resulting from inward rotation of the hydroxy group, or by an intermolecular hydrogen transfer mechanism. From a synthetic point of view it is often worthwhile to protect the hydroxy group and thus avoid this competing process.



Scheme 6

In 1,2-disubstituted series such as *cis*- and *trans*-2-alkyl-1-alkoxybenzocyclobutenols, the *trans* isomer is more likely to lead to a high yield of cycloaddition product than the *cis* since the 1,5-hydrogen shift is precluded. The forced inward rotation of an aryl substituent in 1-methoxy-1-phenylbenzocyclobutene is potentially advantageous and leads to anthracene derivatives.[115] See also the anthraquinone synthesis from the corresponding benzocyclobutenones (Section 6.1.5).

The Kametani group has made considerable use of 1-alkyl-1-cyanobenzocyclobutenols. Ring opening of benzocyclobutenol (**142**) appears to form preferentially the intermediate (**143**) resulting from the outward rotation of the alkyl group and inward rotation of the electron-withdrawing (and small) cyano group which 'protects' against the unwanted 1,5-hydrogen shift.[114] The product obtained from this ring opening–cyclization sequence was elaborated into morphinan derivatives.[110]



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6.2
1,3-Cyclohexadiene Formation Reactions

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6.2.1 INTRODUCTION

6.2.1.1 Scope

The (3Z)-1,3,5-hexatriene (**1**) to 1,3-cyclohexadiene (**2**) interconversion is the prototypical example of the six-electron ($6e^-$) electrocyclization reaction as defined by Woodward and Hoffmann (WH).[1,2] Among the early observations, the complementary stereochemical results (Figure 1) obtained for thermal (disrotatory, dis) and photochemical (conrotatory, con) processes in the vitamin D system (*vide infra*) provided experimental bases leading to the formulation of the WH rules. Despite its theoretical significance, the thermal variant of the $6e^-$ electrocyclization[3] has found relatively little use in synthesis. By contrast, the photochemical counterpart (photocyclization of stilbenes and analogs) constitutes a powerful synthetic procedure for the formation of aromatic compounds.[4] More recently, new ways of inducing electrocyclic processes have been discovered, such as those which proceed by reductive electron transfer[5] or by electrical discharge.[6] The former appears to mimic stereochemically the photochemical process

while the latter is considered to involve vibrationally excited (thermal) ground states. The potential utility of these new methods for inducing $6e^-$ electrocyclizations remains virtually unexplored.

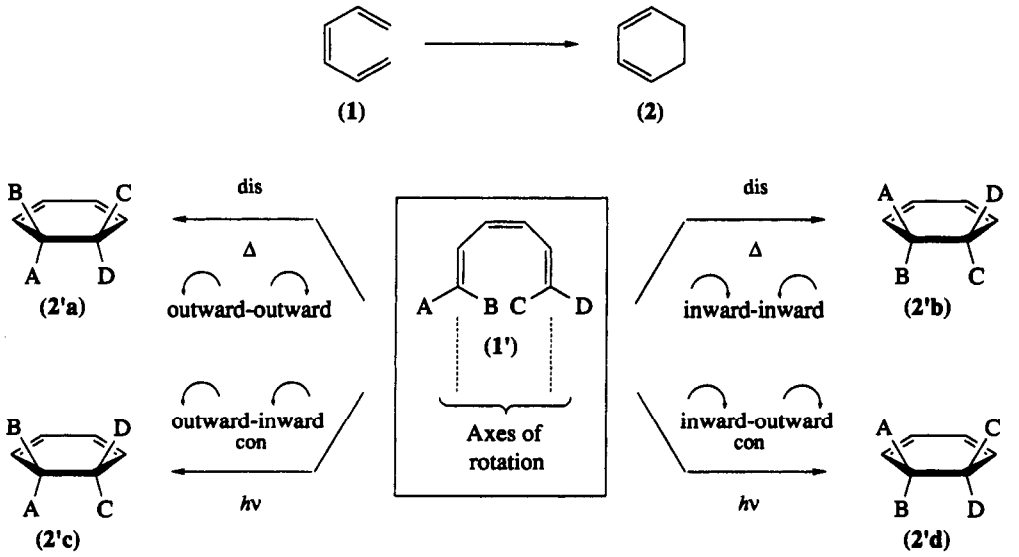


Figure 1 The four stereochemically distinct modes of electrocyclic ring closure wherein the notations 'inward' and 'outward' refer to the axes of rotation as viewed with respect to (**1'**). The principle of the conservation of orbital symmetry predicts disrotatory (dis) or conrotatory (con) ring closure for the thermally or photochemically induced processes, respectively. The same modes (dis or con) are predicted for the reverse ring opening processes

Several excellent reviews and monographs have been devoted to the topic of electrocyclizations,[3,4] but little attempt has been made at systematically describing the utility of $6e^-$ electrocyclizations from a synthetic point of view. The aim of this chapter is to highlight the unique features of this intramolecular formation of six-membered rings in synthesis, a capability primarily only shared by the Diels–Alder reaction and the cyclotrimerization of alkenes among the variety of pericyclic reactions.[7] The emphasis is on selectivity and the resulting 1,3-cyclohexadienes have been classified (Figure 2) in terms of fused and bridged structures according to the position of the cycle with respect to the diene array. Thus this chapter is organized according to the 1,3-cyclohexadiene structural type, independent of their mode of formation, whether photochemically, thermally or otherwise induced.

It is not possible within the restrictions of this review to treat all carbocyclic frameworks (*e.g.* spirocyclics) and a conscious decision was also made specifically to exclude the heterocyclic version of this electrocyclization. The number and variety of heteroatoms and the possible permutations along the hexatriene system that can *a priori* be considered would justify a separate treatment. The reader is referred to the excellent monograph by Marvell[3a] for references to the treatment of electrocyclizations leading to heterocycles. However, in order to provide at least a few leading references, several selected examples of hetero electrocyclizations are included in this chapter together with comments concerning retro electrocyclizations and higher-order electrocyclic processes.

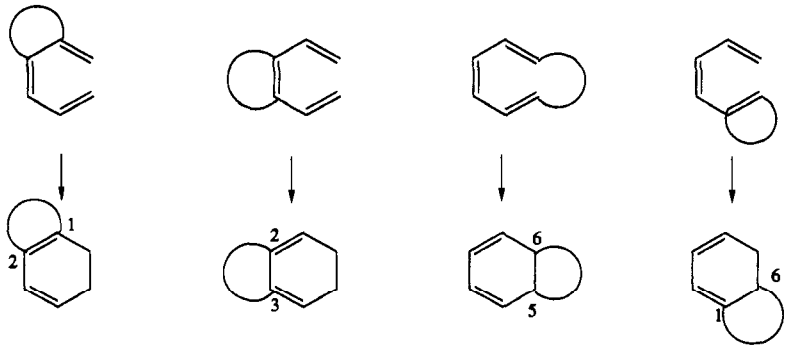
6.2.1.2 Historical Perspective

The investigations by Havinga and coworkers[8] disclosing the detailed stereochemical consequences of the thermal and photochemical interconversions in the vitamin D field provided an important impetus for the elaboration of the WH rules. The reversible photochemical ring opening of provitamin D (**5**) to precalciferol (**3**) and the photochemical ring closure of precalciferol (**3**) to lumisterol (**6**) can be explained by consecutive conrotatory processes (*vide infra*). Thermal treatment of precalciferol (**3**) below 100 °C generates calciferol (**4**) by a 1,7-sigmatropic hydrogen shift, which constitutes the second pericyclic reaction involved in vitamin D biosynthesis. By increasing the temperature to 100–200 °C, a new electrocyclization takes place, resulting in formation of pyrocalciferol (**7**) and isopyrocalciferol (**8**). The configuration of the latter pair of stereoisomers requires a disrotatory motion (Figure 1) of the ends of the

hexatriene. The occurrence of complementary processes, thermal disrotatory ring closure of (**3**) to (**7**) and (**8**) and photochemical conrotatory ring closure of (**3**) to (**5**) and (**6**), is striking, and these results among others led to the development of the concept of the conservation of orbital symmetry and the WH rules.

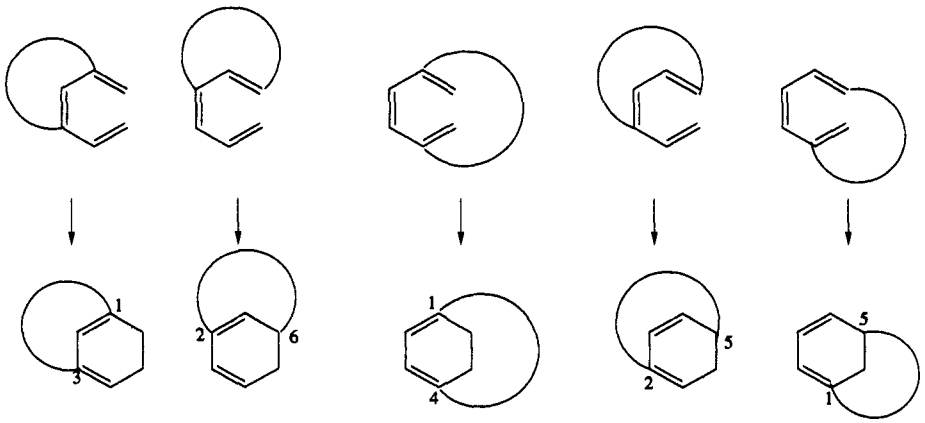
(a) CYCLIC AND ANNULATED HEXATRIENES: MONO-ANNULATED TRIENES

Ortho-condensed systems: [*i,j*]-annulated systems with $j - i = 1$ or 5. *Types I–IV*



Type *I* [1,2] *II* [2,3] *III* [5,6] *IV* [1,6]

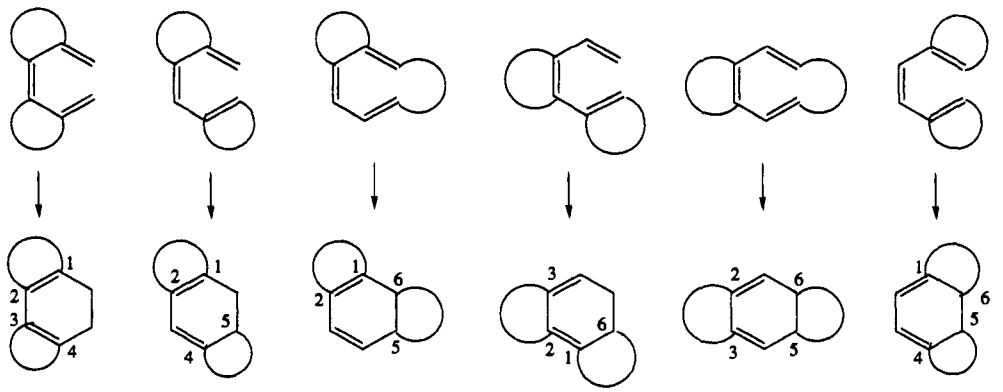
Bridged systems: [*i, j*]-annulated systems with $j - i = 2$–4. *Types V–IX*



V [1,3] *VI* [2,6] *VII* [1,4] *VIII* [2,5] *IX* [1,5]

(b) CYCLIC AND ANNULATED HEXATRIENES: BIS-ANNULATED TRIENES

Only *ortho*-condensed systems: [*i,j*:*k,l*]-annulated systems with $j - i = 1$ or 5, $l - k = 1$. *Types X–XV*



Type *X* [1,2:3,4] *XI* [1,2:4,5] *XII* [1,2:5,6] *XIII* [1,6:2,3] *XIV* [2,3:5,6] *XV* [1,6:4,5]

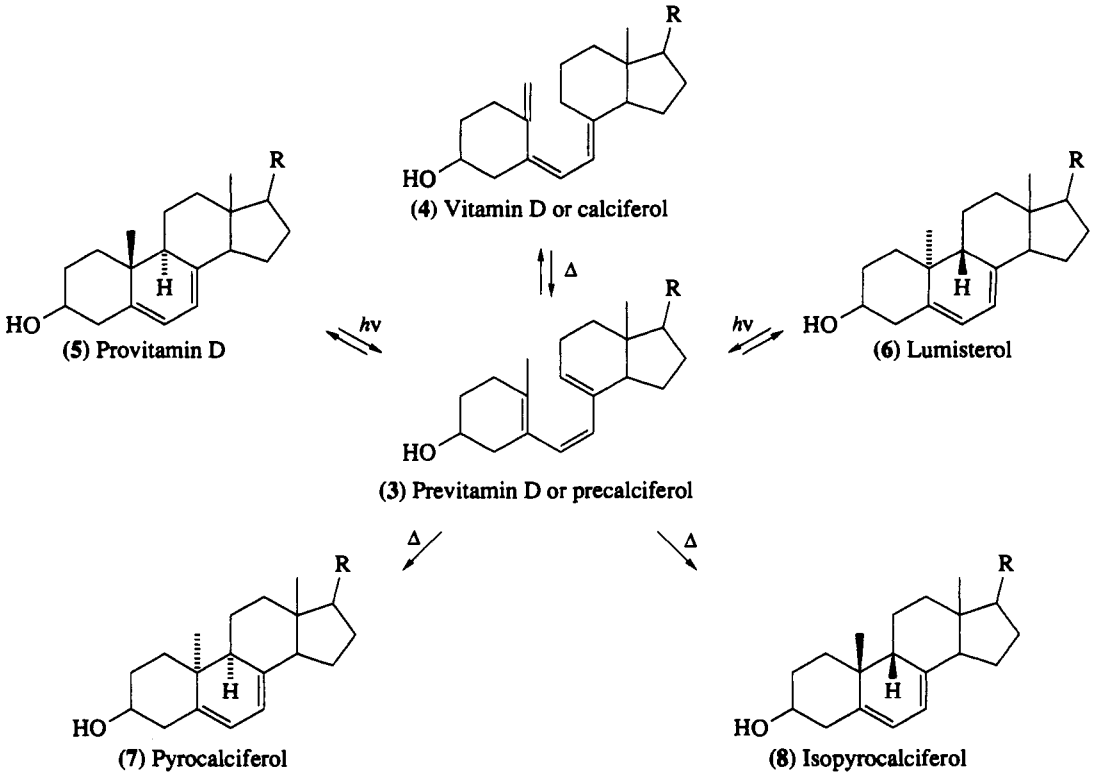
Figure 2

(c) HIGHER ORDER ANNULATED SYSTEMS

Only *ortho*-condensed systems: [*i,j:k,l:m,n*]-annulated systems with $j - i = 1$ or 5, $l - k = n - m = 1$.
Types XVI–XVII

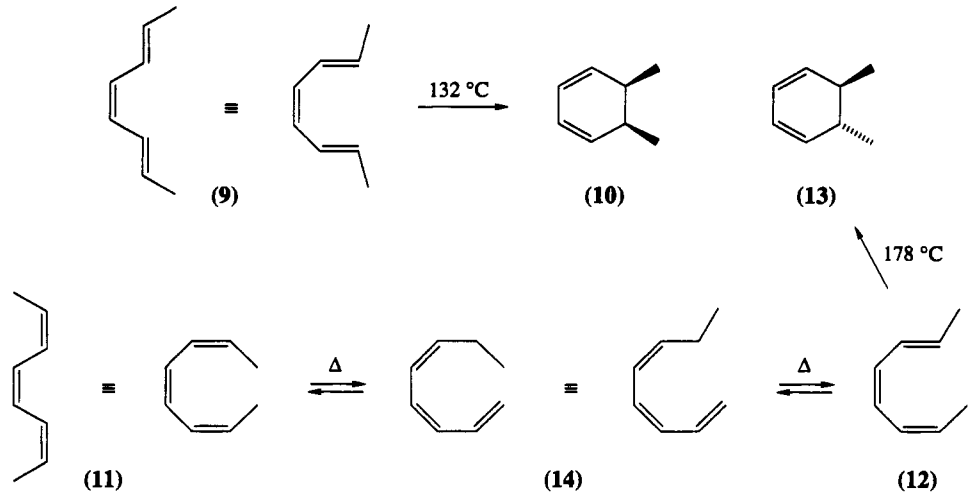
Type *XVI* [1,2:3,4:5,6] *XVII* [1,6:2,3:4,5]

Figure 2 Classification of the six-electron ($6e^-$) electrocyclizations is based on the structure of the resulting cyclohexadiene derivatives (Types I–XVII) irrespective of the method of ring closure, whether thermally, photochemically or otherwise induced



A definitive confirmation of the disrotatory nature of the thermal $6e^-$ electrocyclization was based on studies of the stereoisomers of 2,4,6-octatriene[9] and (*Z,Z,Z*)-1,3,5-cyclononatriene.[10] Heating (*E,Z,E*)-isomer (**9**) at 132 °C gave *cis*-5,6-dimethylcyclohexadiene (**10**) with a diastereomeric purity of 99.5%. Although the (*Z,Z,Z*)-(**11**) and (*E,Z,Z*)-(**12**) isomers are in mobile equilibrium above 100 °C, the complementary *trans*-5,6-dimethylcyclohexadiene (**13**) was formed at 178 °C from the (*E,Z,Z*)-isomer (**12**). The interconversion (**11**) to (**12**) was postulated[9b] to involve the intermediacy of (*Z,Z*)-1,3,5-octatriene (**14**) through a 1,7-sigmatropic hydrogen (1,7-H) shift. A more recent reexamination of this process[11] conclusively demonstrated the intermediacy of (**14**). Similar results were obtained for the (*Z,Z,Z*)-1,3,5-cyclononatriene.[10] The conrotatory nature of the photochemical ring closure was demonstrated by irradiation of (**9**),[12] resulting in a photostationary state consisting of a small amount of *trans* isomer (**13**) as the only significant electrocyclized material (for the stereochemistry of the ring opening process, see Section 6.2.4.1).

An even more detailed mechanistic scrutiny of photochemical and thermal $6e^-$ electrocyclizations of the parent system (**1, 2**) has recently emerged using resonance Raman spectroscopic[13] and isotopic labeling[14] techniques, respectively.



6.2.1.3 Theoretical Treatment of Electrocyclic Processes: Stereochemistry

Theoretical analysis of the interconversion of hexatriene (**1**) to cyclohexadiene (**2**) has eluded a thorough *ab initio* study similar to that carried out for the corresponding $4e^-$ process, the interconversion of butadiene and cyclobutene.[15] Early predictions[16a] using the Polanyi–Evans method of interacting potential energy surfaces predicted that the thermal $6e^-$ cyclization would proceed in a conrotatory sense; similarly the same prediction was obtained using calculations based on the principle of least motion (PLM).[16b] The failure of these methods amply illustrates the power of orbital symmetry requirements in overcoming the steric disadvantage of the thermal disrotatory motion. However, later theoretical evaluations at the MINDO/2 and *ab initio* SCF/6-31G* levels have provided a more satisfactory congruence between experiment and theory.[14,17] There are a number of theoretical approaches which have become popular among experimentalists to treat electrocyclizations and other pericyclizations.[18,19] These approaches include the orbital and/or state correlation diagram method, the transition state aromaticity model, the perturbation molecular orbital method and various other methods. The correlation diagram approach has been selected here for describing how the principle of the conservation of orbital symmetry leads to the WH selection rules.

To depict these symmetry requirements leading to the stereospecificity of the interconversion of (**1**) to (**2**), consider the orbital correlation diagram involving the six π-orbitals of the hexatriene and the four π-orbitals and two σ-orbitals of cyclohexadiene (Figure 3). In the thermal disrotatory process, which maintains a mirror plane of symmetry (or σ-symmetry), ground state reactant (**1**) orbitals ($\pi_a^2\pi_b^2\pi_c^2$) correlate with the corresponding product (**2**) orbitals ($\sigma^2\pi_1^2\pi_2^2$). This suggests that the disrotatory thermal process should possess a relatively low activation barrier (compared to the thermal conrotatory process) and the process is said to be allowed. For the thermal conrotatory process, in which a C_2 axis of symmetry is preserved (ignoring substituents), ground state reactant (**1**) orbitals ($\pi_a^2\pi_b^2\pi_c^2$) correlate with product (**2**) excited state orbitals ($\sigma^2\pi_1^2\pi_3^{*2}$). A relatively high activation barrier is therefore predicted and the $6e^-$ thermal conrotatory closure of (**1**) to (**2**) is considered to be forbidden.

An analysis of the thermal ring opening process (**2**) to (**1**) affords the same prediction. The ground state of (**2**) ($\sigma^2\pi_1^2\pi_2^2$) correlates with the ground state of (**1**) ($\pi_a^2\pi_b^2\pi_c^2$) in the disrotatory mode, but with an excited state of (**1**) ($\pi_a^2\pi_b^2\pi_d^{*2}$) in the conrotatory process. Thus the same prediction obtains for both the forward and reverse process.

A similar analysis of the first excited state of the hexatriene (**1**) closing to (**2**) leads to the opposite prediction, namely that the conrotatory ring closure process should be allowed and that the disrotatory mode should be forbidden (*i.e.* the former should have a lower activation barrier than the latter in the excited state manifold). Thus, for example, the first excited state of (**1**) ($\pi_a^2\pi_b^2\pi_c^1\pi_d^{*1}$) correlates in the disrotatory mode with an excited state of (**2**) ($\sigma^2\pi_1^1\pi_2^2\pi_4^{*1}$) higher in energy than that of (**2**) ($\sigma^2\pi_1^2\pi_2^1\pi_3^{*1}$) when (**1**) undergoes conrotatory closure. That the conrotatory mode is preferred over the disrotatory mode in the first excited state is also predicted for the reverse, the ring opening process (**2**) to (**1**). It is also possible to consider other excited states undergoing electrocyclizations.[18b]

With respect to the electrocyclic reactions of spin doublets (such as cation and anion radicals), the situation is more complex and an extended orbital correlation diagram approach or the Zimmermann orbital

topology criterion have been suggested to be more satisfactory theoretical approaches to the observed stereoselectivities.[20] Except for the electrocyclic ring closure of the hexatriene anion-radical mentioned earlier,[5] all of the corresponding processes involving cation-radicals examined thus far involve ring opening processes.[21] It remains for future experiments to delineate whether electron transfer processes can be utilized for inducing electrocyclic processes at a practical level. In this connection it should be mentioned that certain other cation-radical pericyclic processes (*e.g.* the Diels–Alder reaction) have already been demonstrated to exhibit impressively high regio- and stereo-selectivity and to be synthetically useful.[22]

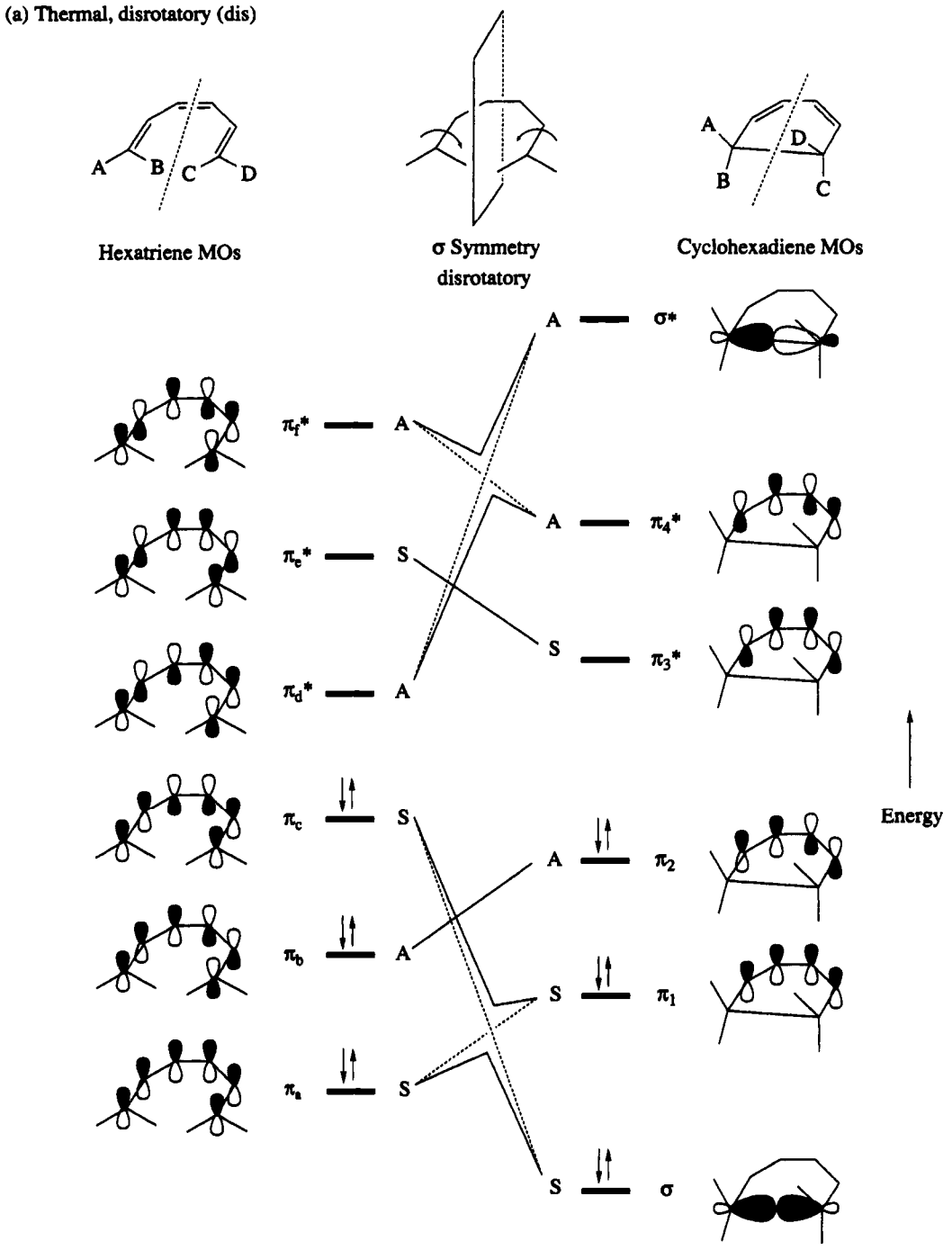


Figure 3

(b) Thermal, conrotatory (con)

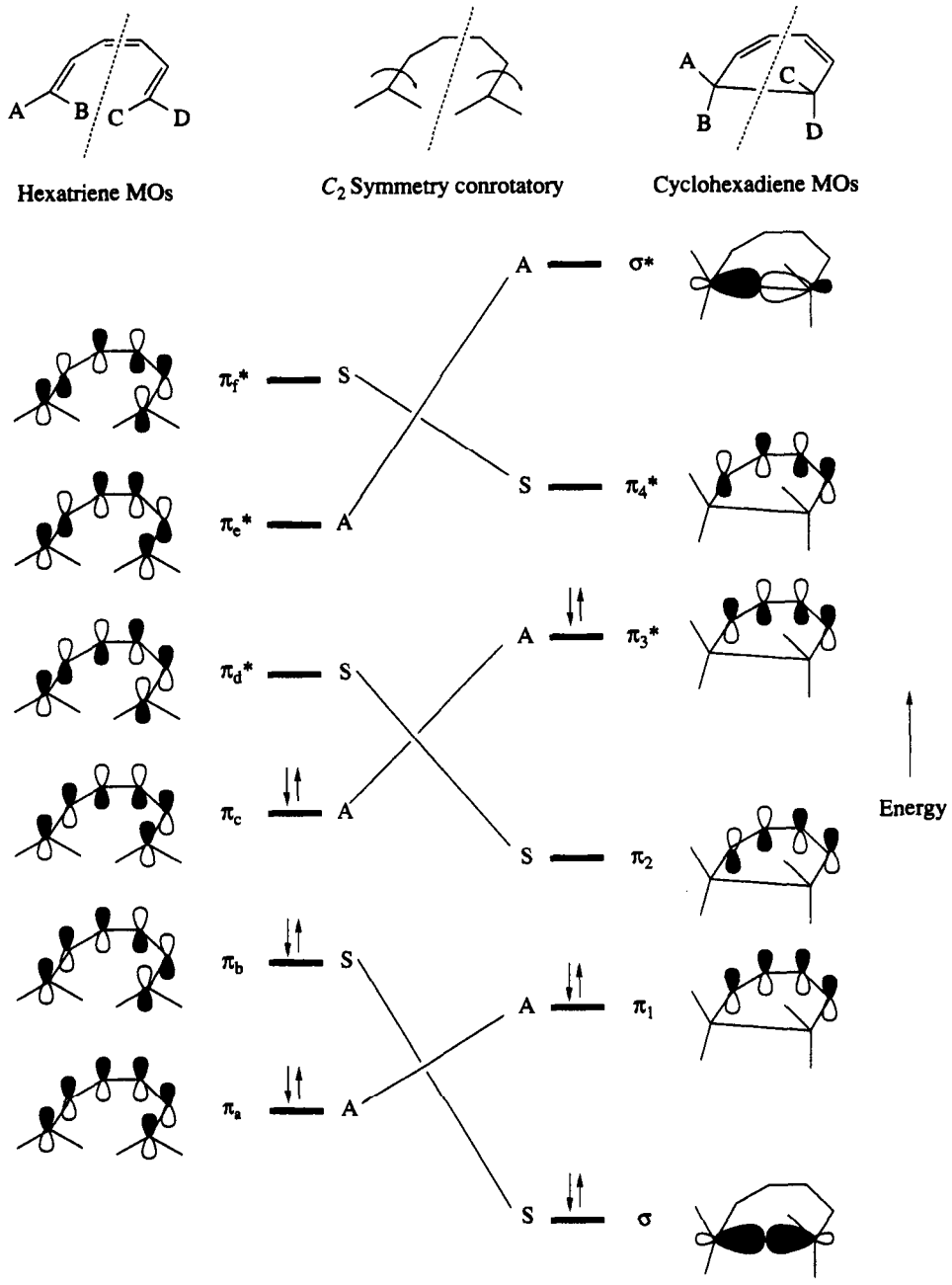
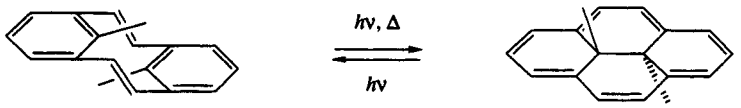


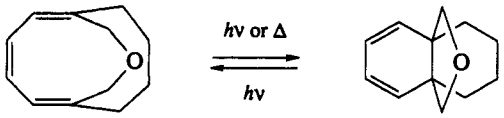
Figure 3 Comparison of the orbital correlation diagrams for the thermal dis (a) and con (b) 6e $^-$ electrocyclic ring closures. Note that the electronic configuration is shown in each case only for the ground state of the hexatriene reverting to the cyclohexadiene *via* the dis and con modes. These diagrams can also be used directly for qualitatively describing other states in either forward (ring closure) or reverse (ring opening) processes. Alternative methods of theoretical analyses lead to similar predictions as the orbital (and/or state) correlation approach

Orbital-symmetry-disallowed energetically concerted reactions[23] can take place when the allowed reaction is made energetically prohibitive due to geometrical constraints. A more rigorous theoretical analysis including configuration interaction,[19,24] avoiding the crossing of states of the same symmetry, has been invoked to account for the extremely facile (~50 °C) thermal conrotatory interconversion of 15,16-dimethyldihydropyrene (**16**) and the 15,16-dimethyl[2,2]metacyclophane-4,9-diene (**15**).[25] A second

example of a thermal, conrotatory reaction is provided by the bridged triene (**17**),[26] which is converted at room temperature to the cyclohexadiene (**18**) in a thermally forbidden process.

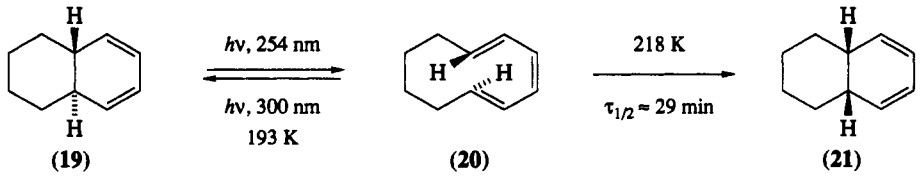


(**15**) (**16**)

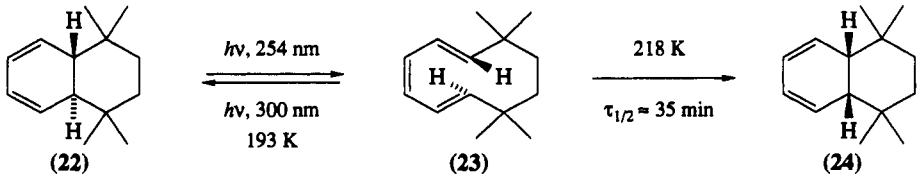


(**17**) (**18**)

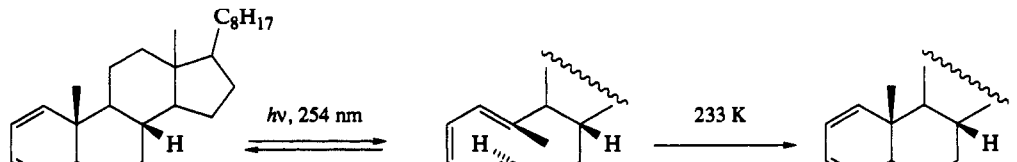
The preservation of chiral integrity of the dissymmetric (*E,Z,E*)-1,3,5-cyclodecatrienes obtained by conrotatory photoisomerization of *trans*-$\Delta^{1,3}$-hexalins has been addressed recently.[27] The photogenerated hexatrienes (+)-(**20**) and (–)-(**23**) were found to preserve their (*R*) and (*S*) chirality, respectively, at 193 K (only ring closure from (+)-(**20**) and (–)-(**23**) to the starting hexalins (–)-(**19**) and (+)-(**22**) was observed). However, above 205 K they lose chiral integrity by competitive ring closure to the achiral *cis*-$\Delta^{1,3}$-hexalins (**21**) and (**24**). Similar behavior was observed for 5α-cholesta-1,3-diene [(–)-(**25**)] with formation of (–)-(**26**), which gave 5β-cholesta-1,3-diene [(+)-(**27**)] upon warming to 233 K.[27]



(**19**) (**20**) (**21**)



(**22**) (**23**) (**24**)



(**25**) (**26**) (**27**)

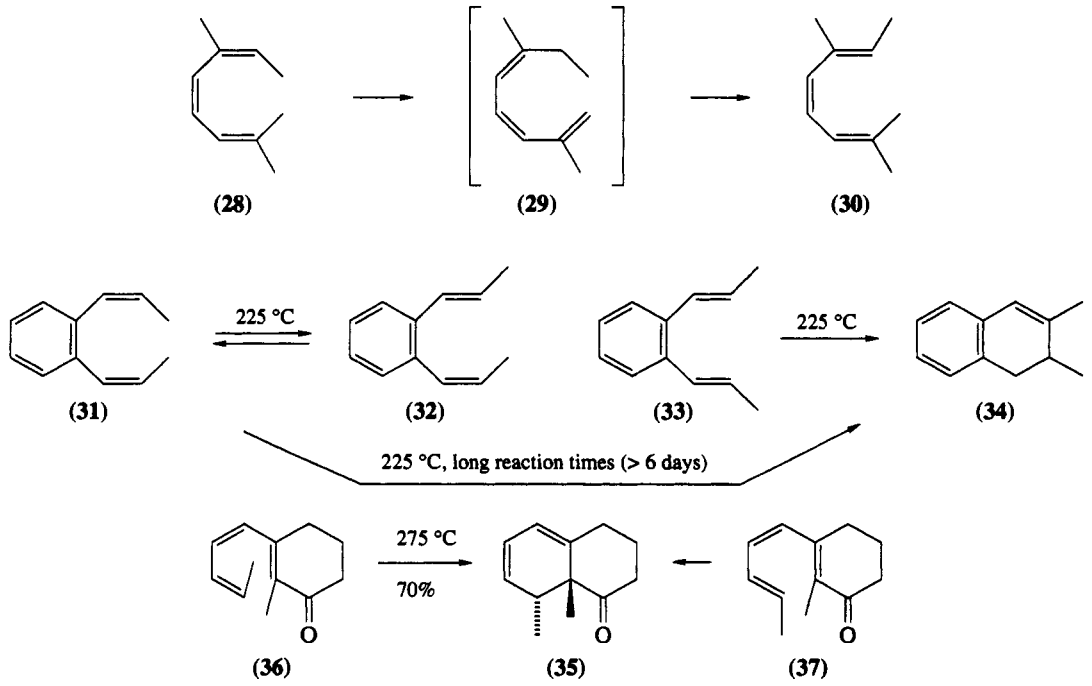
6.2.2 ELECTROCYCLIZATIONS OF 1,3,5-HEXATRIENES

6.2.2.1 General Considerations Including Acyclic Hexatrienes and Selected Ring Fused Systems

The limitation to the widespread synthetic use of the thermal or photochemical cyclization of trienes are twofold: the difficulty in preparing the starting, geometrically correct triene array; and the periselectivity[28] (*i.e.* the competition with other reactions occurring from the same substrate). Much of the following discussion is limited to the latter topic although it must be recognized that an efficacious synthesis of

hexatrienes with appropriate geometry can be a major obstacle in considering $6e^-$ electrocyclizations in a synthesis.

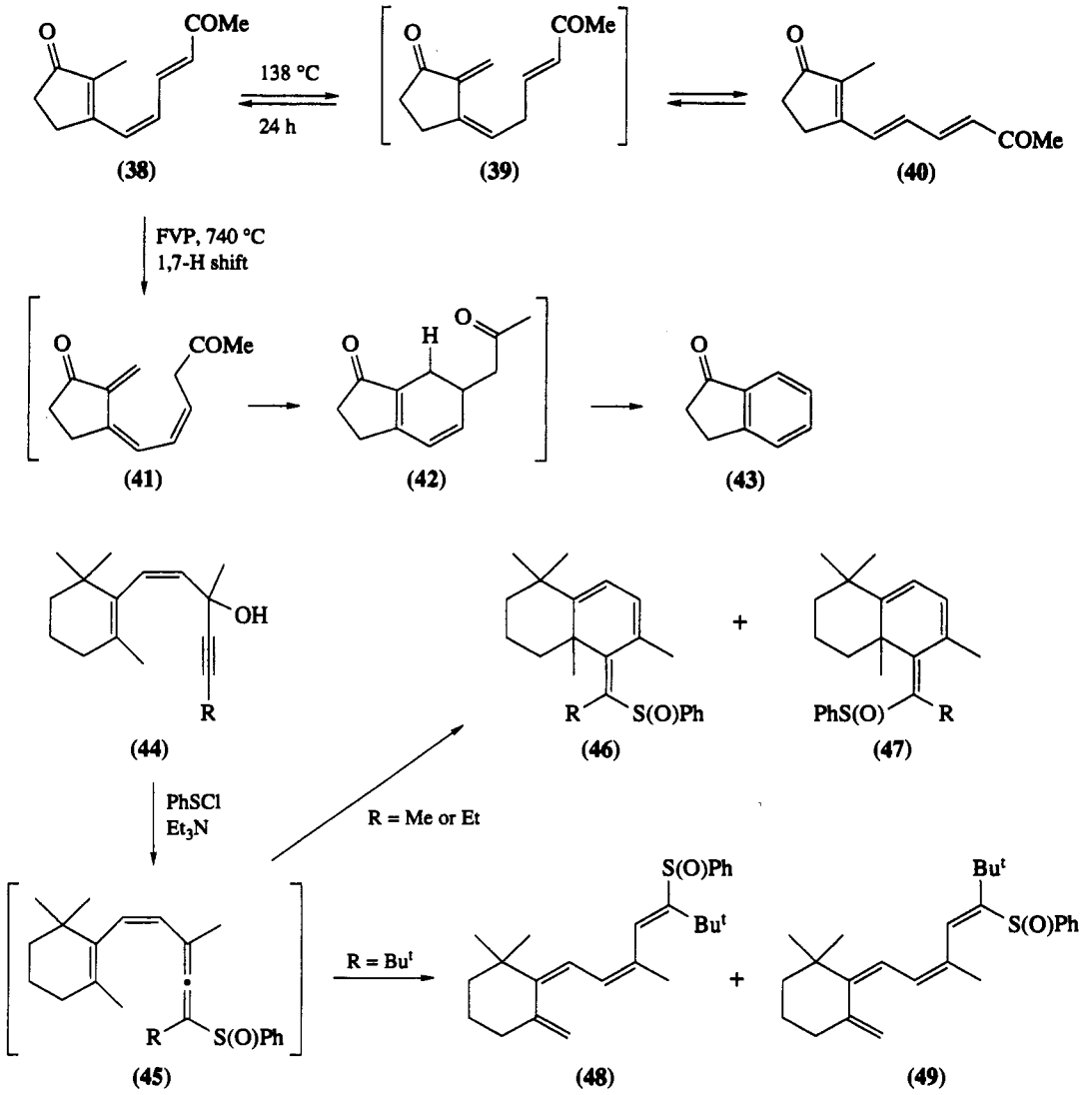
The main competing processes resulting from the thermal treatment of hexatrienes are sigmatropic hydrogen shifts, specifically 1,5- and 1,7-H shifts. Related 1,3- and 1,5-alkyl shifts are uncommon in acyclic trienes and cyclohexadienes. The competition[29] between ring closure and 1,7-H shifts[30] has been clarified from an exhaustive study of the ground state isomerization behavior of alloocimene (**28**).[31] It was concluded that the fastest thermal reaction in unhindered 1,3,5-heptatrienes is the 1,7-H shift, interconverting the (*Z,Z*)- and the (*E,Z*)-isomers (**28**) and (**30**) *via* (**29**), followed by the ring closure. The transformation of (**11**) to (**12**) and then (**13**) represents a related example. Higher temperatures were required for the 1,5-H shift and for direct isomerization of the central and terminal double bonds. Ring opening could be observed on further heating. Similarly, an aromatic 1,7-H shift has been postulated[32] to explain the thermal isomerization of (**31**) to (**32**). At equilibrium (225 °C), 89% (**32**) and 11% (**31**) are present and they do not experience disrotatory electrocyclization unless heated for prolonged periods. The latter condition ultimately leads to (**34**). The (*E,E*)-isomer (**33**) experiences cyclization followed by 1,5-H shift under similar conditions to afford the dihydronaphthalene (**34**). The abnormal stereochemistry of the decalin (**35**) obtained from either (**36**) or its isomer (**37**) may also be explained by a reversibly produced 1,7-H shifted intermediate.[33]



Both 1,5- and 1,7-H shifts have been invoked in the thermal rearrangement of the diketone (**38**).[34] In xylene (138 °C, 24 h), (**38**) isomerized quantitatively to the (*E,E*)-trienedione (**40**), probably *via* intramolecular hydrogen transfer from (**39**). Under flash vacuum pyrolysis (FVP) conditions (740 °C), the indan-1-one (**43**) was the only product observed. Its genesis may involve an initial 1,7-H sigmatropic shift to give (**41**) followed by cyclization to (**42**) and elimination of acetone to give (**43**).

For a vinylallene variant[35] of the $6e^-$ electrocyclization process, a comprehensive study of the effect of substituents at the terminal position of the triene system in (**45**), generated from the propargylic alcohol (**44**) *via* a 2,3-sigmatropic rearrangement, was undertaken. For relatively small groups (R = Me or Et), electrocyclization afforded (**46**) and (**47**), in spite of their sterically congested nature. For the bulkier *t*-butyl group however, only tetraene products (**48**) and (**49**) derived from 1,7-H shifts were observed. Products derived from both electrocylization and 1,7-H shift are observed for the case R = Pr^i in (**45**). The topic of polyene units possessing *sp* hybridized carbon centers will be discussed further in Section 6.2.3.

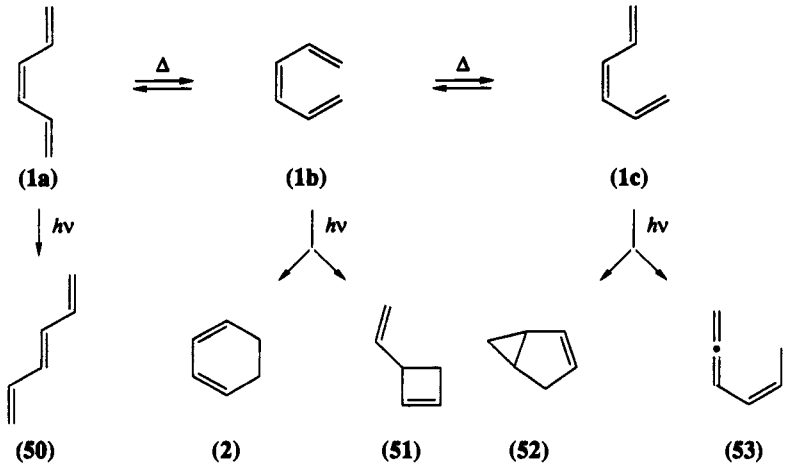
The photochemically induced ring closure of (**1**) to (**2**) has also found relatively little synthetic use due to the seemingly complex nature of the photoproducts obtained upon irradiation of a hexatriene.[36–40] Some of the following principles or factors which can affect the course of a photochemical process have been reviewed by Laarhoven[36] and these include the following. (a) The NEER (non-equilibration of excited state rotamers) principle indicates that each conformer of a polyene yields its own characteristic



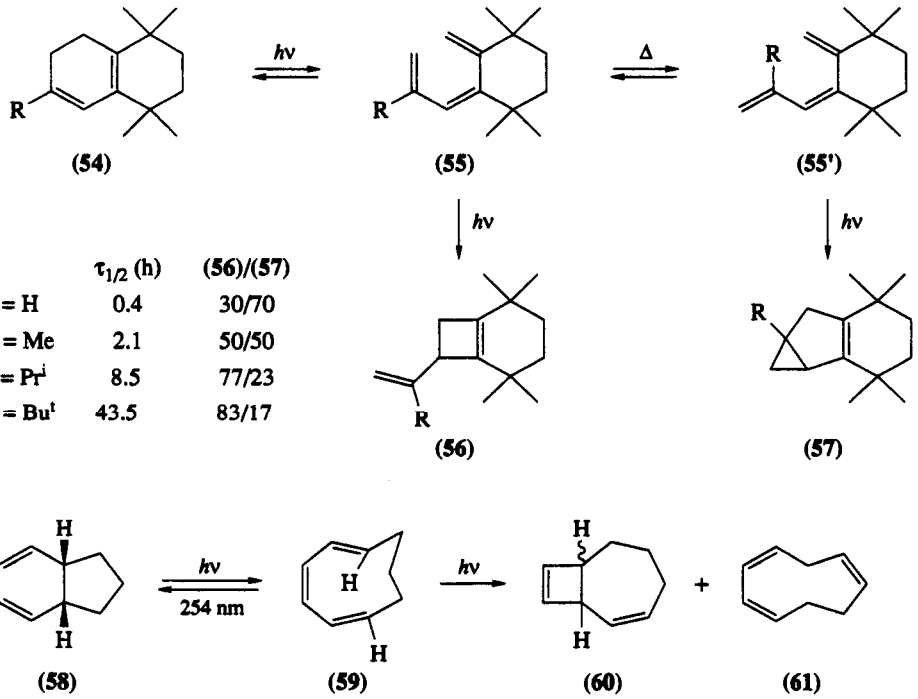
photoproduct. In other words, there is a direct correlation between the composition of a photoproduct mixture and the conformational equilibria of the starting material in its ground state. (b) The principle of least motion, especially important in the photochemical opening of cyclohexadienes, assumes that the geometry of the resulting triene is a function of the position (pseudoaxial or pseudoequatorial) of the bulky substituent on the cyclohexadiene. Related to this, the 'accordancy principle' (see Section 6.2.4.1 for further discussion) states that the mode of conrotatory opening follows the chirality (twist) of the diene. (c) The change in the wavelength of irradiation can affect the selectivity on the excitation of specific conformers as well as change the composition of the photoproducts by giving secondary photoproducts from the primary ones. (d) The temperature and the solvent can influence the course of the photoreaction, as can (e) the influence of substituents (which can cause large changes in the equilibrium position of the different conformers).

For the parent (*Z*)-1,3,5-hexatriene (**1**), the main pathways competing with the desired electrocyclization to (**2**) are the isomerization of the central double bond to give the (*E*)-triene (**50**) as well as the formation of other cyclized products (**51**) and (**52**) and the vinylallene (**53**).[41] The sensitized irradiation of isomeric trienes results primarily in rapid (*Z*)–(*E*) isomerization about the central double bond and dimerization.[42] By contrast to singlet state photochemistry, no electrocyclic or sigmatropic rearrangements occur under sensitized conditions.[41a]

The importance of conformational effects on photoreaction pathways are clearly seen with substituted hexatrienes. For the opening of hexalins (**54**), the ratio of vinylcyclobutenes (**56**) to bicyclo[3.1.0]hexanes (**57**) depends on the size of the substituent R in accordance with a preponderance of one or the other conformer of the photogenerated hexatriene (**55**).[43] In addition, when the (*cZc*) conformer is favored, the



back reaction (ring closure to cyclohexadiene) is more likely to occur, which explains the longer lifetimes of the starting (**54**) possessing the bulkiest substituents. Sigmatropic hydrogen shifts also account for some of the products, which probably result from over-irradiation. The (*E,Z,Z*)-1,3,5-cyclononatriene (**59**) (formed from the corresponding *cis*-tetrahydroindene **58**) affords a vinylcyclobutene, bicyclo[5.2.0]nona-2,8-diene (**60**), together with 1,3,6-cyclononatriene (**61**) resulting from a 1,3-H shift.[44] Photochemical sigmatropic 1,*j*-H shifts when substitution patterns and geometric factors are favorable, can be a major undesirable pathway in attempts to induce $6e^-$ electrocyclizations.[39,45]

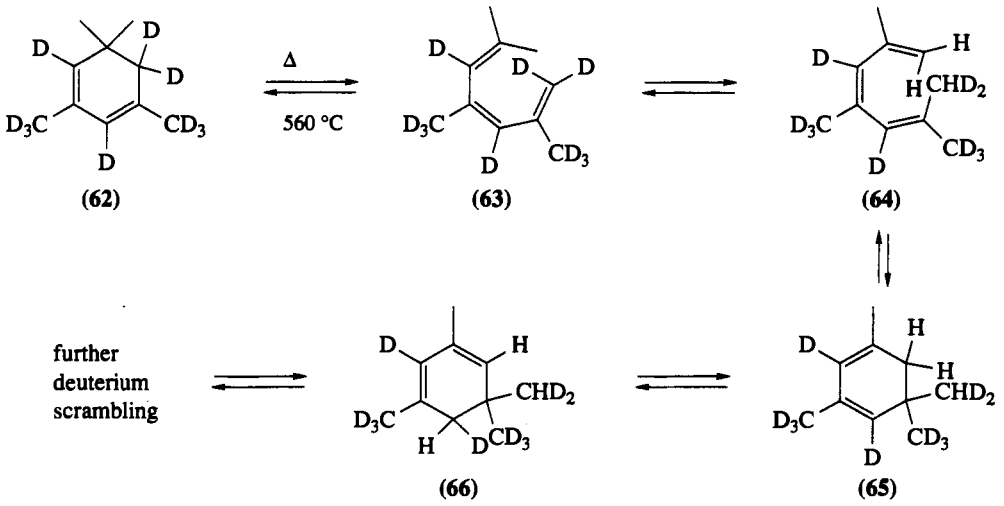


	$\tau_{1/2}$ (h)	(56)/(57)
a: R = H	0.4	30/70
b: R = Me	2.1	50/50
c: R = Pr^i	8.5	77/23
d: R = Bu^t	43.5	83/17

From a thermodynamic standpoint, one can expect that for the thermal conversion of (**1**) to (**2**) and related derivatives, unless the temperature is sufficiently high or strain factors become predominant, cycloreversion will not be observed. A more complete discussion of the factors affecting the thermal equilibration of strained hexatrienes and cyclohexadienes will be discussed in Section 6.2.2.2.1. A kinetic study of the pericyclic transformation of the parent triene (**1**) to 1,3-cyclohexadiene (**2**) provided an activation energy of 29.9 kcal mol^{-1}.[16a] Taking into account the heats of formation of reactant and product (40.6 kcal mol^{-1} for (*Z*)-1,3,5-hexatriene and 25.4 kcal mol^{-1} for 1,3-cyclohexadiene),[46] the

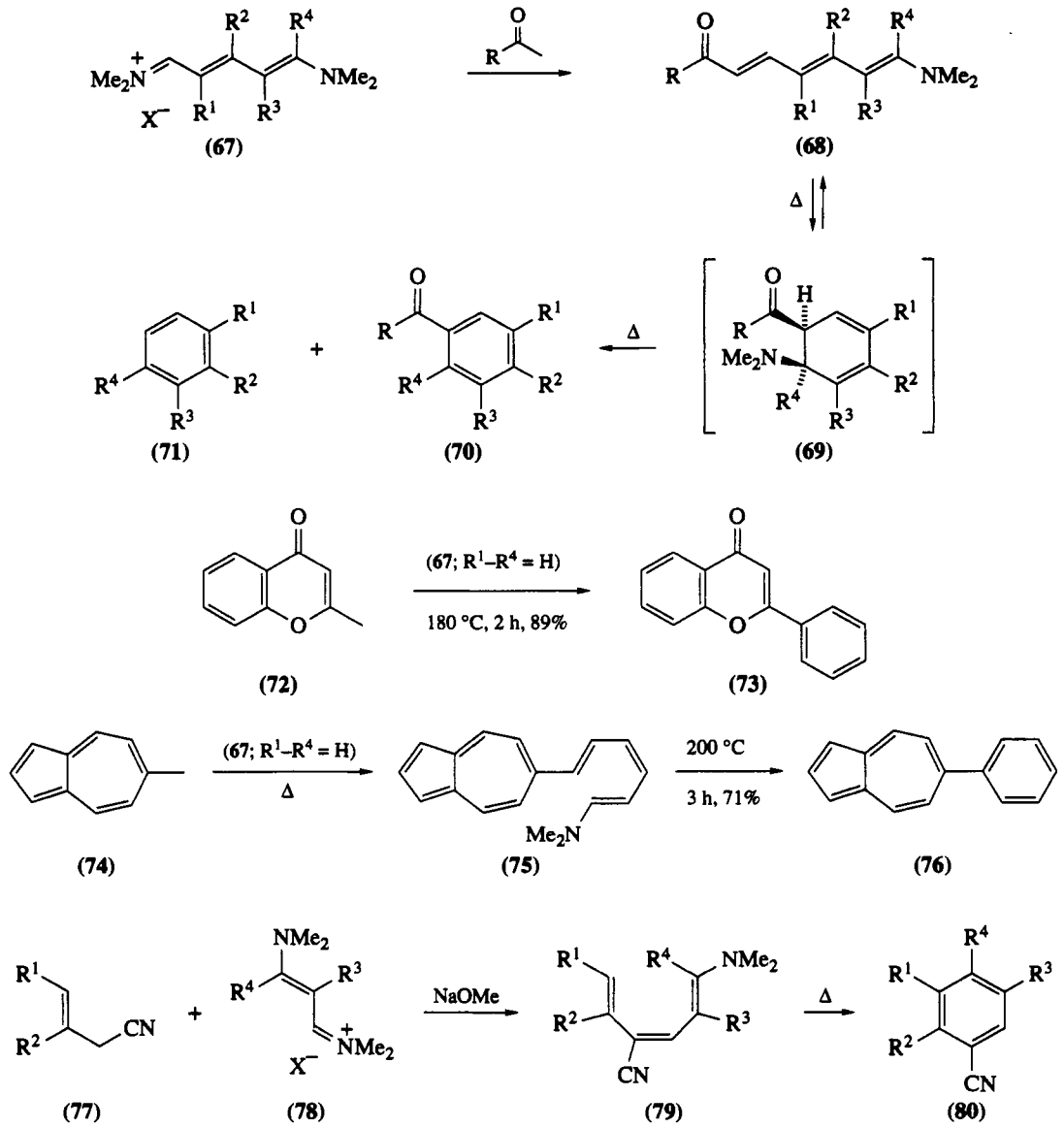
reverse process (*i.e.*, the thermal ring openings of the 1,3-cyclohexadiene) requires a significantly higher activation energy (~44.2 kcal mol^{-1}).

That the thermal ring opening of cyclohexadienes proceeds at sufficiently high temperatures has been demonstrated by the observation of complete scrambling of the labels in the automerization of cyclohexadiene (**62**) at 560 °C in the gas phase.[47–49] The thermal ring opening of cyclohexadienes is thus not generally useful for synthesizing hexatrienes. By contrast, the photochemical ring openings of cyclohexadienes are rather facile processes, and have found at least some synthetic use as will be discussed in Section 6.2.4.1.



With the transition state geometries deduced from semi-empirical approaches,[17] several correlations with experimental results have been developed for different substitution patterns of the hexatriene.[50–55] Structure–reactivity data which have been tabulated[3a] are important considerations in synthesis applications. The general trends which emerge from these studies are the following. Substituents at the C-1 (or C-6) position have moderate (*Z*) or negligible (*E*) effects on the rate of electrocyclization. Substituents at C-2 (or C-5) can cause a two-fold rate increase effect, either at the ground state level (by increasing its energy as a result of deviation from planarity and by increasing the population of the *s-cis* conformation) or by stabilizing a presumed radical character developed at the transition state. For the substituents at C-3 (or C-4) the same effects are operative, although to a lesser extent. These trends parallel the experimental results. For example, for simple hexatrienes substituted at C-2, the ability of phenyl and ethoxycarbonyl substituents as radical stabilizers facilitates (room temperature) electrocyclization.[52]

The electrocyclization of certain 1-dialkylamino-1,3,5-hexatrienes is followed by elimination of dialkylamine to afford benzene derivatives.[56] If the double bond of the 1-aminohexatriene is part of an aromatic or heteroaromatic system, smooth cyclization ensues to give benzannulated derivatives (a topic to be discussed further in Section 6.2.2.2.1 and later sections). The starting aminohexatrienes (**68**) have been conveniently prepared, for example by Knoevenagel condensation of carbonyl compounds (carbanion equivalents) with pentamethynium salts (**67**) (pentadienyl cation equivalents). Aminoheptatrienones (**68**) typically cyclize at temperatures below 50 °C to the benzoyl derivative (**70**) accompanied in some cases by (**71**) (resulting from elimination of the *cis* substituents)[56c] when (**69**) is sterically congested. With other carbanions, the condensation–cyclization–elimination sequence also occurs, as exemplified by the conversion of chromone (**72**) into flavone (**73**) and azulene (**74**) into its derivative (**76**). An alternative benzannulation sequence is exemplified by the condensation of crotonitriles (**77**) with vinylamidinium salt (**78**) to afford (**80**) as shown. With the possibility of using different substituents in both components, this synthetic approach to aromatic compounds is highly versatile.



6.2.2.2 Cyclic and Annulated Hexatrienes

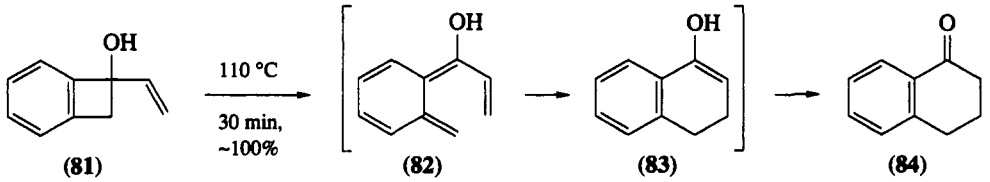
6.2.2.2.1 Mono-annulated trienes

Mono-annulated 1,3,5-hexatrienes leading to *ortho*-condensed 1,3-cyclohexadienes of the types I–IV (see Figure 2) have been well studied. By contrast, bridged trienes leading to 1,3-cyclohexadienes of types V–IX are rare. This section is organized sequentially according to the 1,3-cyclohexadiene type.

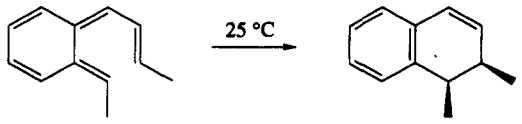
(i) Type I: Ortho-condensed [1,2]-Annulated Systems

The synthesis of a [1,2]-annulated cyclohexadiene requires a relatively less common bis-exomethylene ring-fused hexatriene precursor. Indirect procedures take advantage of other facile thermal or photochemical rearrangements leading to *in situ* generation of the necessary triene substrate. As an example, a reaction initiated by a thermal conrotatory ring opening of vinylcyclobutenol (**81**) gave a quantitative yield of α-tetralone (**84**), which can be considered to involve a disrotatory electrocyclization of the dienol (**82**) followed by enol–keto tautomerism of (**83**).[57a] Other cyclizations of dienol ethers have been re-

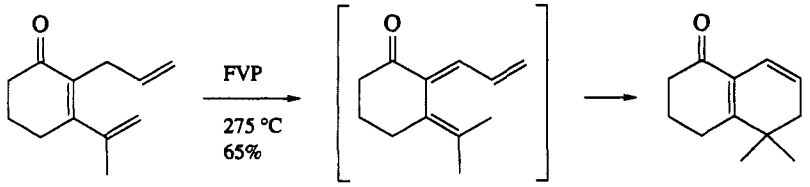
ported,[57b–e] including those promoted by transition metal catalysts.[57d] Note that formation of the aromatic ring on (**83**) facilitates the $6e^-$ electrocyclization process as indicated by the low temperature (25 °C) at which thermal cyclization of (**85**) to (**86**) occurs, thus suggesting that the transformation of (**82**) to (**83**) must be fast.[45d] A 1,5-H sigmatropic shift of cyclohexenone (**87**) also generates the desired bis-exo-methylene subunit in (**88**). Under the reaction conditions the presumed (**88**) affords as the main product tetrahydronaphthalenone (**89**) *via* electrocyclization.[58]



(**81**) (**82**) (**83**) (**84**)

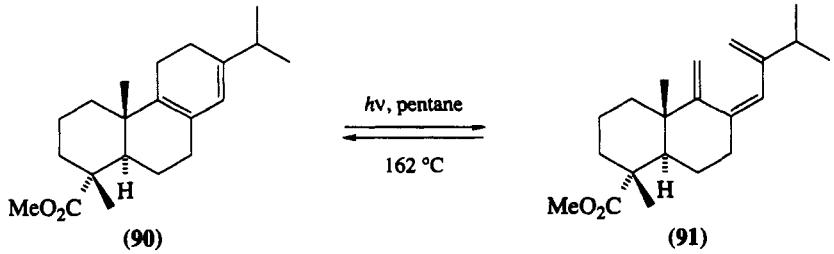


(**85**) (**86**)

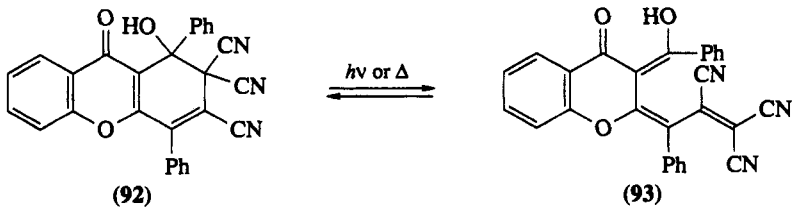


(**87**) (**88**) (**89**)

The photochemical ring opening of palustric ester (**90**), an example of a [1,2]-annulated cyclohexadiene, has been achieved wherein a ~1:1 photostationary state mixture of diene (**90**) and triene (**91**) was obtained. Upon heating for 4 h (162 °C), the photo-mixture regenerates palustric ester (**90**).[59] A related interconversion was observed for a series of photochromic cyclohexadienes of the xanthenone, dibenzofuran and acridone types, exemplified by (**92**) → (**93**).[60]



(**90**) (**91**)

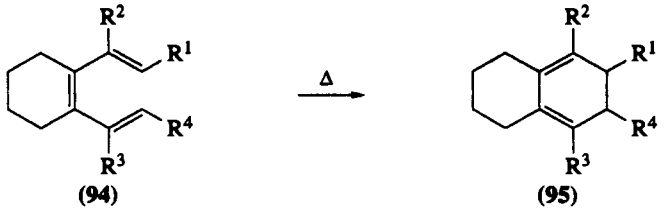


(**92**) (**93**)

(ii) Type II: Ortho-condensed [2,3]-Annulated Systems

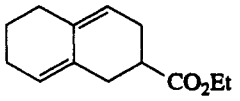
The synthetic advantage of using a triene with the central double bond locked in a (Z) configuration by virtue of ring fusion has provided a series of 1,2-divinylcyclohexenes (**94**) used for structure–reactivity

studies.[51,61] While the parent system (**94a**) cyclizes upon heating at 125 °C, higher temperatures are required for the cyclization of the derivatives (**94b–g**), irrespective of their location and/or stereochemistries. Prolonged heating of (**94c**) led to the rearranged diene (**96**).



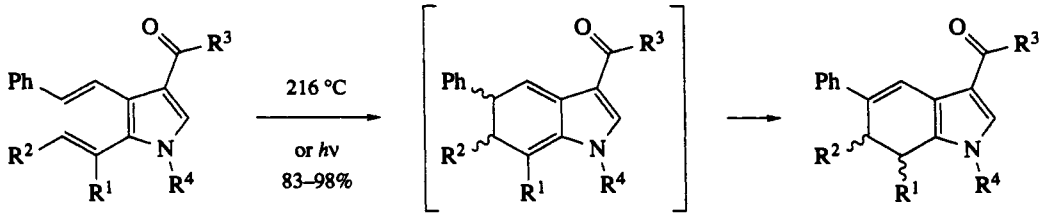
(**94**) (**95**)

	R^1	R^2	R^3	R^4
a:	H	H	H	H
b:	CO_2Et	H	H	H
c:	H	H	H	CO_2Et
d:	*(E)*-Ph	H	H	*(E)*-Ph
e:	*(E)*-Ph	*(Z)*-Ph	H	H
f:	Ph	CO_2Et	H	H
g:	*p*-An	CO_2Et	H	H



(**96**)

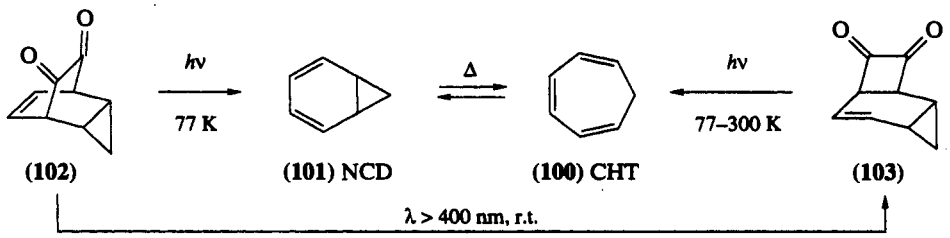
When the central double bond is part of an aromatic ring, the ring closure is retarded and is accompanied by regeneration of the aromatic nucleus. Thus, as described earlier in this review, the dihydronaphthalene (**34**) was obtained upon thermolysis of compound (**33**), a product obtained by an initial electrocyclization followed by a 1,5-H shift.[32] Similarly, a synthesis of the dihydroindole nucleus (**99**) makes use of the thermal (216 °C) or photochemical electrocyclic ring closure of 2,3-dienylpyrroles (**97**) to intermediate (**98**) followed by a 1,5-H shift.[62]



(**97**) (**98**) (**99**)

(iii) Type III: Ortho-condensed [5,6]-Annulated Systems

The cycloheptatriene (CHT)–norcaradiene (NCD) valence tautomerism, or CHT–NCD equilibrium (**100**)–(**101**), has captivated the interest of the scientific community for about a century[63] and considerable theoretical and experimental evidence has clarified the factors favoring one or the other tautomer. A direct experimental observation of NCD (**101**) has recently been reported, together with the kinetics of its conversion into CHT (**100**).[64] NCD was interpreted to be the unstable intermediate generated by low-temperature (77 K) irradiation of solutions of tricyclo[3.2.2.$0^{2,4}$]non-6-ene-8,9-dione (**102**) in a hydrocarbon glass with light of wavelength 240–400 nm. Upon brief warming to ~110 K and recooling, the λ_{max} changed from 265 nm (attributable to **101**) to 261 nm, the absorption maximum corresponding to (**100**). These differences in the UV spectra allowed the measurement of the kinetics for the isomerization of NCD (**101**) to CHT (**100**). The rate constant for the process at 25 °C was estimated to be $1 \times 10^7 s^{-1}$.

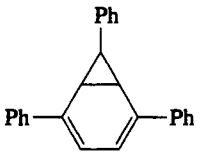


(**102**) (**101**) NCD (**100**) CHT (**103**)

λ > 400 nm, r.t.

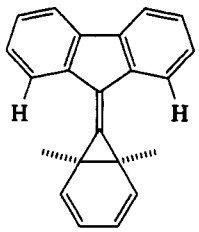
Excellent reviews concerning the NCD problem have appeared describing more than 80 compounds with different substitution patterns.[3a,63] From these data and recent experimental findings, the following factors contributing to the displacement of the isomerization equilibrium towards the NCD form have been proposed: (a) placement of a π-acceptor group at the C-7 position;[65–67] (b) extension of conjugation at appropriate positions in the NCD form[68] as in (**104**) and (**105**); (c) shortening of the C-1–C-6 distance by bridging these positions by a chain of carbon atoms as in (**106**);[69] (d) the nonbonding interactions between the C-7 substituent and proximal π-bonds or substituents as in (**107**).[70,71]

(**104**)



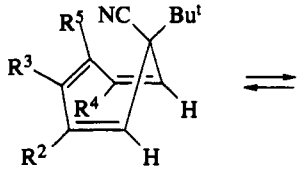
(**105**)

(**106**)

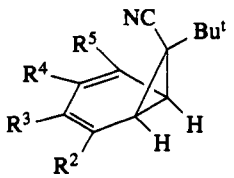


(**107**)

The sensitivity of the CHT–NCD equilibrium towards the substitution pattern is nicely illustrated by the equilibrium between (**108**) and (**109**),[72] noting for reference that the parent system (**108a**)–(**109a**) is displaced towards the CHT (**108a**). Introduction of *t*-butyl groups at the C-3, C-2, C2,4 or C2,5 positions progressively shifts the equilibrium towards the NCD form (**109**). Nonbonding interactions between the C-3 *t*-butyl group and H-2 and between the C-2 *t*-butyl and H-1 are relieved by structural change from CHT to NCD. The synergistic effect of placing *t*-butyl groups at C-2 and C-5 on shifting the equilibrium to the NCD form has been used to study the effect of the π-acceptor strength of the C-7 substituent.[73] At room temperature, ~30% of NCD (**111**) is observed, which allowed the determination of the equilibrium constant by ^{13}C NMR. As expected, the NCD form (**111**) is stabilized in the order of π-acceptor strength of substituents (OMe < H < CF_3). Several other related studies have been reported.[74]

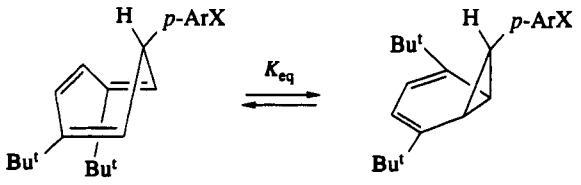


(**108**)



(**109**)

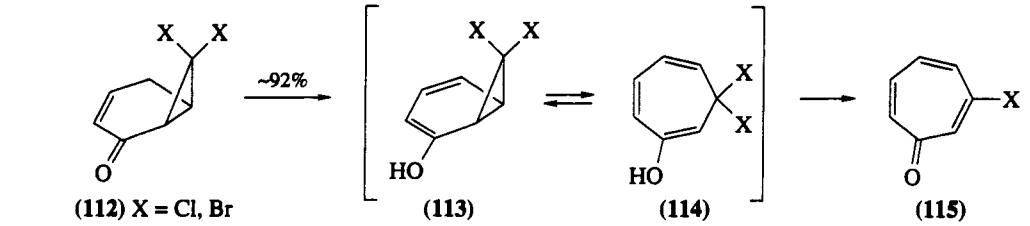
	R^2	R^3	R^4	R^5	% (**109**)
a:	H	H	H	H	19
b:	Bu^t	H	H	H	88
c:	H	Bu^t	H	H	46
d:	Bu^t	H	Bu^t	H	97.4
e:	Bu^t	H	H	Bu^t	99.7

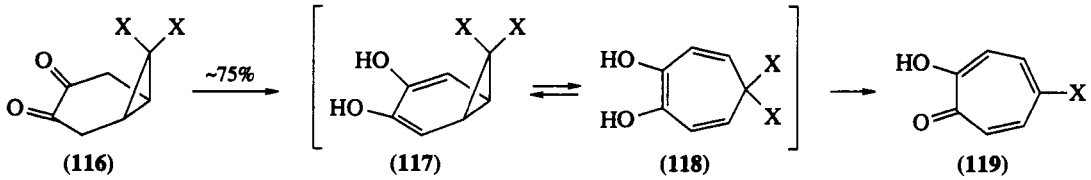


(**110**) X = OMe, H, CF_3 (**111**)

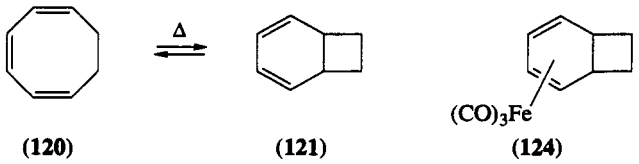
From a synthetic point of view, the CHT–NCD equilibrium has been exploited in a total synthesis of colchicine[75a] and, more recently, in syntheses of tropones (**115**) and tropolones (**119**) from 7-halobicyclo[4.1.0]heptenones (**112**) or 7-halobicyclo[4.1.0]heptane-3,4 diones (**116**), respectively.[75b] Keto–enol tautomerism of (**112**) to (**113**) followed by ring opening to the cycloheptatrienols (**114**) and loss of HX would explain the formation of the tropone (**115**). The tropolone (**119**) probably results from a similar sequence. These examples represent one of few cases that exemplify $6e^-$ retro electrocyclizations presented thus far in this review. Additional examples will be presented later in Section 6.2.4.1.

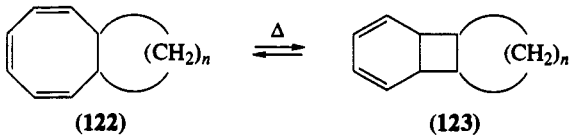
For the related tautomerism between the higher homologues, 1,3,5-cyclooctatriene (**120**) and bicyclo[4.2.0]octa-2,4-diene (**121**),[76] a tabulation of a series of derivatives including thermodynamic data is presented in the treatise by Marvell.[3a] The data reveal a large variation in equilibrium constants by introducing seemingly small changes in the structure. While the electronic effects of the substituents at C-7



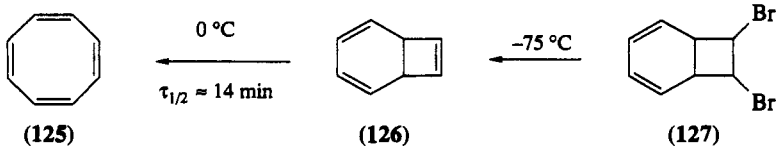


and C-8 do not reveal a striking trend, the effect of adding a bridge between C-7 and C-8 is more clear. Small ring fusion as in (**122**)–(**123**) (n = 1, 2) imparts an increase in the strain to the tautomer (**123**), leading to a shift in equilibrium towards (**122**). Larger cycles tend to be more stable in bicyclic form (**123**).[77] Interestingly, while the equilibrium between (**120**) and (**121**) favors the former open triene form (ratio 85:15 at 100 °C), the iron complex (**124**) exists in the bicyclic form.[78]

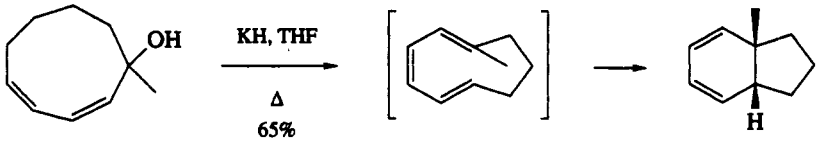




For the cyclooctatetraene (COT)–bicyclo[4.2.0]octa-2,4,7-triene system (**125**)–(**126**), earlier studies using an indirect method afforded an equilibrium composition at 100 °C containing 0.01% of the bicyclic form (**126**) ($\Delta G^{\circ} \approx 6.8$ kcal mol^{-1} less stable).[79] The bicyclic form (**126**) has been prepared, however, by low-temperature dehalogenation of dibromide (**127**) and found to rearrange to COT at 0 °C ($E_a \approx 18.7$ kcal mol^{-1}).[80] Recently, a high-temperature thermal trapping technique has been utilized to assess more completely the transformation between (**126**) and (**125**) in a quantitative manner.[81]

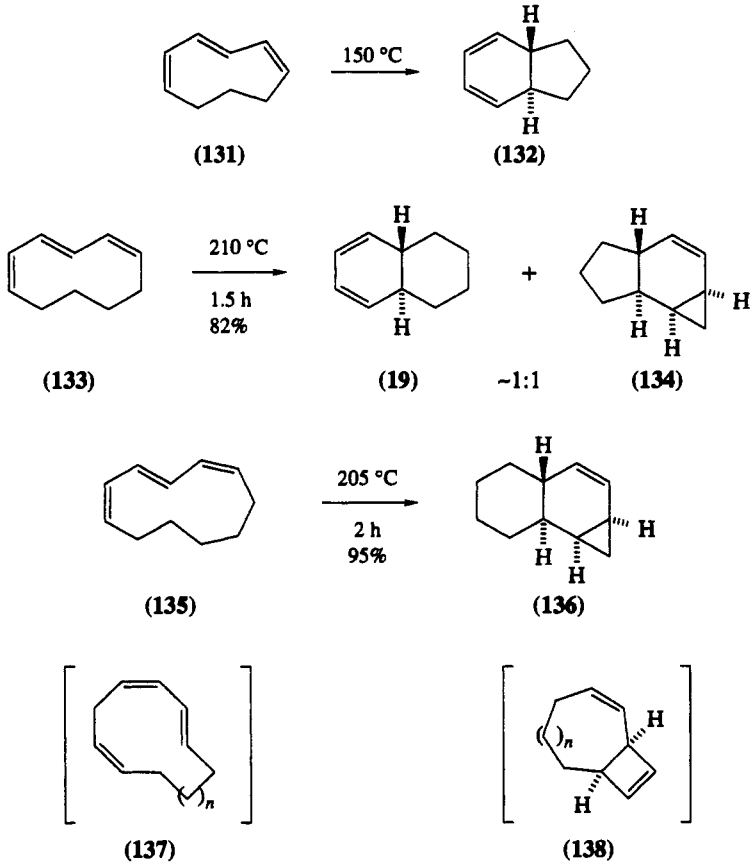


For monocyclic conjugated trienes with a (*Z*) central double bond such as (*E,Z,E*)-1,3,5-cyclodecatriene (**20**) discussed earlier, allowed disrotatory ring closure to a 5,6-fused cyclohexadiene (**21**) is a common isomerization pathway. Methyl substituents at positions C-1 and C-6 of (*E,Z,E*)-1,3,5-cyclodecatriene attenuates the rate of ring closure, probably due to the steric hindrance for approaching the disrotatory transition state.[82] The disrotatory pathway is also reported to be followed in trienes with a putative (*E,Z,E*) geometry, such as (**129**) believed to be formed by base-promoted dehydration of dienol (**128**).[83] The coiled geometry of (**129**) was thought to be kinetically favored over the alternative, more congested all-(*Z*) isomer, the cyclization of which could also explain the formation of the observed bicyclic isomer (**130**).



(128) (129) (130)

When the central double bond of the hexatriene is (*E*), new pathways are followed and the product distribution shows a structure–reactivity correlation with the size of the ring.[84] The thermal rearrangement of the cyclononatriene (**131**) afforded the *trans*-bicyclo[4.3.0]nona-2,4-diene (**132**). By contrast, the larger 11-membered-ring triene (**135**) yielded a different structure, the *trans*-tricyclo[5.4.0.$0^{4,6}$]undec-2-ene (**136**). The 10-membered ring (*Z,E,Z*)-triene (**133**) exhibited intermediate behavior between these two pathways, affording a *ca.* 1:1 mixture of both derivatives (**19**) and (**134**).[84] A most plausible explanation for the formation of (**134**) and (**136**) involves an initial 1,5-H migration to a partially nonconjugated (*E,Z,Z*)-triene (**137**) followed by an intramolecular Diels–Alder reaction. To rationalize the formation of the cyclohexadienes (**132**) and (**19**), two successive 4e⁻ conrotatory electrocyclizations *via* a vinylcyclobutene intermediate (**138**) was proposed to interconvert the (*Z,E,Z*)-trienes (**131**) and (**133**) to the corresponding (*E,Z,Z*)-trienes, from which the observed cyclohexadienes (**132**) and (**19**), respectively, could be generated by normal disrotatory ring closure.



(131) (132)

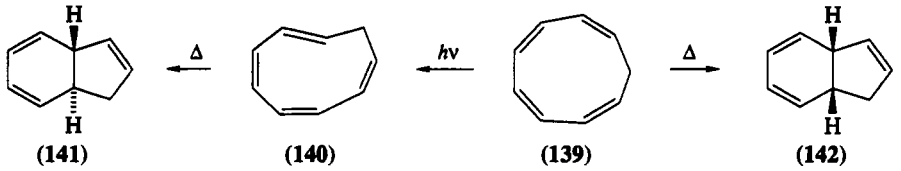
(133) (19) ~1:1 (134)

(135) (136)

(137) (138)

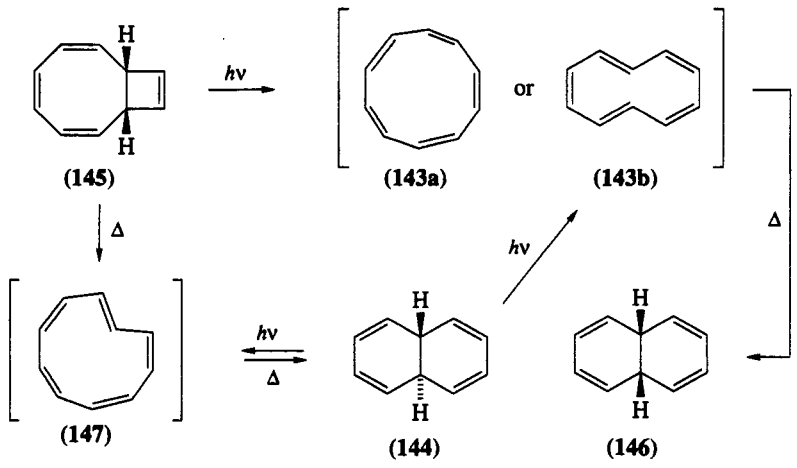
All-(*Z*) cyclononatetraene (**139**) has been shown[10,85,86] to follow the WH rules for its facile thermal rearrangement to *cis*-8,9-dihydroindene (**142**). For this process at 18–35 °C the activation parameters were determined to be $\Delta H^{\ddagger} = 19.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -10.4$ cal mol^{-1} K^{-1}.[85] Low-temperature photolysis of (**139**) followed by warming to 50 °C provided *trans*-8,9-dihydroindene (**141**), probably *via* an initial photochemical isomerization of (**139**) to the (*E,Z,Z,Z*)-tetraene (**140**), followed by ring closure.[86]

The annulenes from [10]annulene to [16]annulene react quite selectively by 6e⁻ disrotatory processes.[87] Thus the low-temperature photochemical generation[88,89] of cyclodecapentaene (**143**) from *trans*-9,10-dihydronaphthalene (**144**) or from (**145**) was followed by its thermal isomerization to *cis*-9,10-dihydronaphthalene (**146**). The (*E,Z,Z,Z,Z*)-cyclodecapentaene (**147**) has been postulated as inter-

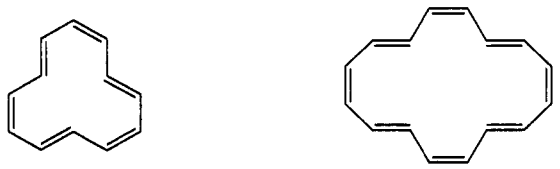


(141) (140) (139) (142)

mediate in the interconversion of *cis*- (**146**) and *trans*-9,10-dihydronaphthalene (**144**). Similar low-temperature $6e^-$ electrocyclizations at or below 25 °C characterize the behavior of [12]annulene (**148**)[90a,b] and [16]annulene (**149**).[90c,d]



(145) (143a) (143b) (147) (144) (146)

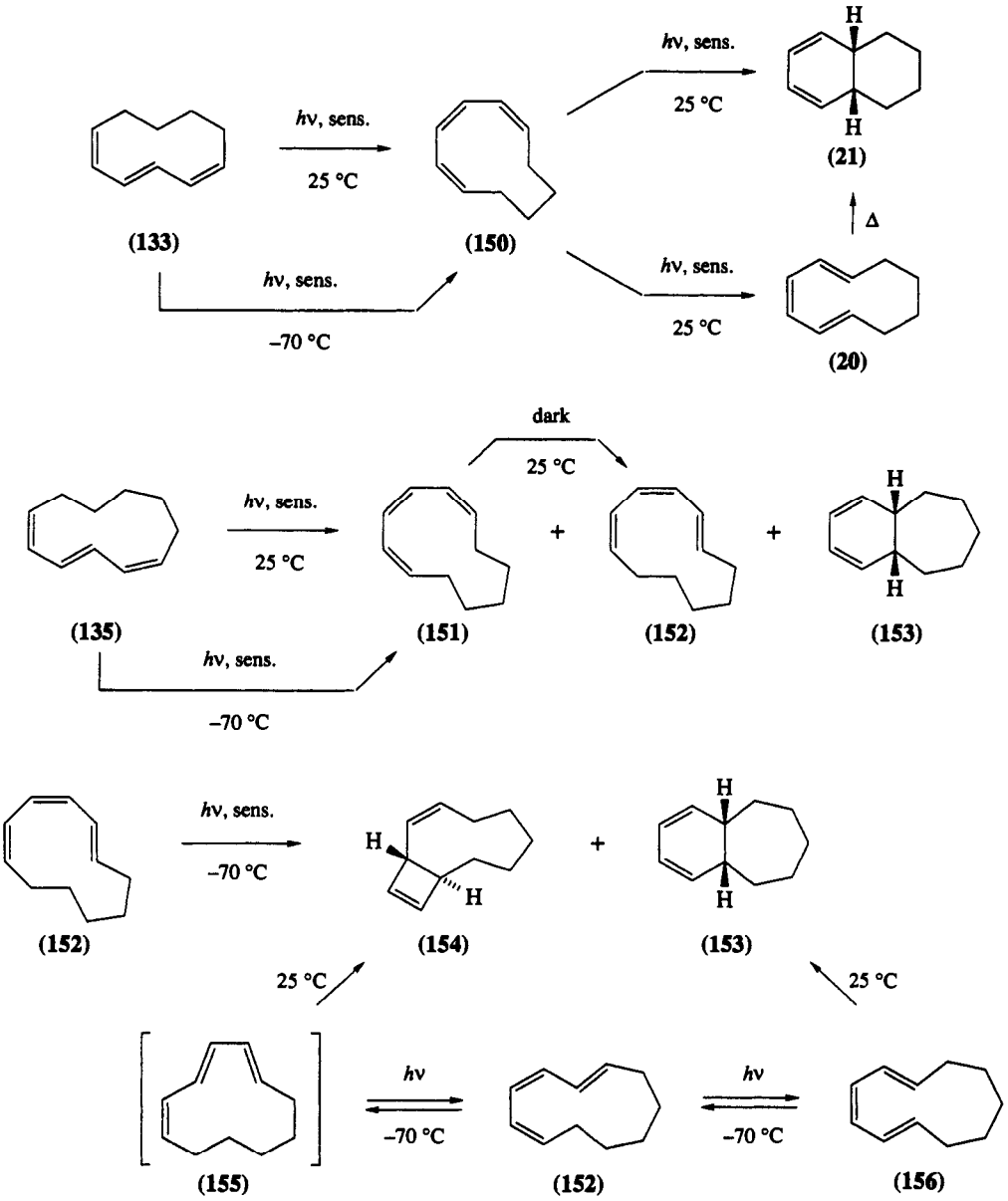


(148) (149)

The triplet-sensitized photochemistry of medium-ring cyclic trienes has been investigated[91] in order to evaluate the role of the ground state conformation on triplet energy transfer. Sensitized irradiation of (*Z,E,Z*)-1,3,5-cyclodecatriene (**133**) at –70 °C resulted in a selective (*Z*)–(*E*) isomerization of the central double bond to give (**150**). Upon warming to room temperature, the hexalin (**21**) was formed, presumably *via* thermal electrocyclization of the (*E,Z,E*)-triene isomer (**20**), itself formed by sensitized two-bond isomerization of (**150**).[92] The higher homolog, (*Z,E,Z*)-1,3,5-cycloundecatriene (**135**), follows the same pathway, although the products are less stable and other thermal processes compete. The primary photoproduct at –70 °C is the (*Z,Z,Z*)-triene (**151**), which suffers a 1,7-H shift to the (*E,Z,Z*)-triene (**152**). Upon prolonged irradiation the *cis*-bicyclo[5.4.0]undeca-8,10-diene (**153**) is also formed. The triplet photochemistry of the (*E,Z,Z*)-triene (**152**) affords at room temperature a photoequilibrium mixture of the starting triene (~30%) and the bicyclic diene (**153**; ~70%). At lower temperature (–70 °C), besides starting (**152**; 80%) and (**153**; 5%), *trans*-bicyclo[7.2.0]undeca-2,10-diene (**154**; 15%) was also detected. The formation of the latter can be considered to involve the thermal electrocyclization of the (*E,E,Z*)-triene isomer (**155**), which in turn can be envisaged to be in photoequilibrium with the corresponding (*E,Z,E*)-triene isomer (**156**) *via* (**152**).[91]

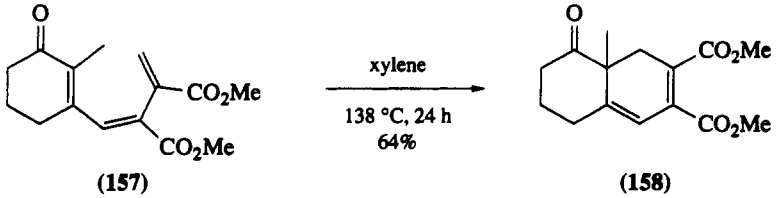
(iv) Type IV: Ortho-condensed [1,6]-Annulated Systems

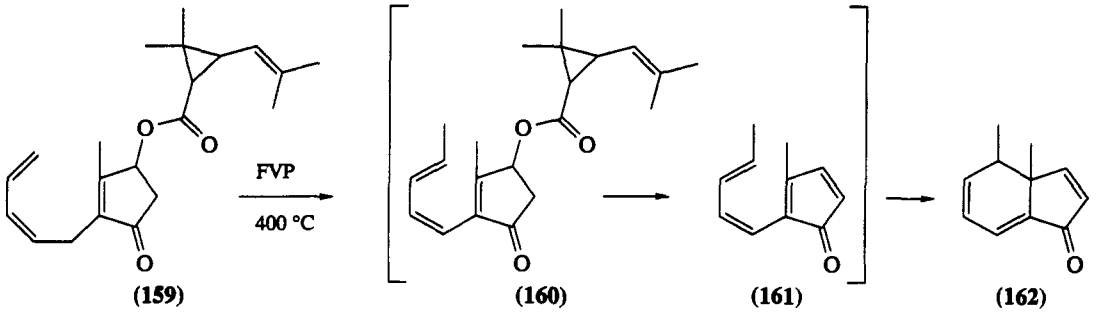
This type of electrocyclization is illustrated by the formation of (**35**) and the related formation of (**46**) and (**47**) (see also Section 6.2.3) discussed earlier. Another example is the thermal conversion of trienone (**157**) to the ketone (**158**).[93] A similar transformation of a related triene intermediate has been postulated to account for the formation of (**162**) from (**161**) by pyrolysis of pyrethrin-I (**159**), which initially produces (**160**).[94]

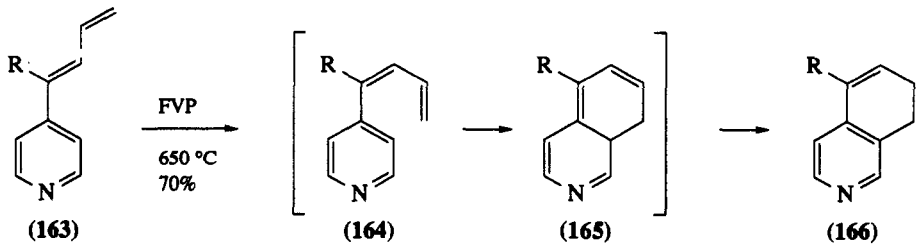


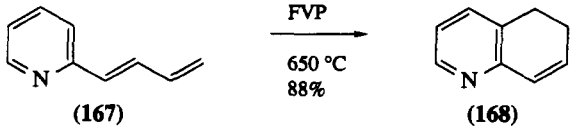
The synthesis of 7,8-dihydroisoquinolines (**166**) can be efficiently achieved by FVP techniques. The reaction also provides an entry into the dihydroquinoline (**168**) and 1,2-dihydronaphthalene skeleton (**170**) by FVP of (**167**) and (**169**), respectively. Note that the method involves initial (*E*) to (*Z*) isomerization, electrocyclization and then a 1,5-H shift.[95]

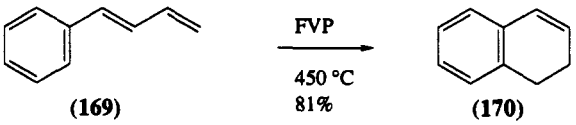
Using the aforementioned cyclization of 1-aminohexatrienes, *cf.* (**68**) to (**70**) and (**79**) to (**80**), several aromatic compounds have been synthesized upon elimination of a dialkylamine from a dihydroaromatic precursor formed by the $6e^-$ electrocyclization process. As an example, dihydrophenanthrene (**175**) can be synthesized in two different ways depending on the choice of the allyl anion synthon (**171** or **173**) or



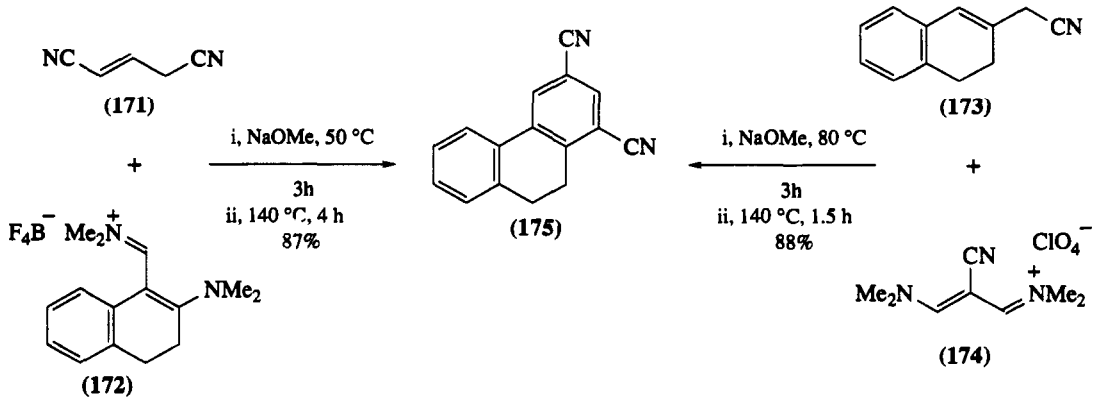


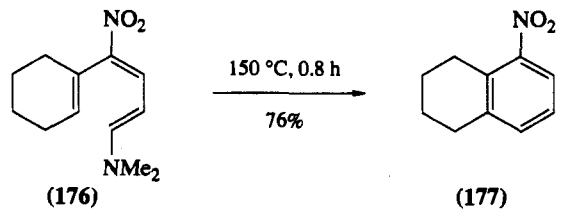


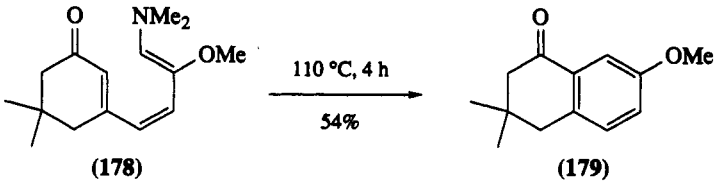




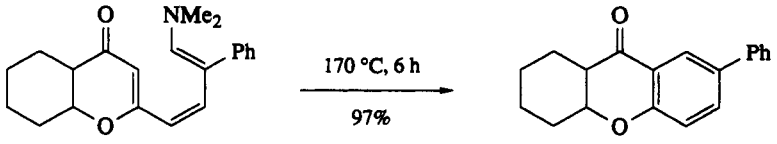
the corresponding allyl cation synthon (**172** or **174**, respectively). The syntheses of 5-nitrotetralin (**177**), tetralone (**179**) and xanthone (**181**) further illustrate this versatile approach.[56]





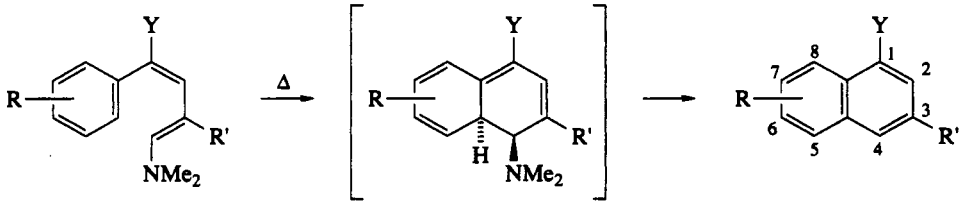


(178) (179)



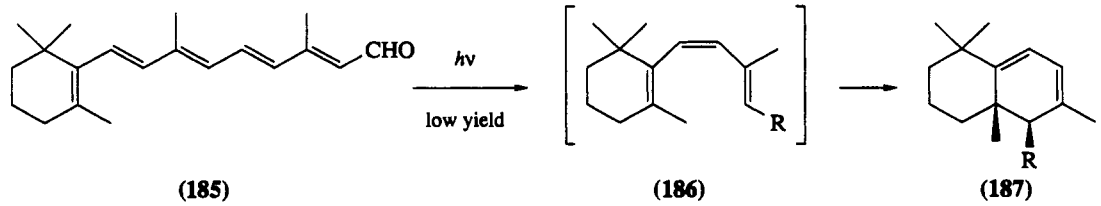
(180) (181)

In this benzannulation approach, the disruption of aromaticity upon cyclization requires higher activation energies compared with the open-chain aminohexatrienes. Another potential problem is associated with the regioselectivity of the cyclization. Although the cyano group (Y = CN) strongly favors the naphthalene derivative of (**184**) with the R group at C-5, a more sterically demanding R′ group can reverse the regioselectivity. When this problem is not present, efficient syntheses of aromatic compounds are readily achieved and a variety of complex aromatic arrays (naphthalenes, phenanthrenes, chrysenes, triphenylenes, benzo[*c*]phenanthrenes, pyrenes, *etc.*) can be synthesized.

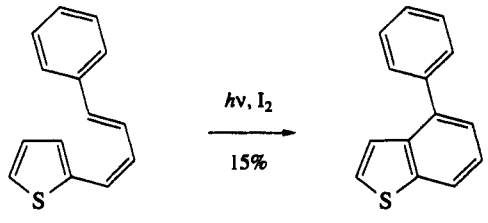


(182) (183) (184)

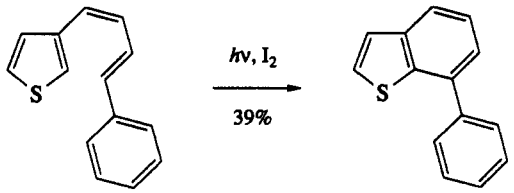
This electrocyclization leading to a 1,6-fused cyclohexadiene also takes place with polyenes. A photochemical example from the vitamin A field is exemplified by the conrotatory photocyclization of the (7*Z*)-isomer (**186**) of retinal (**185**) to the bicyclic derivative (**187**).[96] The photocyclization procedure has also been used in the aromatic series.[97,98] Thus the photocyclization–oxidation reaction of 1-phenyl-4-(2′-thienyl)-1,3-butadiene (**188**) gave 4-phenylbenzo[*b*]thiophene (**189**). Similarly, the 3′-thienyl analogue (**190**) afforded 7-phenylbenzo[*b*]thiophene (**191**), the reaction exhibiting high selectivity for cyclization to the logically more reactive thiophene nucleus.[97b]



(185) (186) (187)



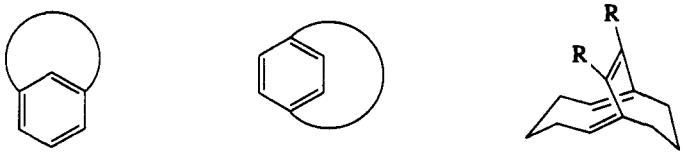
(188) (189)



(190) (191)

(v) Types V–IX: Bridged Systems

Examples in this series, whose cyclohexadiene units are all formally related by oxidation to *meta* (types V, VI and IX) and *para* (types VII and VIII) bridged cyclophanes of the kinds (**192**) and (**193**), respectively, appear not to exist in the literature (or they are at least rare and have escaped the attention of the authors of this review). Cyclophanes appear in standard textbooks[99] and there is a recent example of a 2,5-bridged hexa-1,3,5-triene, namely (**194**),[100] related by electrocyclization to a type VII 1,4-bridged cyclohexadiene. It is interesting that (**194**) is representative of a doubly orthogonal conformer of hexa-1,3,5-triene. However, the electrocyclization of hexatrienes to bridged 1,3-cyclohexadienes appears not to have been previously investigated.



(**192**) (**193**) (**194a**) R = Me
(**194b**) R = H

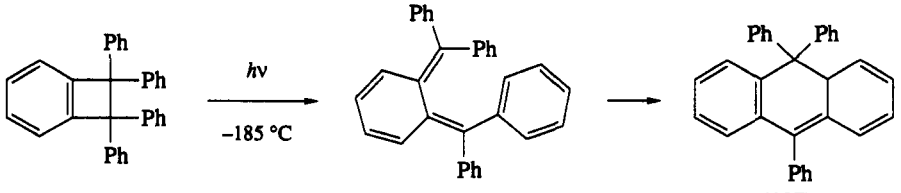
6.2.2.2.2 Bis-annulated trienes

With a discussion of the 6e⁻ electrocyclic reactions of acyclic (Section 6.2.2.1) and mono-annulated hexa-1,3,5-trienes (Section 6.2.2.2.1) completed, it may be apparent to the reader that the topic of bis-annulated systems (this section) and higher-order annulated systems (Section 6.2.2.2.3) may be considered fairly direct extensions of the lower-order annulated systems. Accordingly, only a selection of the major types of bis- and higher-order annulated systems (presented in the order, types XI, XV and XIII and then higher-order annulated systems) will be presented.

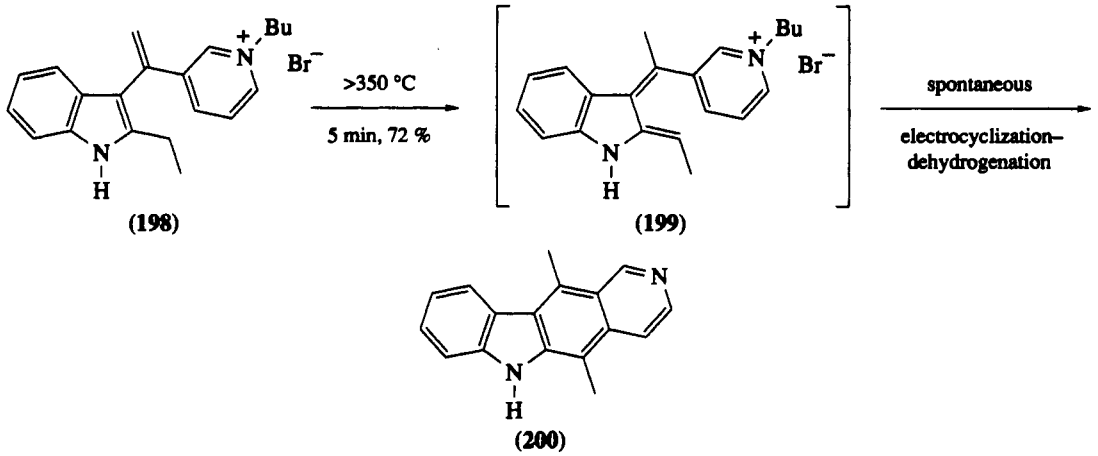
(i) Type XI: [1,2:4,5] Bis-annulated Cyclohexadienes

This approach to cyclohexadienes can be considered an extension of that described for the precursor to type I cyclohexadiene in which the vinyl group is part of a cyclic structure. An example is the low-temperature photochemical generation of the bis-exomethylene compound (**196**) from the benzocyclobutene (**195**), which was followed by an electrocyclic reaction to give compound (**197**).[101] Thermolysis of (**198**) also leads to an assumed bis-exo-methylene intermediate (**199**), which electrocyclizes with involvement of the pyridinium ring to afford the alkaloid ellipticene (**200**) after dehydrogenation.[102]

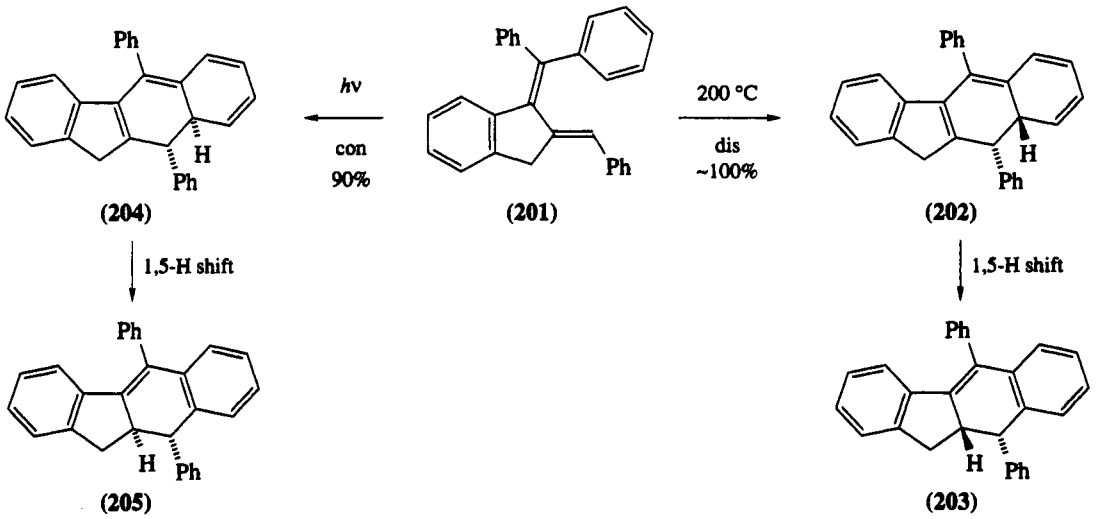
Extensive investigations of the thermal and photochemical reactions of *trans*-2-benzylidene-1-(diphenylmethylene)indane (**201**) and derivatives[103] have been carried out. It has been shown that thermolysis of (**201**) (200 °C) yields the benzofluorene (**203**) in near quantitative yield. Thermal disrotatory closure of (**201**) to (**202**) followed by a 1,5-H shift would account for the *cis* stereochemistry of the product



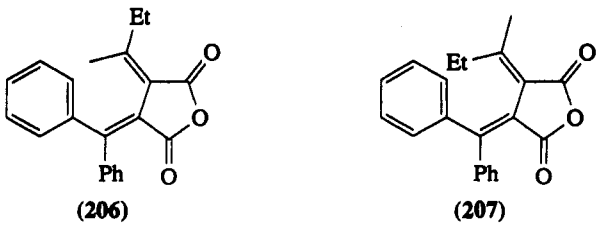
(**195**) (**196**) (**197**)

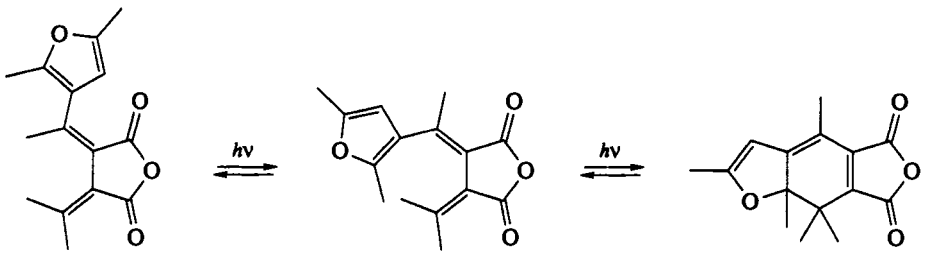


(**203**). By contrast, photochemical irradiation of (**201**) at 366 nm affords (**205**), the stereoisomer of (**203**). It is proposed that (**201**) undergoes photochemically induced conrotatory ring closure to (**204**) followed by its thermal 1,5-H shift to give the observed (**205**).



Similar results were obtained for the so called 'fulgides' (bis-methylene succinic anhydrides, *e.g.* **206** and **207**).[104] The related furyl analog (**208**) *via* (**209**) experiences photochemical (313–366 nm) ring closure to the deep red-colored cyclohexadiene (**210**) in which the competing 1,5-H shift cannot take place.[105] Cycloreversion occurs on irradiation with white light, which confers photochromic behavior to compounds like (**206**)–(**209**). The high yield of photocoloration, the linearity of response of the fulgide (**209**) to irradiation and the ease of directly determining the concentration of (**210**) make this system a convenient actinometer.[105]

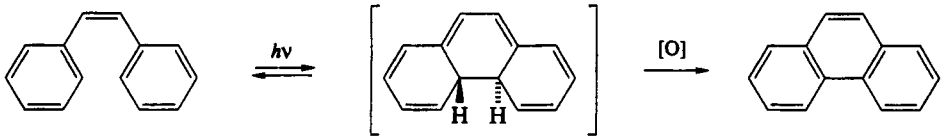




(208) (209) (210)

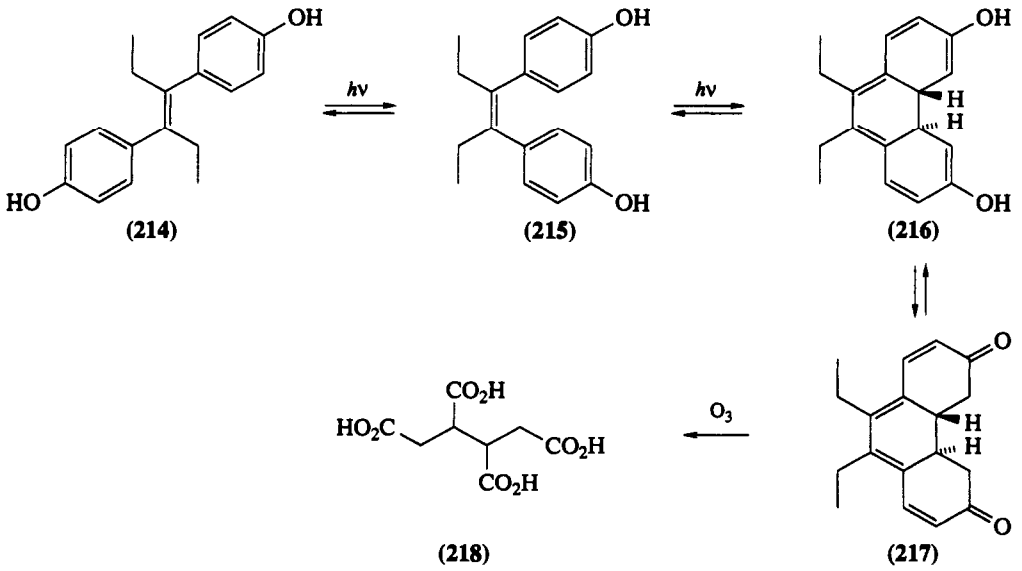
(ii) Type XV: [1,6:4,5] Bis-annulated Cyclohexadienes

The photocyclization of stilbenes (**211**) (including its *in situ* oxidation) to phenanthrenes (**213**) and that of conjugated arylalkenes to polycyclic aromatics constitute one of the most studied and widely used applications of organic photochemistry.[4,106] Its potential synthetic utility is amplified by the existence of a number of natural products (mainly alkaloids)[107] that contain a phenanthrene subunit in their structure. In view of the plethora of examples contained in several excellent reviews,[4,106] only selected examples will be presented here with focus on the selectivity of the process.



(211) (212) (213)

The initial photochemical step, (**211**) to (**212**), can be most simply viewed as a perturbed $6e^-$ electrocyclic process, suggesting a *trans* configuration *via* conrotation for the dihydrophenanthrene intermediate (**212**). In support of this hypothesis, the stabilization of (**216**) by tautomerism to (**217**) in the photolysis of diethylstilbestrol (**214**),[108a] followed by ozonolysis, afforded only the racemic form of 1,2,3,4-butanetetracarboxylic acid (**218**).[108b] The majority of dihydrophenanthrenes, however, are thermally unstable and undergo conversion to phenanthrenes (under oxidative or non-oxidative conditions) or 1,*j*-H shifts to isomeric 9,10-dihydrophenanthrenes.[109]

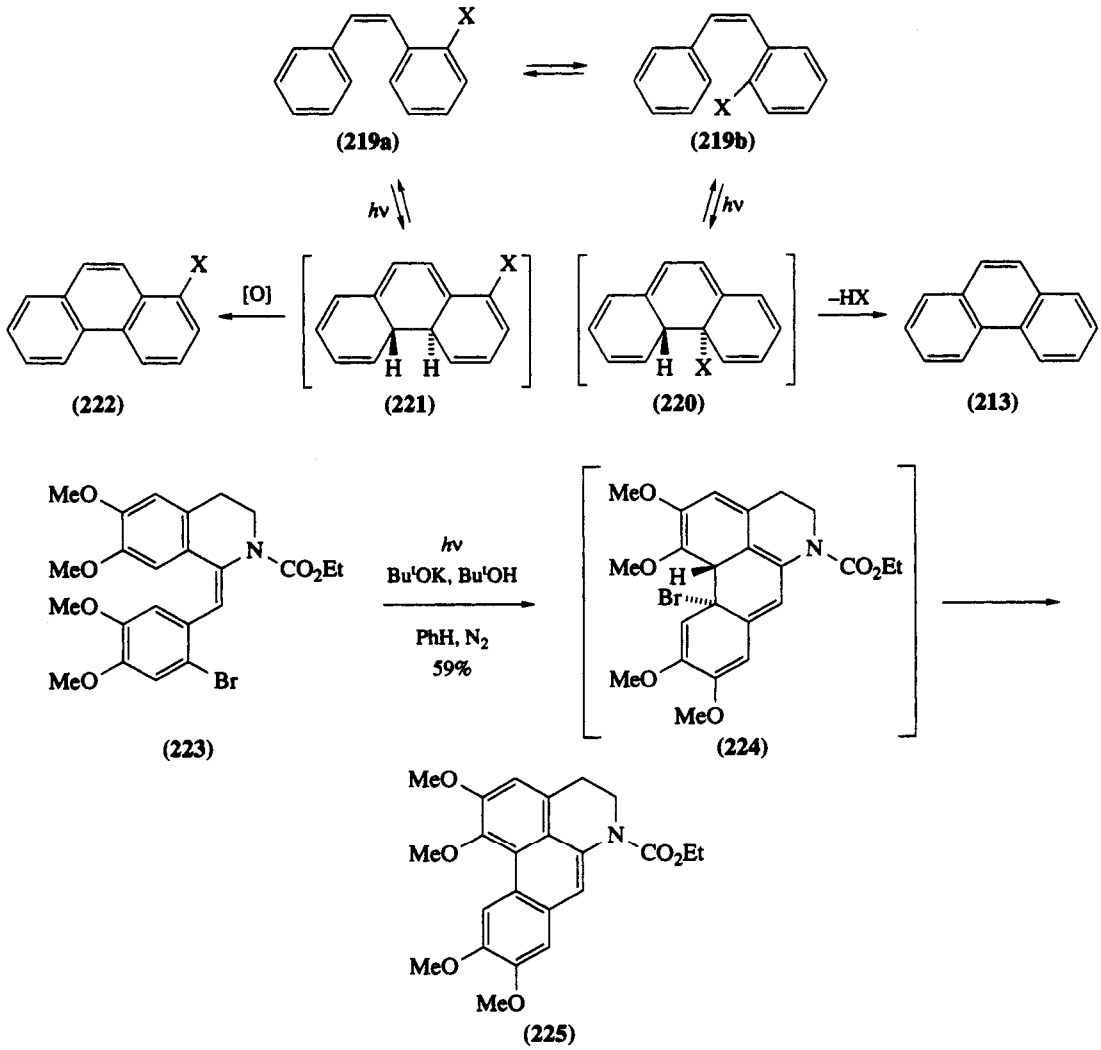


(214) (215) (216) (217) (218)

The dehydrogenation step in air-saturated solutions is thought to proceed by a radical chain mechanism, but for preparative purposes it is advantageous to use a small amount of iodine. Other oxidizing

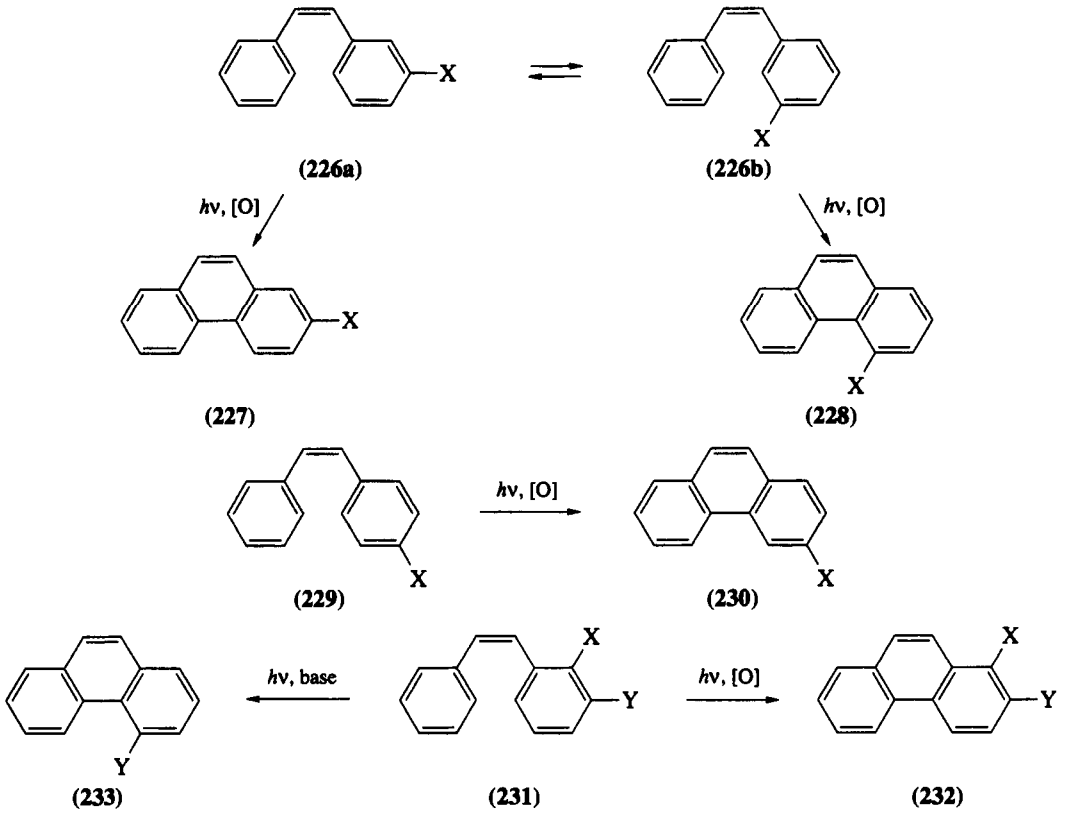
agents which have been used include selenium and thiyl radicals and π-acceptors such as TCNE, TCNQ, chloranil and bromanil.[110]

When leaving groups are placed at an *ortho* position as in (**219**), and oxidant is excluded from the reaction medium, irradiation leads to a dihydrophenanthrene of the type (**220**) followed by a highly exothermic elimination reaction to give phenanthrene (**213**). The alternative pathway to (**222**) is interrupted at the dihydrophenanthrene stage (**221**) because of the absence of oxidant. As an example, an efficient synthesis[111] of aporphinoid alkaloid (**225**) is based on the photocyclization of *o*-bromostilbene derivative (**223**) *via* *E*2 elimination of HBr with KOBu^t or, alternatively, by photolysis of the C—Br bond assisted by intramolecular radical complexation.[112] It should be noted that (**224**) is a tris-annulated type of cyclohexadiene which is not explicitly categorized in Figure 1.



The effect of substituents on the regioselectivity of the cyclization has been studied in *m*- (**226**) and *o*-substituted stilbenes (**219**) [the *p*-substituted (**229**) produce 3- or 6-substituted phenanthrenes (**230**)].[4] Generally, *m*-substituted stilbenes afford equal amounts of the 2- (**227**) and 4- (**228**) substituted phenanthrenes, in spite of the greater steric congestion in the latter. This has been rationalized in terms of the development of an early transition state for the photoexcitation of a mixture of ground-state conformers (**226a**) and (**226b**) before steric factors in the dihydrophenanthrene intermediate become significant. Selectivity in this series has been ascribed to several factors, such as selective destruction of the 4-substituted phenanthrenes during extended irradiation,[113] steric hindrance in polysubstituted cases, inefficient trapping of one of the dihydrophenanthrene intermediates, and finally, the influence of *m*-cyano and *m*-ethoxycarbonyl substituents, which afford, preferentially, 2-substituted phenanthrenes.[114] With respect to the effect of the *o*-substituents in (**219**), the different selectivity under oxidative (**222**)

and non-oxidative (**213**) conditions has already been mentioned, wherein the latter becomes the predominant product when oxidant is excluded from the reaction mixture. A widely used approach to control selectivity uses an *ortho* substituent as in (**231**) either to direct the cyclization of stilbenes to 2-substituted phenanthrenes (**232**) or to block this position to give the alternative phenanthrene (**233**). Molecular orbital theoretical analyses have been developed in order to rationalize the selectivities observed for stilbene cyclizations.[106a,115]



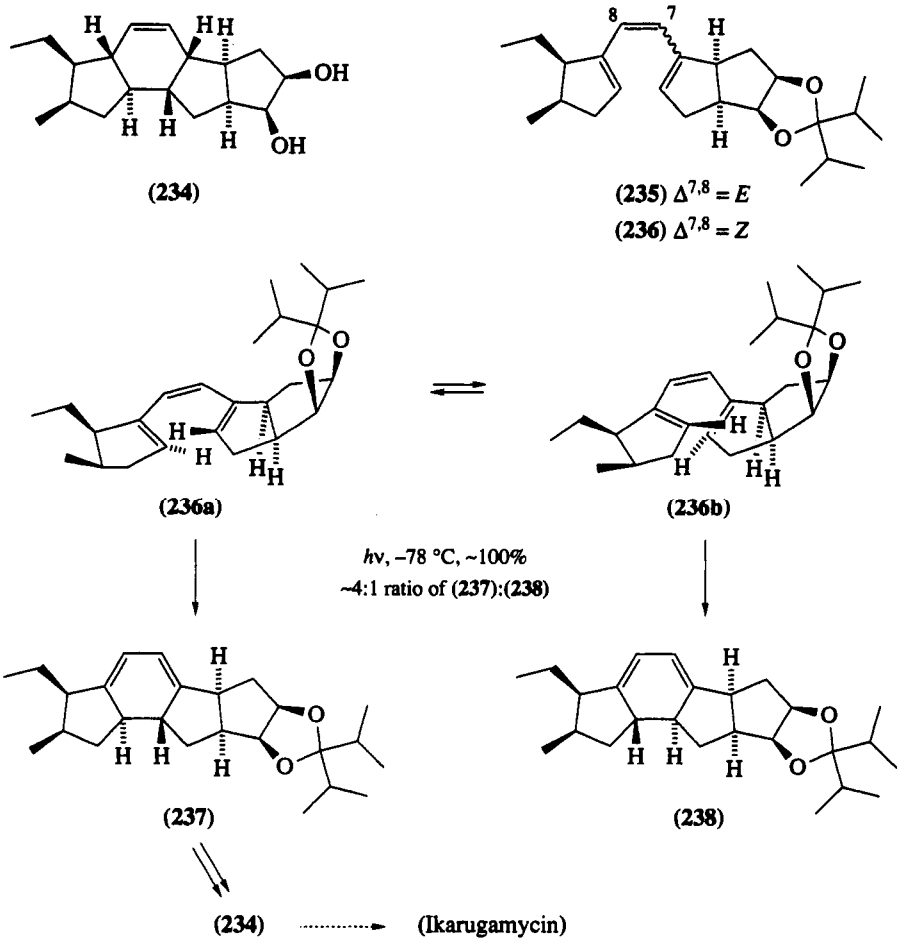
This type of cyclization has recently been used in the carbocyclic field to synthesize the tetracyclic glycol (**234**), an advanced intermediate in the synthesis of the antimicrobial and amoebicidal agent ikarugamycin.[116] Thus photocyclization of a 2:1 mixture of trienes (**235**) and (**236**) led to a 4:1 mixture of the two possible conrotatory closure products (**237**) and (**238**), which likely reflect the conformational bias in the ground state of the (*Z*)-triene (**236a** and **236b**, respectively).[36]

(iii) Type XIII: [1,6:2,3] Bis-annulated Cyclohexadienes

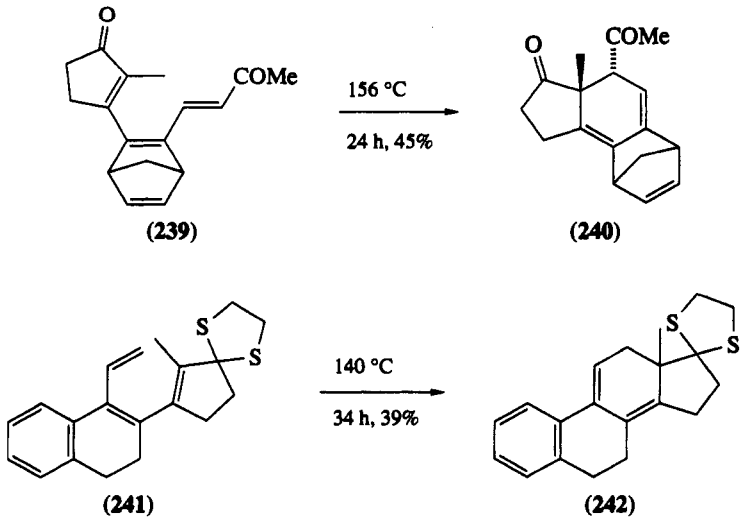
Only a few cases of thermal electrocyclizations of [1,2:3,4] bis-annulated trienes have been described. That the central double bond is part of a ring system eliminates the possibility of secondary thermal processes that were operating in the precursors to the simpler type IV cyclohexadienes. For example, the cyclization of diketone (**239**) to (**240**) takes place smoothly without interference from other thermal processes.[34]

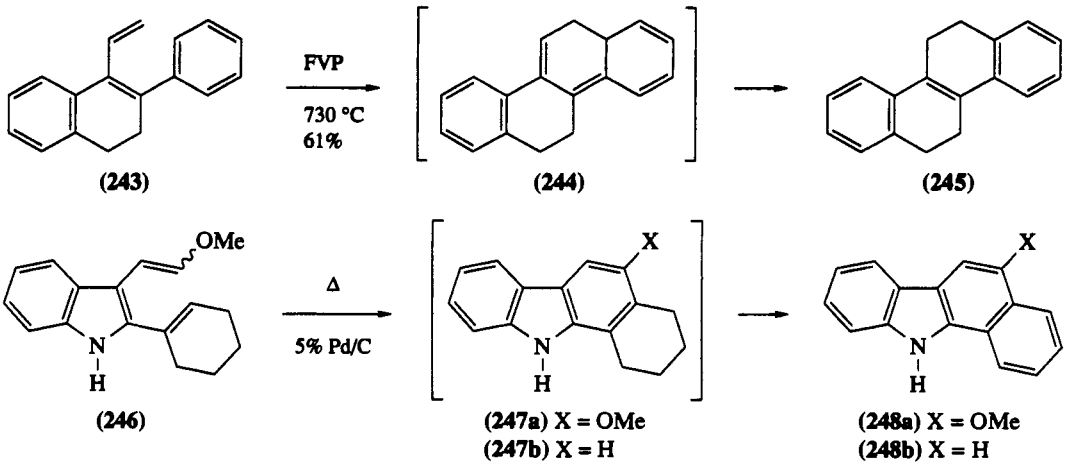
A new entry into the aromatic steroid nucleus is based on this approach to construct the c-ring of cyclohexadiene (**242**) by thermolysis (xylene, 140 °C, 34 h) of the triene (**241**). Photolysis is an alternative, but the yields were lower. A phenyl group can be used as a component of the triene system, although more drastic conditions (180 °C, 4 days or FVP, 730 °C, 0.1 mmHg) are required to disrupt the aromaticity of its nucleus as in compound (**243**), which gives as a final product 5,6,11,12-tetrahydrochrysene (**245**).[117]

The thermolysis of vinylindoles (**246**) to carbazoles (**247**) in the presence of 5% Pd/C combines electrocyclic ring closure with rearomatization. Depending on the conditions, thermolysis of vinylindole (**246**) gives a mixture of benzocarbazoles (**247a**; 22%) and (**247b**; 17%) (xylene, 150 °C), (**247a**; 23%) and (**248b**; 16%) (1,2-dichlorobenzene, 180 °C), or (**247a**; 20%) and (**248a**; 29%) (decalin, 210 °C).[118]

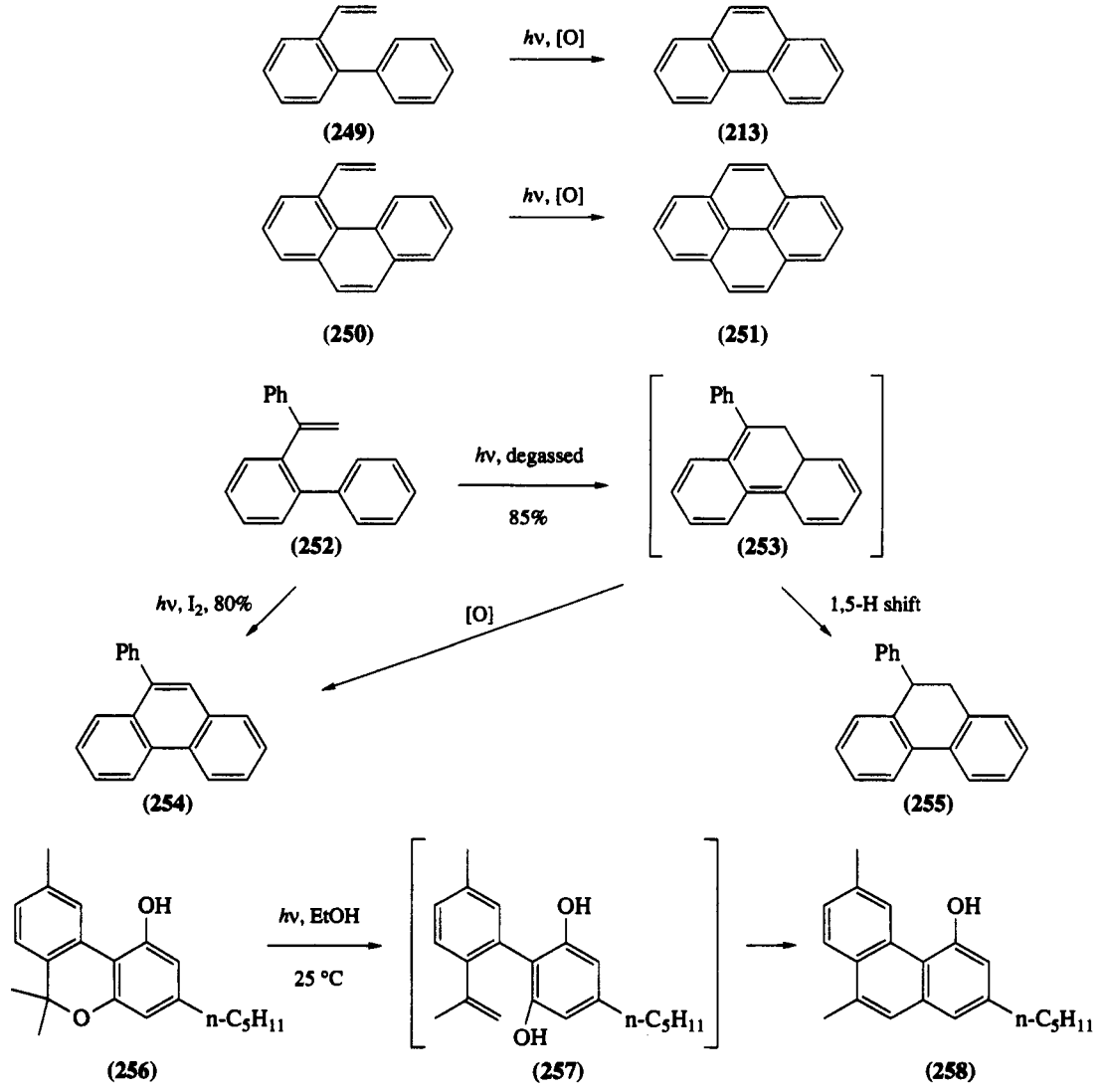


By contrast to the thermal process, the photochemistry of 2-vinylbiphenyl (**249**) and 4-vinylphenanthrene (**250**) has been widely used in connection with syntheses of polycyclic aromatic compounds, complementing the most commonly used stilbene to phenanthrene transformation.[4,106d] For example, the product obtained from the conrotatory photocyclization of 2-(α-styryl)biphenyl (**252**) can be trapped by an oxidant to give the phenanthrene (**254**) or suffers a 1,5-H shift to give the dihydrophenanthrene

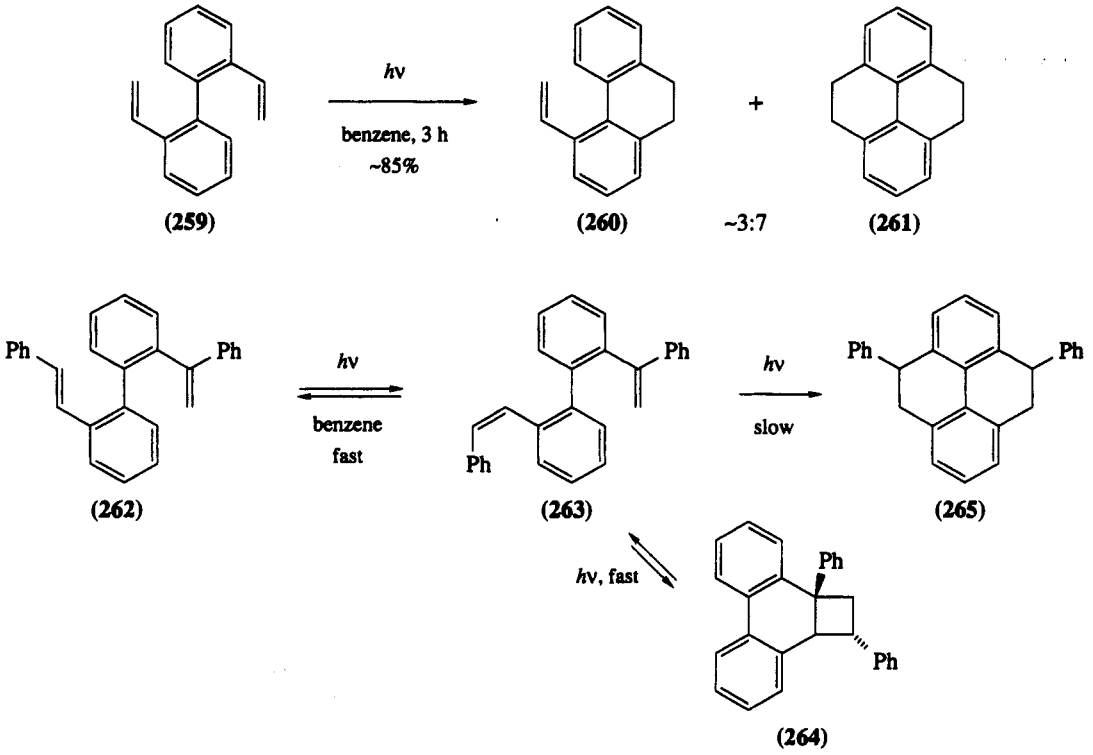




(255).[119] Similarly, the photochemical opening of cannabinol (256) to (257) was followed by ring closure and dehydration to the hydroxyphenanthrene (258), elimination of H_2O being the internal trap of the initial cyclization product (257).[120] Note that the initial ring opening of (256) is an example of a photo-induced hetero electrocyclization reaction (Section 6.2.4.2).



2,2′-Divinylbiphenyl derivatives upon irradiation exhibit a competition between electrocyclic ring closure and [2 + 2] photocycloaddition, the nature of the resulting products being dependent on the experimental conditions and the substituents attached to the double bond. The simple divinylbiphenyl (**259**) produces a mixture of the singly and doubly electrocyclized products (**260**) and (**261**), respectively, the latter being obtained quantitatively upon prolonged irradiation. When a stilbene moiety is present in the system as in (**262**), the [2 + 2] intramolecular cycloaddition to (**264**) (after fast *E–Z* equilibration) is the main reaction taking place at short irradiation times. On further irradiation, (**264**) is quantitatively converted into tetrahydropyrene (**265**).[121]

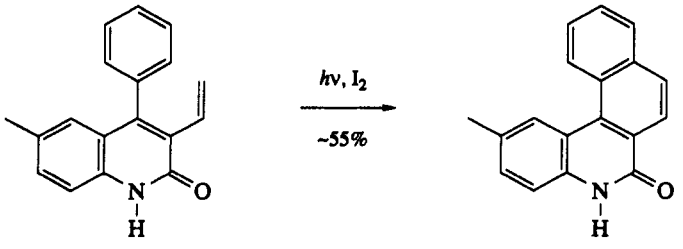


(**259**) (**260**) (**261**) (**262**) (**263**) (**264**) (**265**)

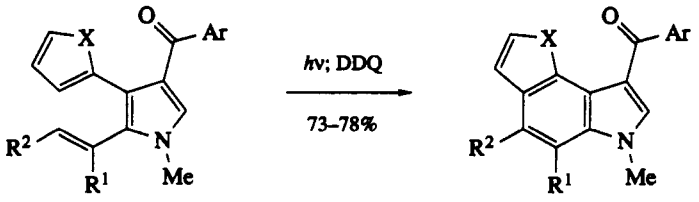
The ring-bearing moiety of the hexatriene can also be fused to a heterocycle. In the presence of an oxidant (I_2), the photolysis of a variety of 4-phenyl-3-vinylquinolones such as (**266**) yields benzo[*k*]phenanthridones (*e.g.* **267**) in good to excellent yields.[122] Similarly, photolysis of pyrroles (**268**) followed by treatment with DDQ gave fused indoles (**269**) (which contain a fused benzene, furan or thiophene ring).[62]

6.2.2.2.3 Higher-order annulated systems

The known examples of the synthesis of higher-order annulated systems (exemplified by types XVI–XVII in Figure 2) involve photochemical cyclization followed by oxidation of arene analogs of stilbenes.

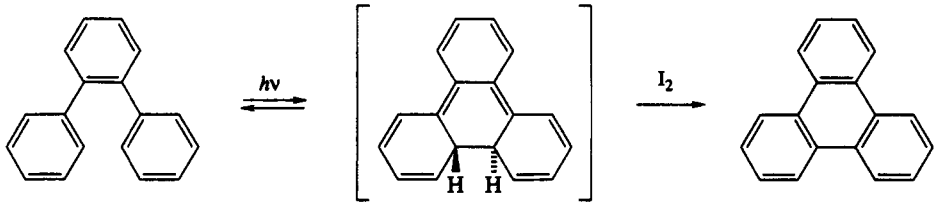


(**266**) (**267**)



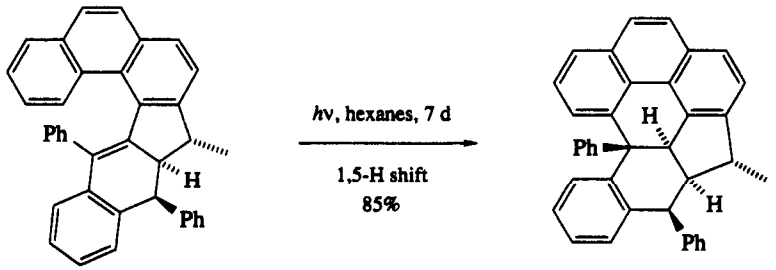
(268) (269)

For example, the reported transformation of (270) to (272) is an extension of the transformation of (211) to (213) discussed earlier. As oxidant, I_2 in high concentrations is recommended due to the high propensity of the dihydrotriphenylene (271) to undergo ring opening (three aromatic rings would be formed to give starting material 270).[123] An aromatic solvent is also required to transfer energy to the reactant in its singlet state, thus avoiding the dissipation of energy due to the light absorption of the product triphenylene (272). Many other examples are known, making this method an excellent choice for the preparation of polycyclic aromatic compounds.[4,106b,123]



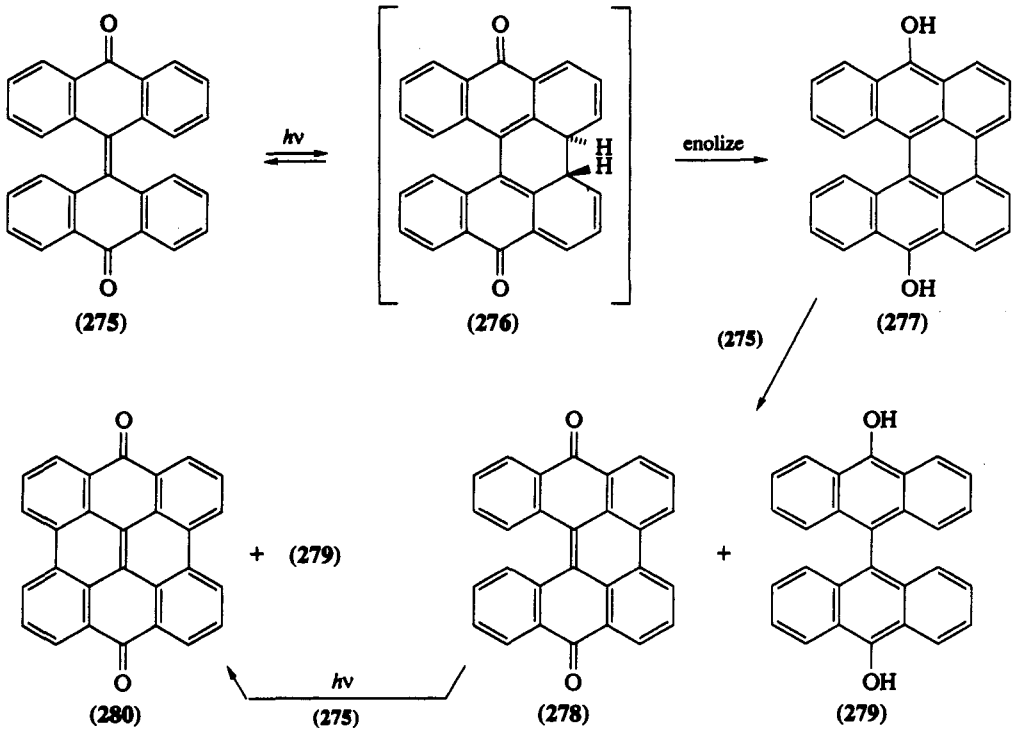
(270) (271) (272)

The polycyclic compound (274) can be efficiently obtained by photochemical irradiation of the 4-styrylphenanthrene derivative (273), with isolation of a dihydro intermediate.[124] Of course, only two of the three ring fused double bonds in this example are aromatic. The transformation of (268) to (269) presented earlier, wherein the R^1 and R^2 groups are part of a cycloalkenyl ring, represents another example of this kind.[62]



(273) (274)

Finally, the dianthrones and other doubly bridged tetraphenylethylenes can also be considered part of this group.[125] For example, dianthrone (275) upon photolysis leads to the presumed dihydro intermediate (276), which by two successive enolizations gives (277). Furthermore, a hydrogen transfer reaction between (277) and the dianthrone (275) gives helianthrone (278) and dianthranol (279). On extended irradiation, helianthrone (278) further cyclizes to afford mesonaphthodianthrone (280) and another molecule of (279) (wherein 275 can be viewed as oxidant to afford 279).

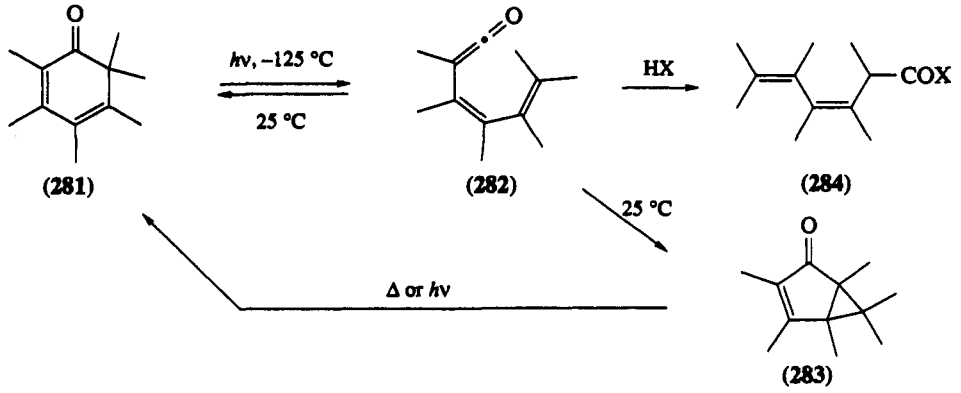


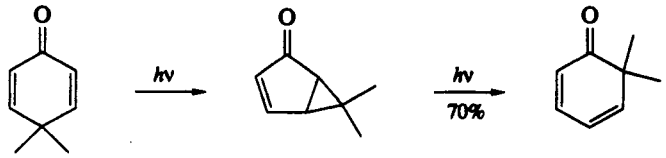
6.2.3 ELECTROCYCLIZATION OF *sp*-CARBON CONTAINING SYSTEMS

6.2.3.1 Ketenes

In 1968, Griffiths and Hart established that although dienylketene (**282**) (generated as the only photochemical product from cyclohexadienone **281**) cyclizes thermally to (**281**), other thermal cyclizations compete, such as the formation of the bicyclo[3.1.0]hexenone (**283**) or solvent (amines or alcohols) addition product (**284**).[126] The thermal formation of bicyclo[3.1.0]hexenones (**283**) from ketenes (**282**) can be photochemically reversed. Thus 2,4-cyclohexadienones (**287**) can be obtained from 2,5-cyclohexadienones (**285**).[127,128] The stereospecificity of the thermal ring opening of the bicyclo[3.1.0]hexenones to dienylketenes has been established.[128]

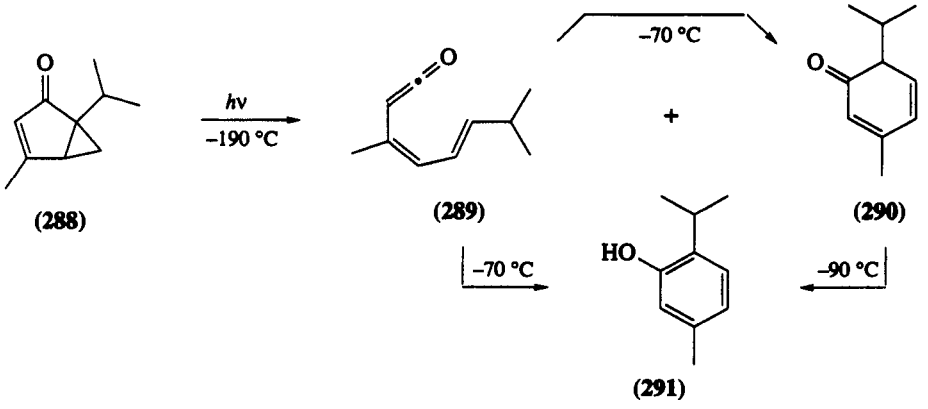
Studies of the low-temperature photochemistry of umbellone (**288**) established a dual pathway for its conversion to thymol (**291**).[129] Besides the opening of (**288**) to ketene (**289**), its direct conversion to the cyclohexadienone (**290**) was also postulated. However, this reaction depends on the substitution pattern, and in the case of lumisantonin (**292**) only traces of cyclohexenone (**294**) were detected in the photolysis



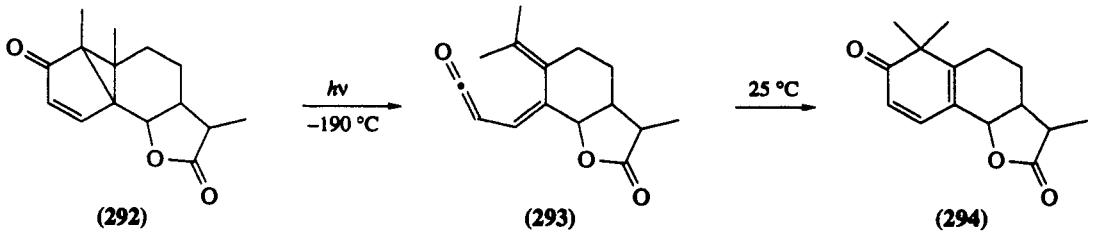


(285) (286) (287)

mixture.[129] Most recently, the chemistry of dienylketenes has been reviewed[130a] and efforts have been directed towards substituent control of stereochemistry of the dienylketene to cyclohexadienone cyclization and synthesis applications in the diterpenoid area.[130b–d]

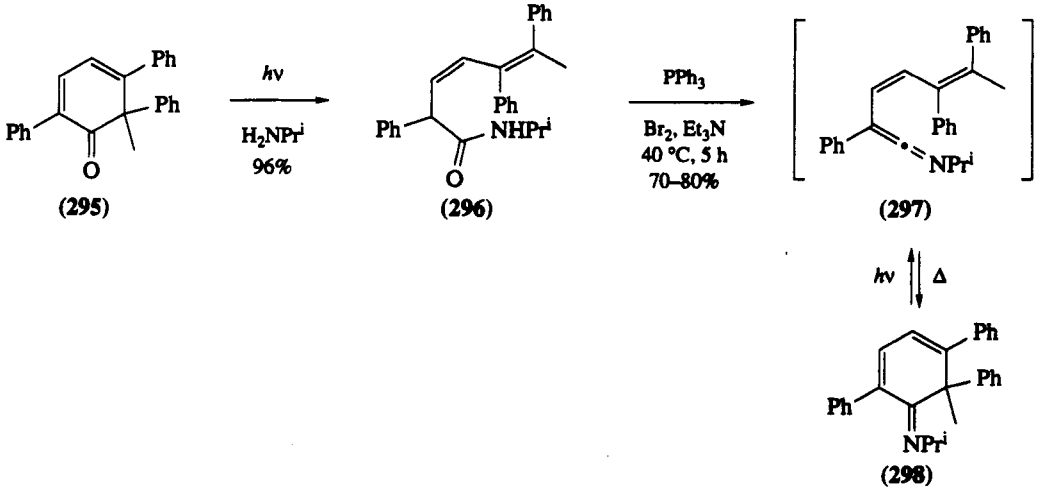


(288) (289) (290) (291)



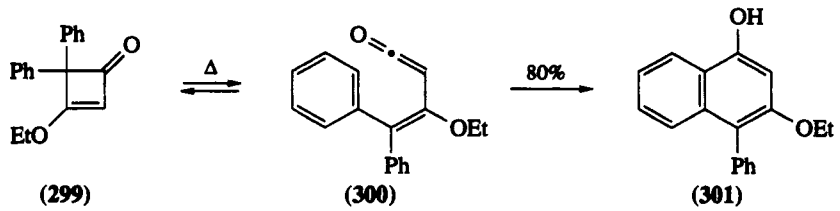
(292) (293) (294)

The competition of nucleophilic attack by solvent at the ketene *sp* center has been shown to be useful for obtaining aza analogues of dienylketenes, namely dienylketenimines (**297**) from ketene intermediates generated from (**295**). Upon dehydration, the addition product (**296**) afforded directly the *N*-alkylated cyclohexadienimines (**298**) in good yield. The expected dienylketenimines (**297**) were not isolated. Regeneration of spectroscopically detectable (**297**) can be achieved by photochemical irradiation of (**298**), its stability above 0 °C being solvent dependent.[131]



(295) (296) (297) (298)

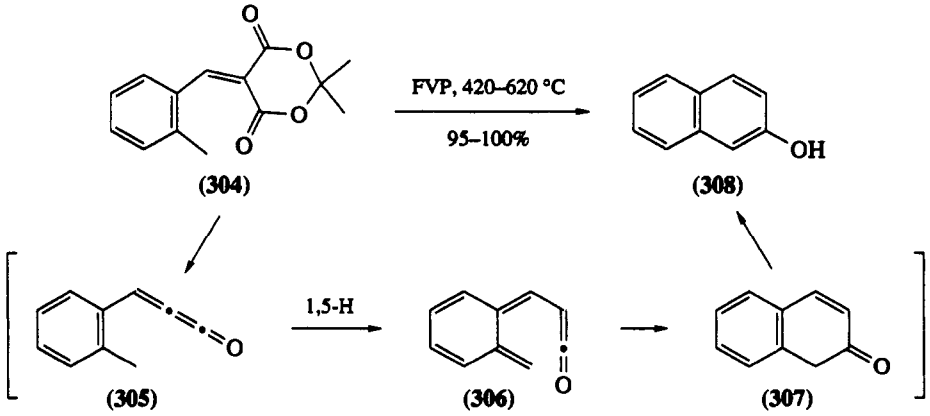
Another method to generate the dienylketene functionality is by thermal ring opening of arylcyclobutenones.[132] Thus the naphthol (**301**) was one of the products resulting from the condensation of diphenylketene and ethoxyacetylene[132a] and its formation likely involves opening of cyclobutenone (**299**) to the ketene (**300**) and electrocyclic closure of the latter. Similar results were obtained upon heating cyclobutenones (**302**)[132b] and (**303**),[132c] although the ability of the latter to ring open to two stereoisomeric dienylketenes led to additional products besides the naphthol.



(299) (300) (301)

(302) (303)

Naphthols are also obtained from arylmethyleneketenes generated by FVP of derivatives of Meldrum's acid (**304**).[133] The initial formation of 2-methylbenzylideneketene (**305**) can be envisaged, followed by a 1,5-H shift leading to the *o*-quinonoid ketene (**306**). Thermal cyclization to (**306**) and tautomerization provides a rationale for formation of 2-naphthol (**308**).[133a] This represents a transformation of *o*-tolualdehydes (starting materials for the preparation of **304**) to 2-naphthols. The related five-membered ring heterocyclic aldehydes with adjacent methyl substituents also experience the same thermal transformation, thus allowing the preparation of hydroxy derivatives of benzothiophene, benzofuran, dibenzofuran, indole and carbazole in good yields.[133b]

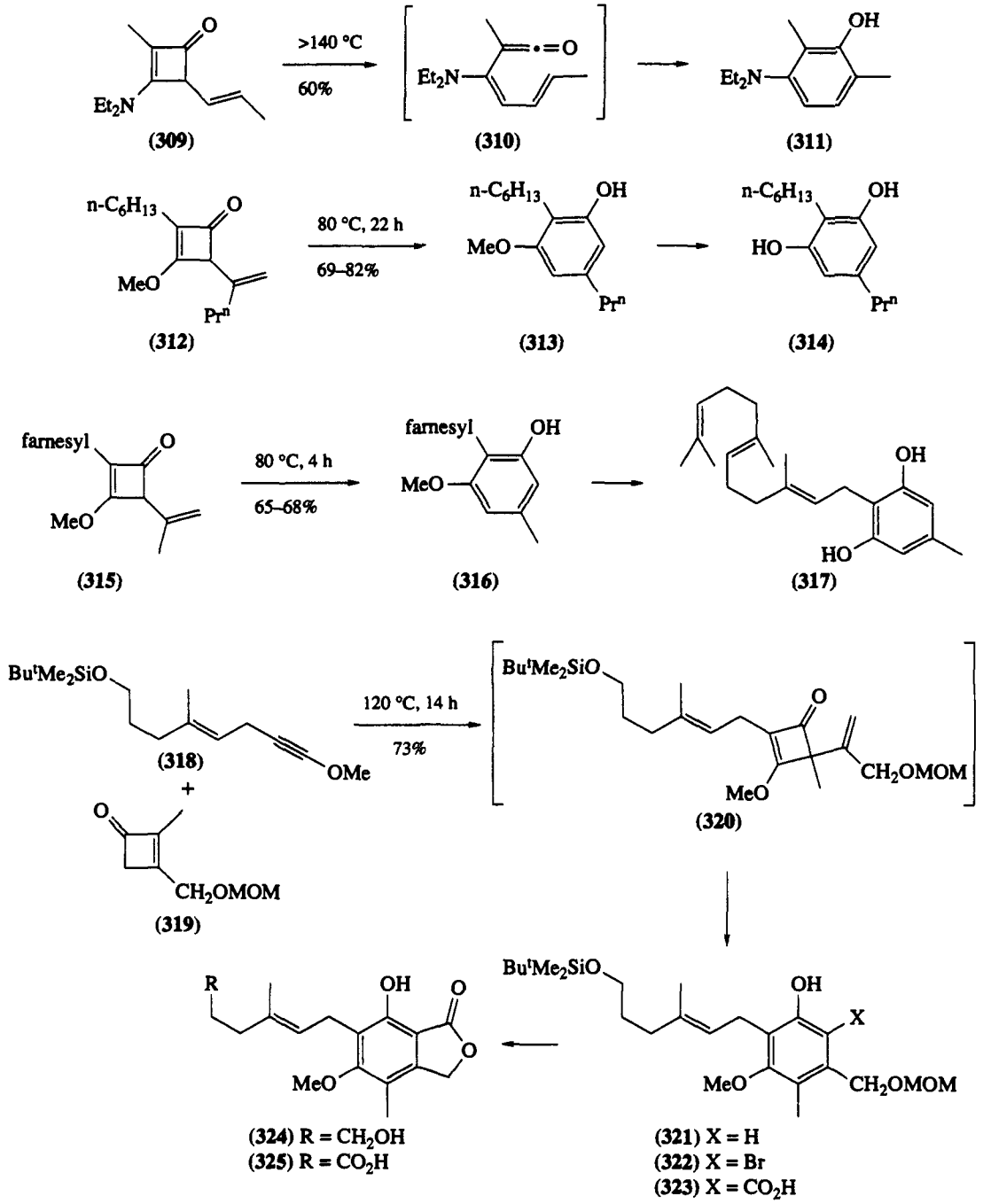


(304) (308)

(305) (306) (307)

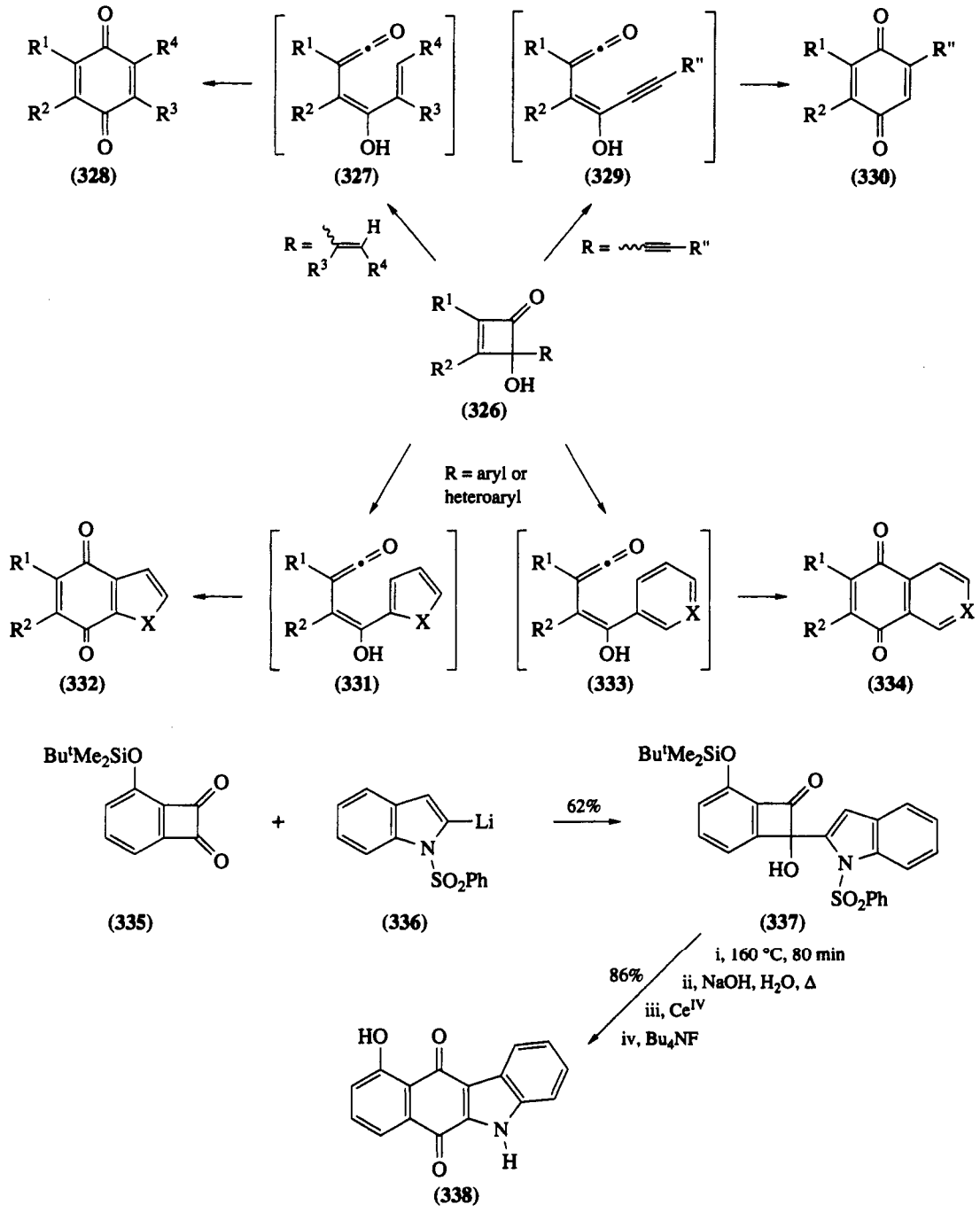
Phenols (**311**) are also the final products from the thermolysis (>140 °C) of aminocyclobutenones (**309**), generated by rearrangement of aminobicyclo[2.2.0]hexenones (addition products of ynamines and cyclobutenones) *via* ketene intermediate (**310**).[134] A related transformation (starting from ketenophilic acetylene derivatives and vinylketenes, leading after rearrangement to vinylcyclobutenone derivatives **312** and **315**) has been applied to the regiocontrolled synthesis of differentially protected resorcinol derivatives (**313**) and (**316**), respectively.[135] Demethylation of (**313**) and (**316**) provided the antifungal antibiotics DB-2073 (**314**) and grifolin (**317**), respectively.[135a] The hexasubstituted aromatic ring of mycophenolic acid (**325**) has also been synthesized using the same key strategy, combined with the regioselective bromination of the resulting phenol (**321**) at the C-6 aromatic position. Thus the cascade of electrocyclic reactions following thermolysis of a mixture of alkynyl ether (**318**) and cyclobutenone (**319**) provided the pentasubstituted resorcinol derivative (**321**), which was brominated to (**322**) and then

transformed to the carboxylic acid (**323**). The phthalide (**324**) obtained upon heating (**323**) with catalytic HCl in MeOH was oxidized to mycophenolic acid (**325**).[135b]



With related 4-vinyl- or 4-alkynyl-cyclobutenones (**326**) carrying a hydroxy group at the C-4 position, a similar sequence provides highly substituted quinones (**328**) or (**330**).[136] Extension of this approach to 4-aryl (or heteroaryl) cyclobutenones provides a general synthesis of highly substituted quinones of general structures (**332**) and (**334**).[136b–g] The transformation of (**336**) to (**338**) is representative of the methodology. Interestingly, the lithium reagent (**336**) adds selectively to the unsymmetrically substituted benzocyclobutenedione (**335**). This was followed by an outward rotation[15b] of the hydroxy group in the electrocyclic ring cleavage of the adduct (**337**) to give, after appropriate functional group transformation,

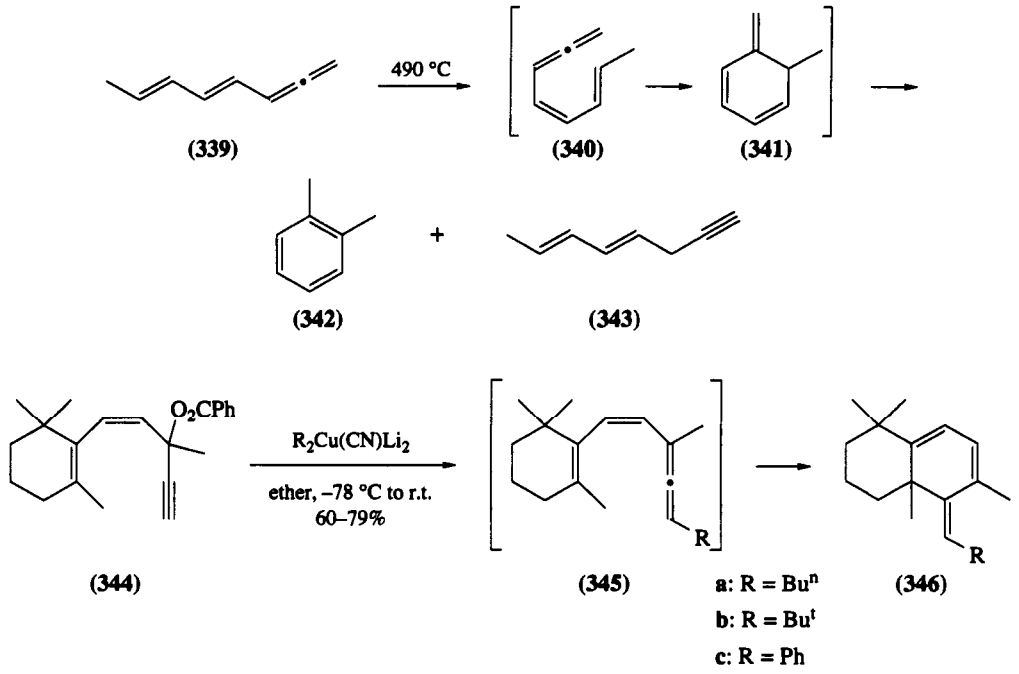
the quinone (**338**) as a 13:1 mixture of regioisomers.[136b] A diradical mechanism has been proposed for the rearrangement of alkynylcyclobutenones.[136f,g]



6.2.3.2 Allenes

The participation of an allenic *sp* center in an electrocyclic reaction was earlier demonstrated in the pyrolysis (490 °C) of the pentadienylallene (**339**) to give *o*-xylene (**342**) together with alkyne (**343**).[137] The high temperature required is primarily necessary to effect isomerization of the double bond to the (*Z*) configuration as in (**340**), because both the $6e^-$ electrocyclization of (**340**) to (**341**) as well as the aromatization of the latter to (**342**) possess lower activation barriers. That the $6e^-$ electrocyclization of dienyl-

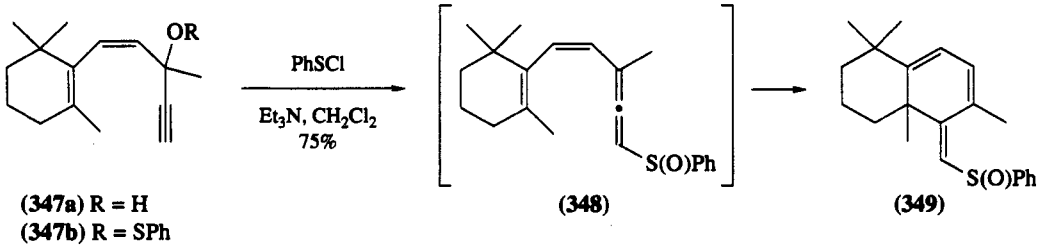
allenes possesses a low activation barrier is evidenced by the formation of (**346**), presumably *via* dienylallene (**345**) from benzoate (**344**) by an S_N2' reaction of the latter with a higher-order cuprate.[138a]

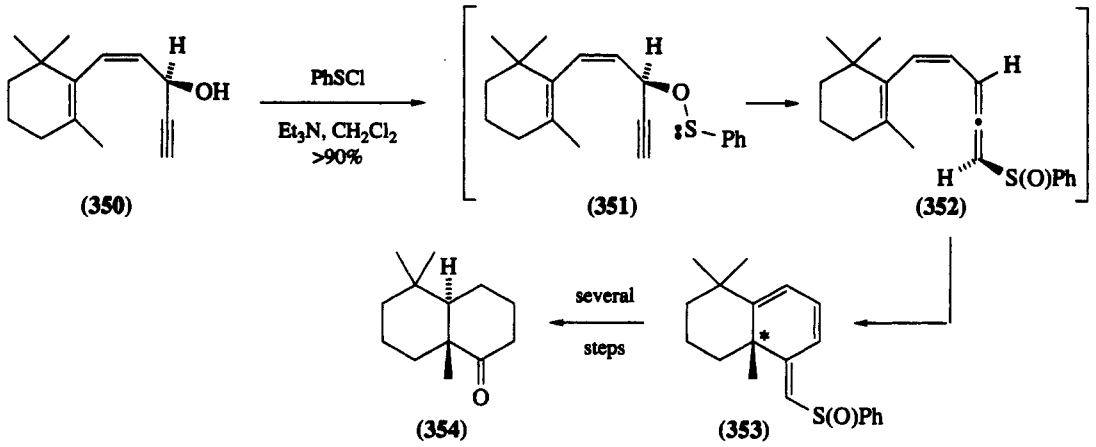


When the allenyldiene sulfoxide (**348**) was generated by treatment of the propargylic alcohol (**347a**) with phenylsulfenyl chloride, the allene spontaneously electrocyclized to the drimatriene sulfoxide (**349**). Related transformations were presented earlier in this chapter (*cf.* **44** to **46** and **47**).[35a] This multistep one-pot process is believed to occur by initial formation of the sulfenate ester (**347b**) which undergoes a 2,3-sigmatropic shift to give (**348**) in a completely stereoselective manner with respect to the allene configuration. This is followed by a completely stereoselective $6e^-$ electrocyclization in only one of the allowed disrotatory modes to afford (**349**). This stereomechanistic conjecture is firmly supported by the finding that optically enriched (*R*)-(**350**) afforded (**353**) in excellent yield with the (expected) stereochemistry and stereochemical purity. The absolute configuration of (**353**) at its bridgehead center was established by its transformation to (**354**), the antipode of which is known.[138b]

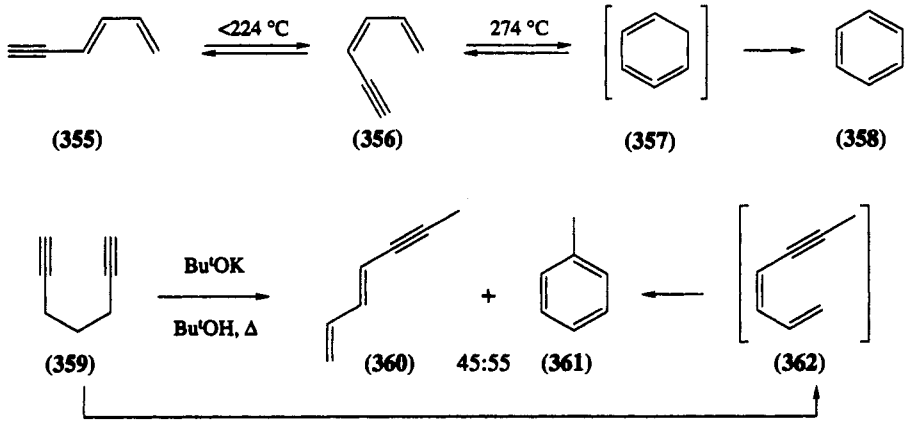
6.2.3.3 Alkynes

There are two obvious difficulties concerning the feasibility of effecting pericyclic reactions of alkynes.[139] The first concerns the geometry of the mandatory cyclic transition state. The second concerns the stability of the resulting products. While the geometry of an sp^2 center is well suited for attaining the cyclic array of the bent molecular framework, the presence of an alkynic center with bond angles of 180° demands a colinearity of three contiguous bonds. As a consequence, the transition state geometry requires considerable bond deformation. For the $6e^-$ electrocyclization process, the resulting product is a 1,2,4-cyclohexatriene. The less-unsaturated 1,2-cyclohexadiene is already known to be a species with a

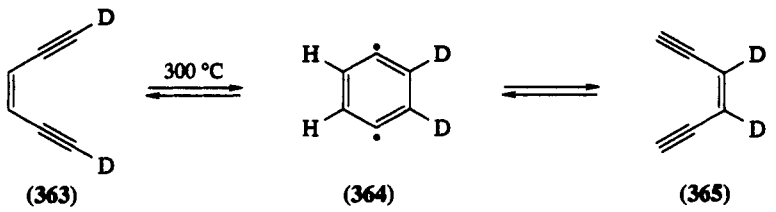




high degree of deformation and reactivity.[140] For the prototypical example in this series, namely (**356**) to (**357**), doubts about the mechanism of the conversion of (*Z*)-(**356**) and (*E*)-(**355**) to benzene (**358**) still remain.[141] Although the base-catalyzed thermal isomerization of 1,6-heptadiyne (**359**) to toluene (**361**) (and *trans*-dienyne **360**) is presumed to occur *via* (*Z*)-dienyne (**362**), the pericyclic nature of this process is uncertain[142a] (*cf.* the recent studies of neocarzinostatin[142b–m]).

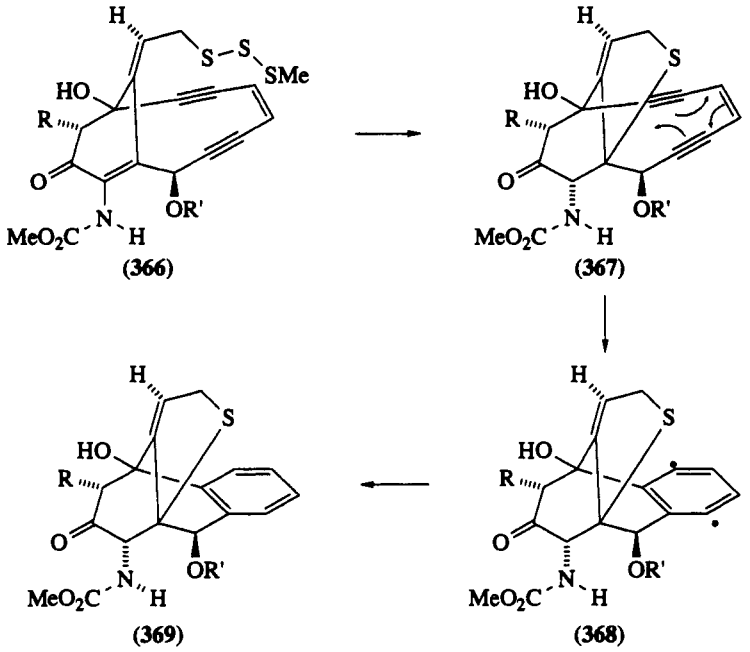


When both termini of the triene are alkynic units,[143] the reaction takes place *via* a diradical intermediate.[144] Heating of (*Z*)-1,6-dideuteriohex-3-ene-1,5-diyne (**363**) at 300 °C caused rapid scrambling of the deuterium label to give exclusively a mixture of (**363**) and the 3,4-dideuterio isomer (**365**). Also, when heated in different solvents, products of typical radical reactions were observed. These data together with detailed kinetic analysis and spectroscopic studies have led to the hypothesis of the intermediacy of the 1,4-dehydrobenzene diradical (**364**) (*p*-benzyne) in the process.[144]



Intense synthetic and mechanistic efforts in this area are currently in progress[145] (see also the studies of neocarzinostatin[142b–m] and dynemicin A[145v–aa]) as a consequence of the isolation and structural elucidation of two potent antitumor agents, esperamicin and calichemicin, both with general structure (**366**). Both compounds in their aglycone component possess an enediyne bridge, which has been hypothesized to be involved in the DNA-damaging action through its isomerization to a diradical (**368**) after thiol con-

jugate addition (following nucleophilic attack on the central sulfur atom) to the α,β-unsaturated carbonyl group. The co-occurrence of (**369**) from the same microorganism further supports the mode of action of this antitumor agent.[145] An important question is whether the process (**367**) to (**368**) (or for that matter, the transformation of **356** to **357** or **363** to **364**) should even be considered a classical concerted pericyclic process.



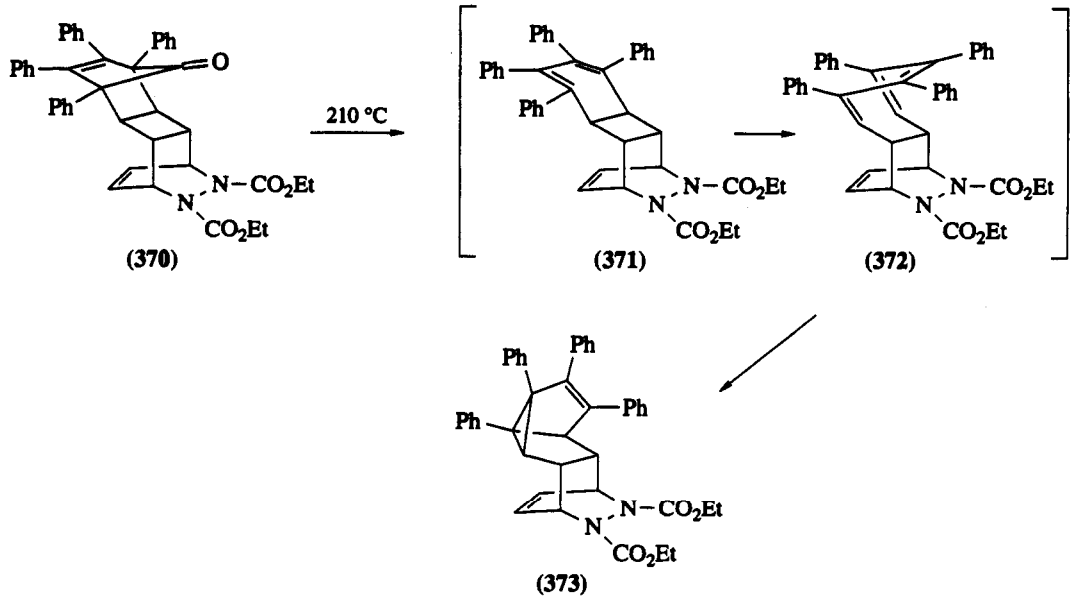
6.2.4 MISCELLANEOUS RELATED TOPICS

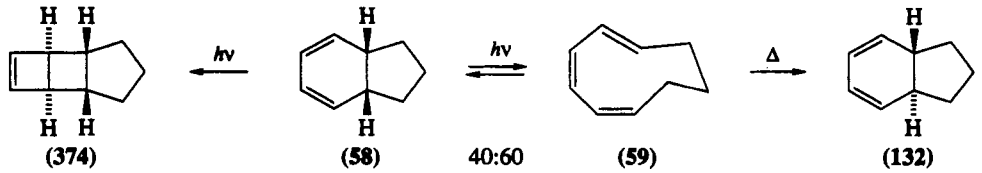
6.2.4.1 Retro Electrocyclizations: Triene Syntheses

The discussion presented earlier (Section 6.2.2.1) revealed that ring opening of a 1,3-cyclohexadiene to a 1,3,5-hexatriene is kinetically sluggish (*e.g.* the automerization of **62**) and thermodynamically disfavored unless other factors such as ring strain intervene (*e.g.* **101**, **102** and related derivatives). The literature on thermal cycloreversions in triene syntheses is sparse, although there are some reports of the involvement of this step as part of a cascade of rearrangements of certain 1,3-cyclohexadienes. For example, a $6e^-$ electrocyclic ring opening has been postulated to take part in the formation of the dihydrosemibullvalene system (**373**).[146] The thermal decarbonylation (~210 °C) of the tetracyclone adduct (**370**) could be viewed as being followed by thermal $6e^-$ electrocyclic ring opening to (**372**) and then intramolecular cycloaddition to afford (**373**). Of course, the transformation of (**371**) to the putative (**372**) is completely analogous to the transformation (**121**) to (**120**) discussed earlier.

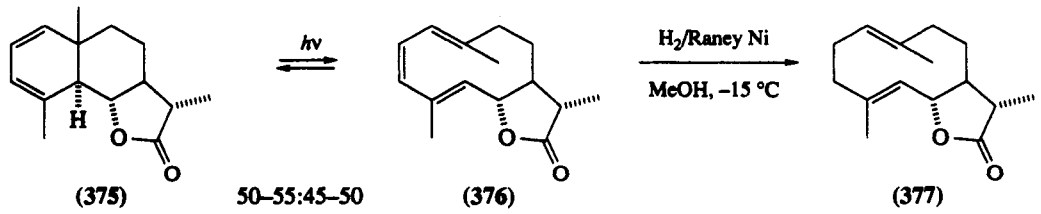
By contrast, the retro electrocyclization by photochemical irradiation is well known. For example, the photochemical transformation ($6e^-$ conrotatory ring opening) of provitamin D (**5**) to previtamin D (**3**) and then thermal isomerization (1,7-H shift) of the latter is a well-established sequence leading to vitamin D (**4**). It is a sequence[8] involved in vitamin D biosynthesis and in the laboratory synthesis of vitamin D. Moreover, the process is used commercially.

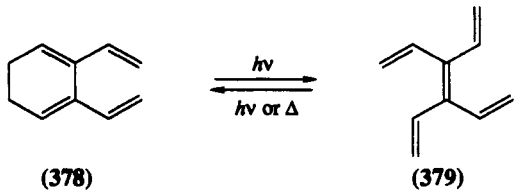
At low photochemical conversions the reversible transformation to the (*Z*)-hexatriene may dominate. However, the composition of the photostationary state depends upon the substitution pattern of the cyclohexadiene which controls the preferred conformation. It is believed that a planar 1,3-cyclohexadiene produces preferentially a bicyclo[2.2.0]hex-2-ene, *e.g.* molecules of the type (**374**), while dienes with skewed structures form hexatrienes.[37] Another factor that changes dramatically the composition of the photolysis mixture is the wavelength of irradiation.[44a] At 254 nm the photostationary state mixture of *cis*-bicyclo[4.3.0]nona-2,4-diene (**58**) and (*E,Z,Z*)-1,3,5-cyclononatriene (**59**) is 40% and 60%, respectively. At 300 nm, irreversible formation of tricyclo[4.3.0.$0^{2,5}$]non-3-ene (**374**) becomes the preferred pathway. The ratio of extinction coefficients of (**58**) and (**59**) at the wavelength used would explain the shift in the photoequilibrium mixture.[44a]



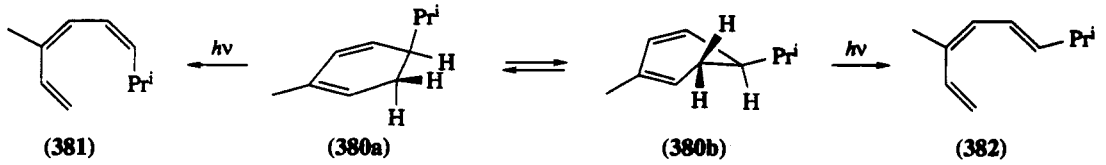


An example of a synthetic application in the natural products field concerns the ring opening of diene (**375**) to a *ca.* 1:1 mixture of starting material and triene (**376**), which upon hydrogenation yields dihydrocostunolide (**377**).[147] A synthesis of tetravinylethylene (**379**) was achieved by photoinduced (–78 °C) equilibration of tetraene (**378**) (containing ~4:1 of cyclic to acyclic form).[148]



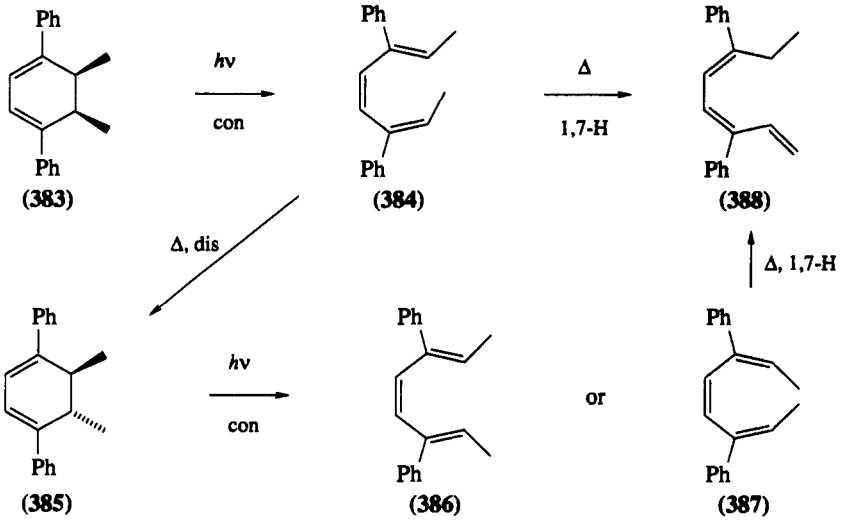


A study of the photochemical isomerization of α-phellandrene (**380**)[149] provided a basis for the formulation of the 'accordancy principle' (Section 6.2.2.1). This states that the sense of the photochemically allowed conrotatory ring opening of a 1,3-cyclohexadiene is a function of the chirality of the diene. In the case of α-phellandrene (**380**), the conformer with a pseudoaxial isopropyl group (**380a**) is photoisomerized to the (*Z,Z*)-triene (**381**), while the conformer with a pseudoequatorial isopropyl group (**380b**) is converted to the (*E,Z*)-triene (**382**). Particularly noteworthy was the observed increase in the relative amount of (**382**) with a decrease in temperature, which was attributed to an increase in population of the more stable conformer (**380b**). Prolonged irradiation gave a mixture of isomeric trienes as well as tricyclic compounds.

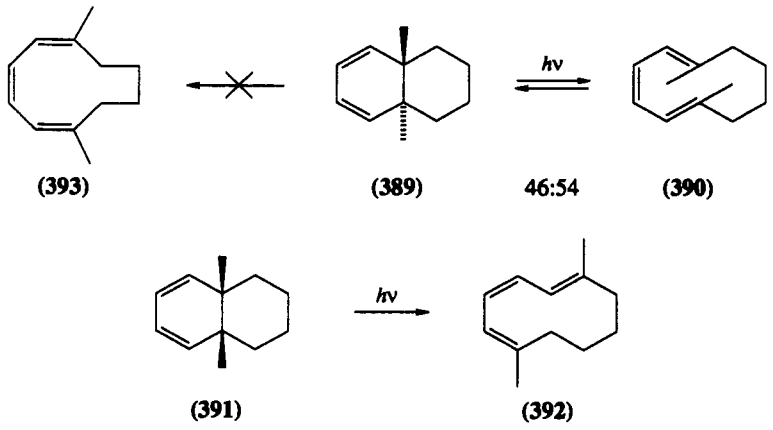


(381) (380a) (380b) (382)

The stereospecific conrotatory nature of the photochemically induced ring opening of 1,3-cyclohexadienes has been established.[45b] Thus photochemical ring opening of *cis*-5,6-dimethyl-1,4-diphenyl-1,3-cyclohexadiene (**383**) gave the (*E,Z,Z*)-hexatriene (**384**). Of the two possible products of conrotatory ring opening of the *trans* isomer (**385**) (namely **386** and **387**), the latter was considered to be produced because it underwent a thermally induced 1,7-H shift (also obtained from **384** in the same manner) to the triene (**388**). Similar results have been obtained for the hexalin series.[43,44a]



The role of the ground-state conformations has also been investigated in 9,10-dimethylhexalins and related steroids.[82] The *trans*-hexalin (**389**) gave selectively (*E,Z,E*)-triene (**390**), while *cis*-hexalin (**391**) provided the (*Z,Z,E*)-isomer (**392**) as initial product, in agreement with the conrotatory nature of the reaction. The opposite mode of conrotation for (**389**) resulting in (*Z,Z,Z*)-triene (**393**) was not observed and has been ascribed to a disruption of conjugation by passing through a state where the developing *p*-orbitals would be orthogonal to the diene. Similar results were obtained for related steroids[82] and bicyclo[4.*n*.0]dienes (**21**), (**58**) and (**153**) described earlier.[44]

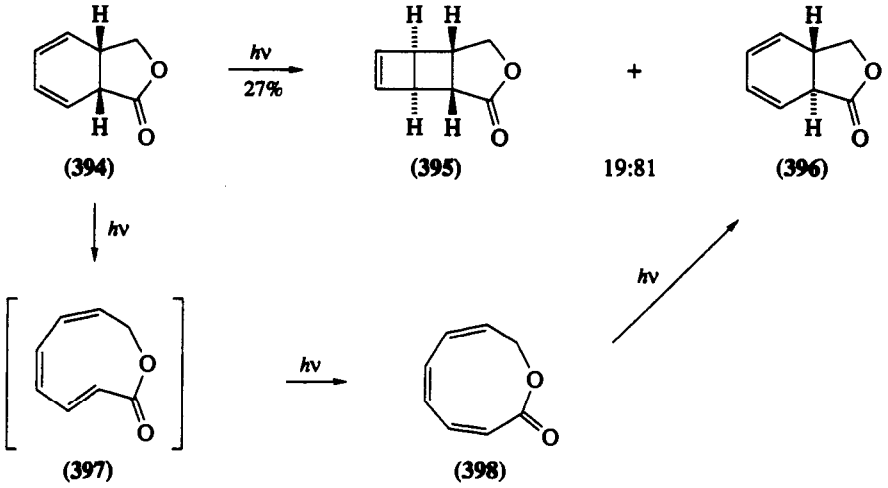


(393) (389) 46:54 (390)

(391) (392)

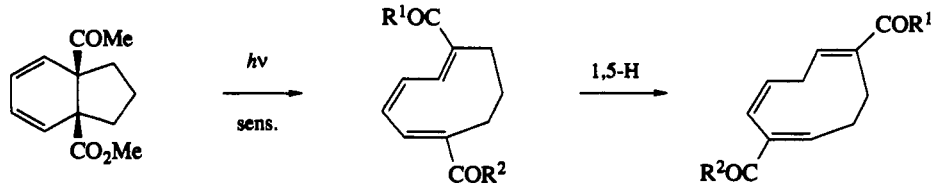
Although not isolated, a trienyl-lactone intermediate (**397**) has been assumed to be responsible for the formation of *trans*-1,2-dihydrophthalide (**396**) (together with tricyclic compound **395**) in the photolysis

of *cis*-1,2-dihydrophthalide (**394**). The isolation of intermediate (**398**) with (*Z,Z,Z*) stereochemistry (resulting from a photochemical double bond isomerization of the putative (**397**) provides some support for the suggested pathway.[150]



(**394**) (**395**) (**396**) (**397**) (**398**)

Finally, although sensitized irradiation of cyclohexadienes usually gives dimers, cyclohexadiene (**399**) gave trienes (**401**) in a ~1:1 ratio. The products of initial electrocyclic ring opening to the (*E,Z,Z*)-hexatrienes (**400**) are considered to undergo a 1,5-H shift (including geometric isomerization) to afford the observed isomeric trienes (**401**).[151]



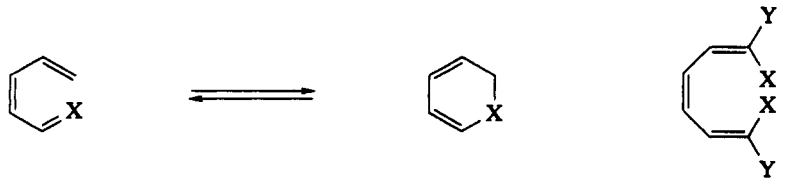
(**399**) (**400**) **a**: R^1 = Me, R^2 = OMe (**401**)
b: R^1 = OMe, R^2 = Me

6.2.4.2 Heterocyclic Applications

As indicated in the Introduction, only a brief survey of hetero electrocyclizations will be presented here. The reader should refer to Marvell's excellent treatise[3a] or other sources[152] for leading references. However, there are several unique features of the heterocyclization process that are worth considering in this limited survey. In particular, when the heteroatom is placed at the end of the triene system, cyclizations often prove to be exceedingly facile. To focus on this feature of the reaction substrate, the following discussion will be restricted to electrocyclizations in which the heteroatom (oxygen and nitrogen since they are the most common) is located at the end of the triene.

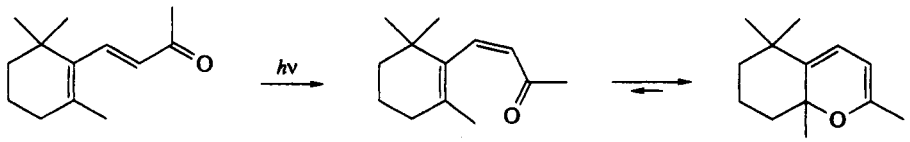
The replacement of a carbon atom in (**402a**) by a heteroatom such as oxygen or nitrogen (**402b,c**) leads normally to an increase of the reaction rate of the electrocyclization.[3a] Steric effects probably play a major role in the observed rate enhancement although stereoelectronic and polar factors may also be important factors. Regarding steric effects, when the terminal sp^2 carbon is replaced by a heteroatom, one (nitrogen) or both (oxygen) of the terminal hydrogen atoms is replaced by a 'smaller' heteroatom lone pair. In point of fact, replacement of the two inside hydrogen atoms by deuterium in the parent system (**1**) as in (**404a**) reveals a slight acceleration in rate.[14] Thus cyclization of (**404b**) exhibits the expected normal secondary kinetic isotope effect for sp^2 to sp^3 rehybridization upon thermal disrotatory cyclization. In the case of (**404a**), disrotatory electrocyclization occurs with an inverse secondary kinetic isotope effect, wherein the steric isotope effect overrides the small, normal (sp^2 to sp^3 rehybridization) isotope effect.[14] The exceptionally rapid cyclization of dienylallenes (**45**) to (**46**) plus (**47**), (**345**) to (**346**), (**348**) to (**349**) and (**352**) to (**353**) is also probably due to the attenuation of steric factors (one of the terminal sp^2 carbon as in **402a** is replaced by the *sp* carbon of the allene).[35a,138] The stereoelectronic

factor refers to the direct participation of the heteroatom lone pair in the cyclization. These types of transformations in which bonding and non-bonding atomic orbitals interchange roles have been defined as 'pseudopericyclic reactions'.[153]



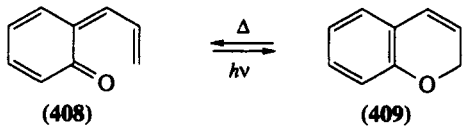
(402) **a**: X = CR_2; **b**: X = O; **c**: X = NR (403) (404a) X = D, Y = H (404b) X = H, Y = D

An early example of the reversible interconversion of dienones to α-pyrans was first observed for the α-pyran (**407**) obtained upon irradiation of β-ionone (**405**).[3a,154] In certain systems this reversibility is responsible for the (*Z*)–(*E*) isomerization of the terminal double bond of α,β-(*Z*)-isomers of 2,4-dienals and 2,4-dienones.[155]

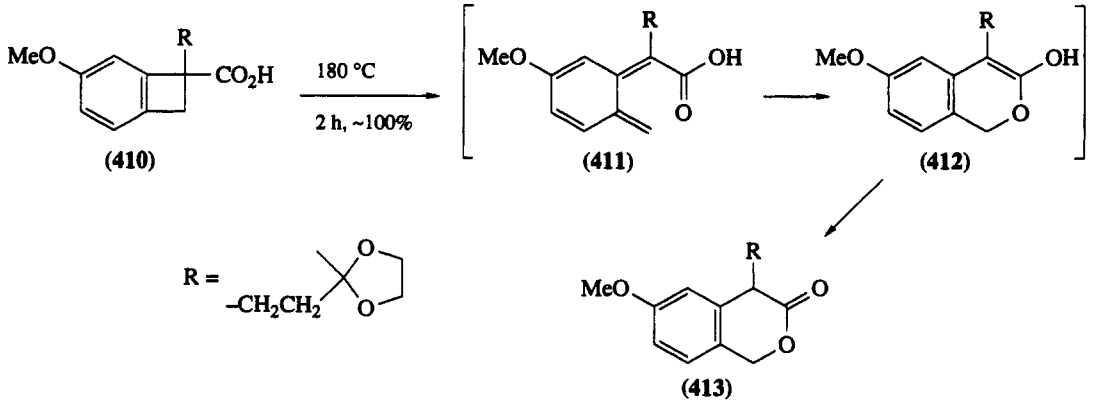


(405) (406) (407)

Conversion of (**408**) to chromone (**409**) is photochemically reversible and thus the system is photochromic.[156] Recently,[157] electrocyclic ring opening of benzocyclobutenes in tandem with a hetero electrocyclic ring closure is reported to provide a new route to isochromanones. Thus benzocyclobutene (**410**) upon thermolysis experiences ring opening to the *o*-quinodimethane (**411**) followed by electrocyclic ring closure and then ketonization to afford the isochromanone (**413**). The scheme can be further combined in tandem with other pericyclic processes (*e.g.* 3,3-sigmatropic reactions), providing a new methodology for the synthesis of natural products.[157c,d]



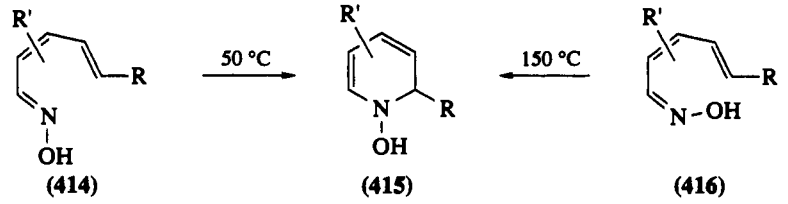
(408) (409)



(410) (411) (412) (413)

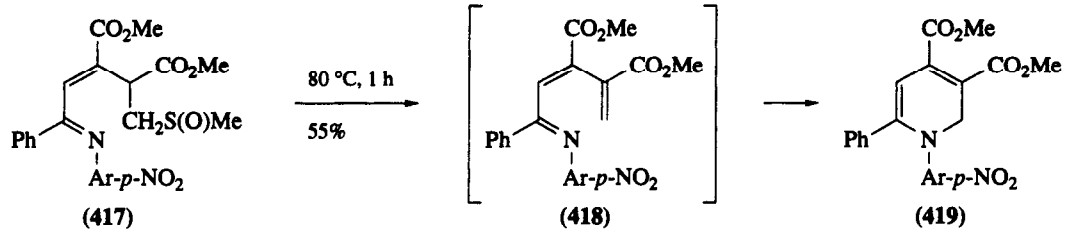
The electrocyclic ring closure of 1-azatrienes to 1,2-dihydropyridines is a favorable process.[3a] The possibility of stereoisomerism at the nitrogen atom in certain derivatives (oximes and their benzoates) provides an important argument in favor of the steric and/or stereoelectronic factors discussed above for

the observed rapid rate of cyclization. While the (*E,Z,E*)-isomer (**414**) yielded cyclic products derived from (**415**) at 50 °C, the (*Z,Z,E*)-isomer (**416**) required 150 °C to afford the same product.[158]

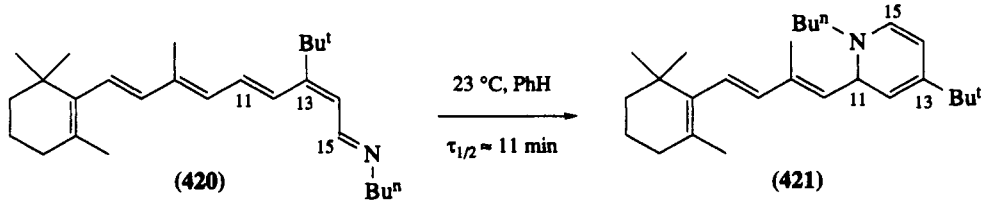


(**414**) (**415**) (**416**)

Recent examples of the hetero cyclization process include the conversion of azadiene (**417**) to dihydropyridine (**419**)[159a] and the Schiff base of 13-*t*-butyl-13-*cis*-retinal (**420**) into the dihydropyridine (**421**).[159b,c]

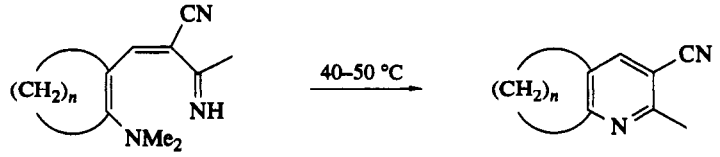


(**417**) (**418**) (**419**)

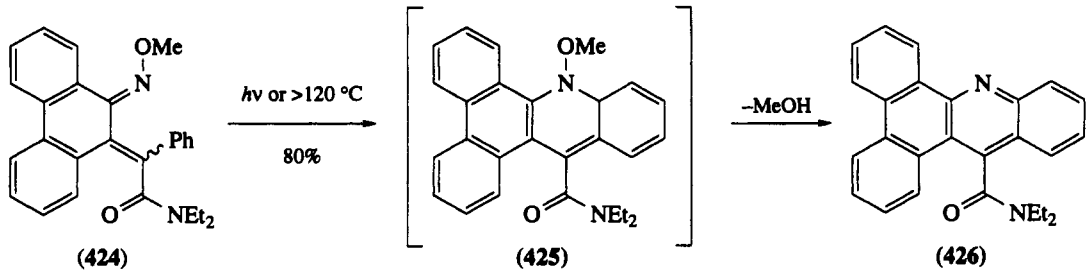


(**420**) (**421**)

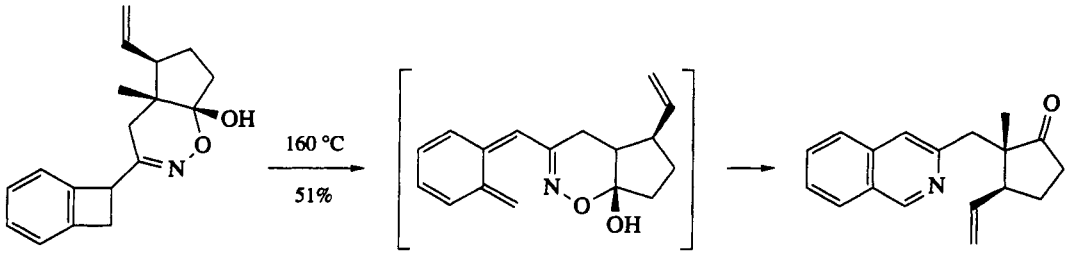
Other related reactions have led to complex aromatic systems, including pyridines or fused analogues (quinolines). Thus the transformation of (**422**),[160] (**424**),[161] and (**427**)[162] to (**423**), (**426**) and (**429**) exemplify the utility of the method.



(**422**) a: $n = 3$; b: $n = 4$; c: $n = 5$ (**423**)



(**424**) (**425**) (**426**)



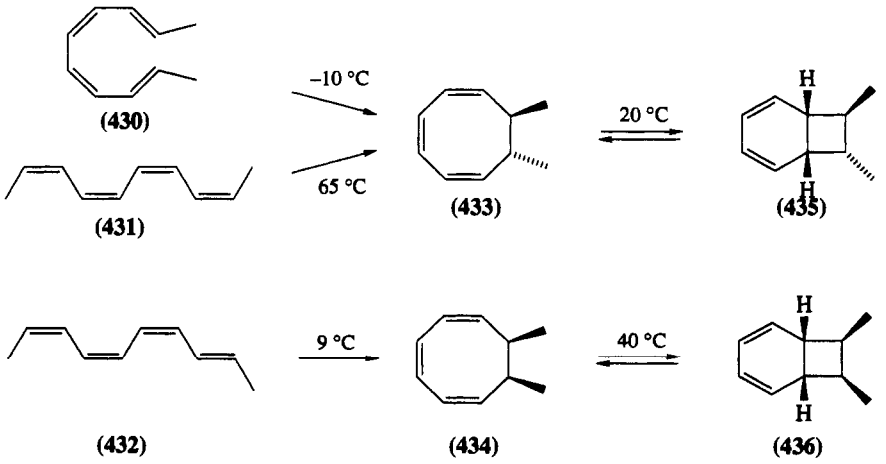
(427) (428) (429)

6.2.4.3 Higher-order Electrocyclic Processes

This final section will consist of a brief survey of the electrocyclization of systems with more than 6 electrons, which are not explicitly treated in this series with special emphasis on 8-electron systems. The excellent book published in 1980 by Marvell[3a] is therefore an obligatory reference here.

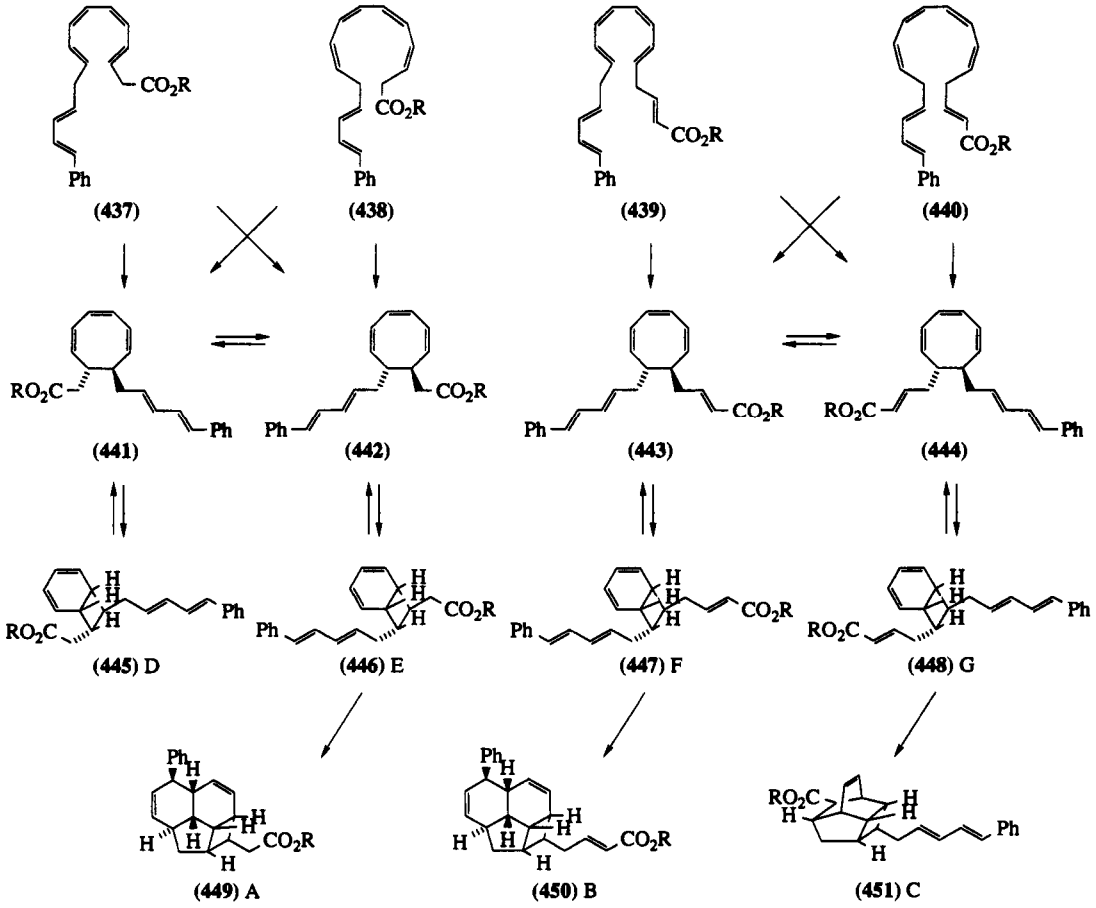
There are abundant examples in the literature which reveal that the thermal electrocyclization of $8e^-$ systems to form eight-membered rings proceeds with lower activation energies than for the lower vinylog, (*Z*)-hexatrienes. The helical geometry of the transition state leads to less steric congestion about the reacting termini of the octatetraene and this likely accounts for the facility of the thermal $8e^-$ conrotatory process. Minor structural differences can induce cycloreversion of the process.[3a]

The predicted[1] conrotatory nature of this electrocyclization has been definitively established.[163] The conrotatory mode was found to operate in the individual thermal electrocyclization of the stereoisomeric decatetraenes (**430**), (**431**) and (**432**). The former pair (**430** and **431**) afforded the *trans*-cyclooctatriene (**433**), while the latter (**432**) led to the *cis*-cyclooctatriene (**434**). Both cyclooctatrienes (**433**) and (**434**) were observed to be in equilibrium with the corresponding $6e^-$ electrocyclized derivatives (**435**) and (**436**), respectively.



An elegant exploitation of the general understanding of pericyclic processes is reflected in the synthesis of the endiandric acids A–G, which was accomplished both in a stepwise and in a one-pot 'cascade' form.[164] In the latter case, generation (by catalytic hydrogenation) of the suitable polyunsaturated methyl ester progenitor (**437**) afforded the endiandric acids D and E methyl esters (**445**) and (**446**) at room temperature. The cyclooctatrienes (**441**) and (**442**), resulting from the initial $8e^-$ conrotatory process, could not be isolated and were found to cyclize to (**445**) and (**446**) resulting from a further $6e^-$ electrocyclization. Brief heating of the mixture at 100 °C afforded the endiandric acid A methyl ester (**449**), presumably the intramolecular Diels–Alder adduct of (**446**). The overall process represents the stereospecific formation of four new rings and eight chiral centers in a single operation from an achiral open-chain precursor. Similar experiments on the tetraene (**439**) gave, upon heating, a 4.5:1 mixture of endiandric acids F and G methyl esters, (**447**) and (**448**). Brief thermolysis of the mixture at 100 °C led to the isolation of endiandric acids B and C methyl esters (**450**) and (**451**) whose formation can be viewed as following a similar sequence as described before. In this case the process encompasses the transformation of an achiral precursor into two different skeletal arrangements with the concomitant formation of four cycles and eight asymmetric centers. The powerful predictive value of the WH rules serves in this case to

resolve the seemingly anomalous finding of racemic natural products with eight asymmetric centers and points to the possibility of biogenesis without enzymatic intervention.[164]



The stereochemistry of a thermally induced $10e^-$ electrocyclization (predicted to be disrotatory) has not been firmly established and the main synthetic application is found in the formation of azulenes and ring-fused azulenes as in the transformation (**452**) to (**453**).[165] Thermolysis of (**454**) with spontaneous elimination of dimethylamine from intermediate (**455**) afforded the fused azulene structure (**456**).[56] The chemistry of even higher order ($12e^-$ to $20e^-$) pericyclic processes has been recently reviewed.[166] An example of an unusual sequence of pericyclic processes is the transformation of heptahendecafulvadiene (**457**) to the pentacyclic hydrocarbons (**462**) and (**463**) in a 2:1 ratio. The pathway for this transformation can be viewed as an initial conrotatory $20e^-$ electrocyclization followed by a cascade of $10e^-$ and $6e^-$ pericyclic processes.[167]

ACKNOWLEDGEMENT

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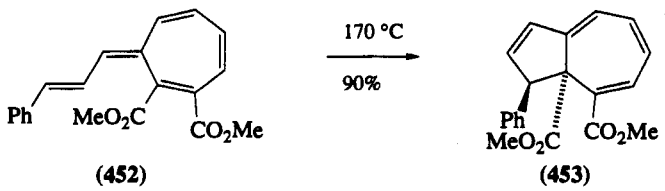
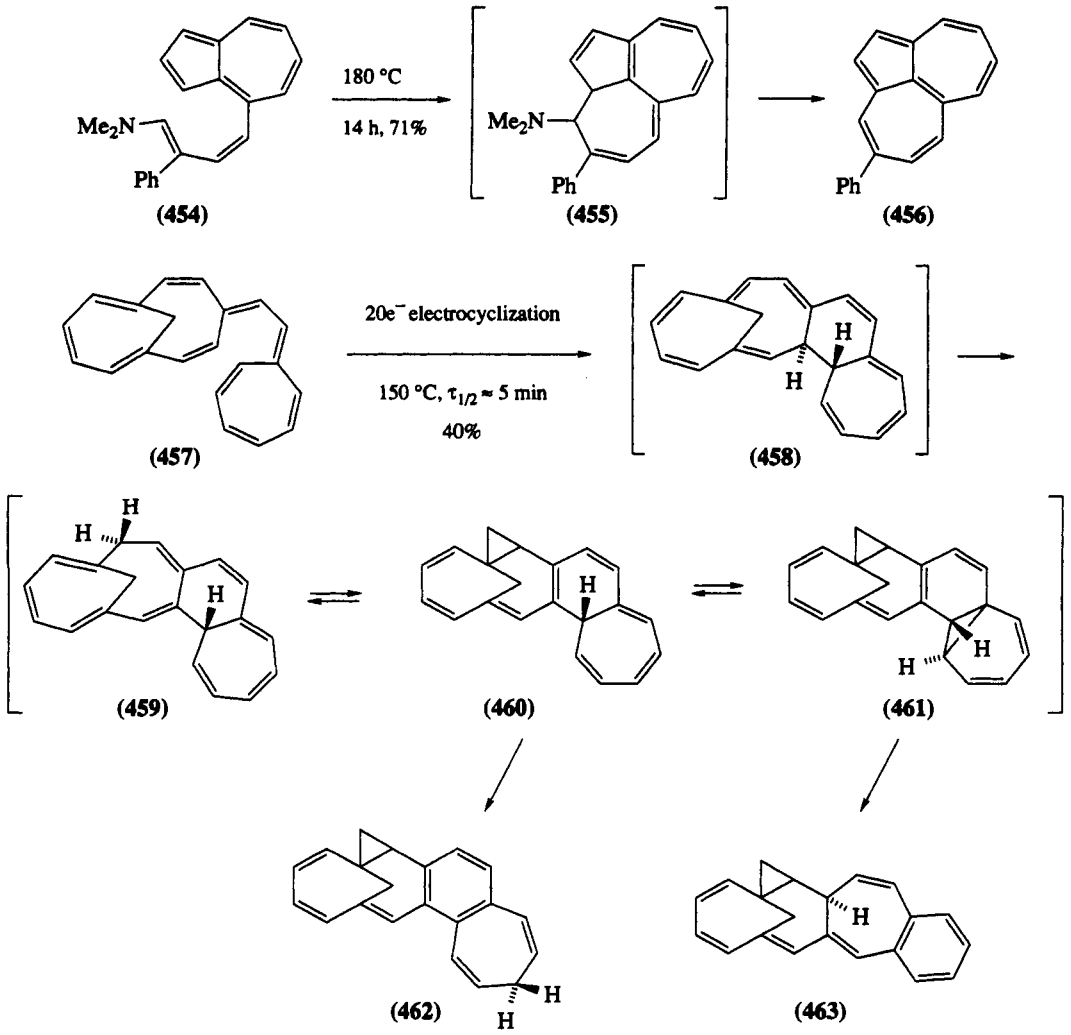


(**452**) (**453**)



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6.3
Nazarov and Related Cationic Cyclizations

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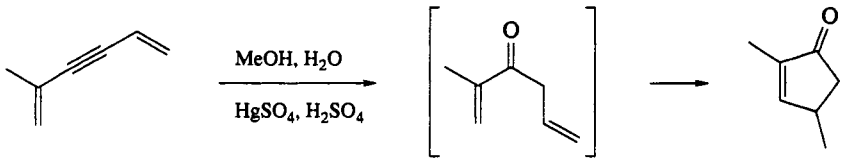
6.3.1 INTRODUCTION

6.3.1.1 Historical Background

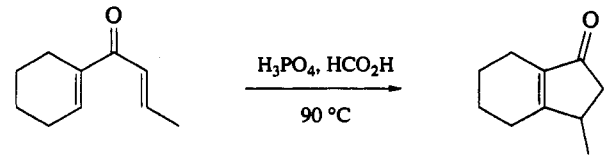
During the 1940s and 1950s Nazarov and his coworkers extensively studied the formation of allyl vinyl ketones by hydration of dienynes and their subsequent acid-catalyzed closure to 2-cyclopentenones (Scheme 1).[1–38] The reaction was notable as one of the first general methods for the selective construction of isolated and, more importantly, ring-fused cyclopentenones. In many instances the dienynes could be transformed directly to cyclopentenones without isolation of intermediates.



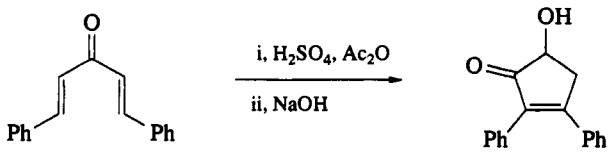
Scheme 1

The acid-catalyzed hydration cyclization of dienynes predates Nazarov. It was first reported and thoroughly examined by Marvel between 1933 and 1939.[39–45] While Marvel correctly proposed the intermediacy of allyl vinyl ketones, he formulated the cyclization products as 3-cyclohexen-1-ones. The structural assignment of many of these products was subsequently challenged.[46,47]

Ironically, until 1953, Nazarov incorrectly described the mechanism of the general transformation which now bears his name. In 1952, Braude and Coles[48] were the first to suggest the intermediacy of carbocations and demonstrated that the formation of 2-cyclopentenones actually proceeds *via* the α,α′-divinyl ketones (equation 1). This fact together with further mechanistic clarification, has led to the specific definition of the Nazarov cyclization as the acid-catalyzed closure of divinyl ketones to 2-cyclopentenones. This process was already documented in 1903 by Vorländer[49] who isolated a ketol of unknown structure by treatment of dibenzylideneacetone with concentrated sulfuric acid and acetic acid followed by mild alkaline hydrolysis (equation 2). The correct structure of Vorländer's ketol, finally proposed in 1955,[50] arises from Nazarov cyclization followed by oxidation and isomerization. Other examples of acid-catalyzed cyclizations of divinyl ketones exist in the early literature.[51,52]

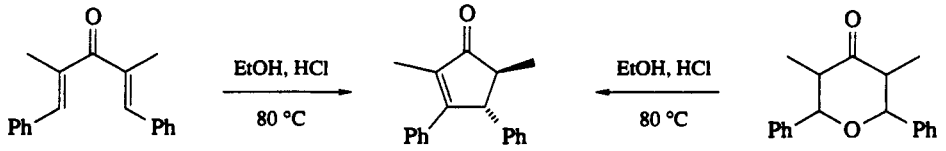


(1)



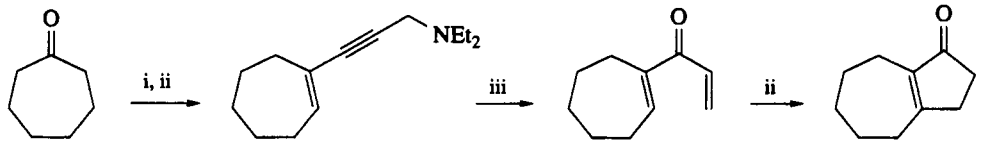
(2)

Shoppee[53] has clarified an early report by Japp and Maitland[54] on the formation of a cyclopentenone by treatment of either divinyl ketone or tetrahydropyrone with ethanolic hydrochloric acid (Scheme 2). This case illustrates a broader definition of the Nazarov cyclization that includes a wide variety of precursors.



Scheme 2

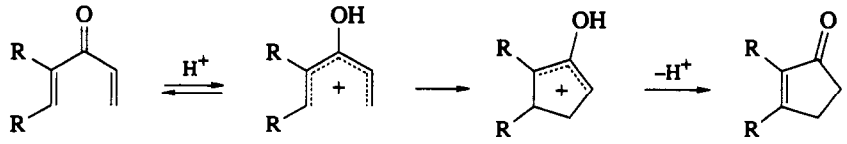
Most of the variants of the Nazarov cyclization are operational equivalents in that they involve starting materials which are transformed into divinyl ketones under conditions which also induce subsequent closure to 2-cyclopentenones. Thus, the identification of divinyl ketones as key intermediates by Braude and Coles was critical in several ways for the development of the Nazarov cyclization in suggesting the use of precursors other than dienynes. A case in point is the 1953 report by Raphael[55] on the use of a propargyl amine as the divinyl ketone precursor (Scheme 3). A second important, although somewhat later advance was the recognition that Lewis acids can effectively induce the cyclization of divinyl ketones, an improvement over the classical reagent, 90% phosphoric acid.



i, Li–C≡CCH$_2$NEt$_2$; ii, H_3PO_4, HCO_2H; iii, $Hg(OAc)_2$, H_2SO_4

Scheme 3

A third and critical advance in the development of the Nazarov cyclization was the demonstration that it belongs to the general class of cationic electrocyclic reactions (Scheme 4). This broadened its definition to include reactions which involve pentadienylic cations or equivalents and thus expanded the range of precursors for cyclopentenones. Further, the stereochemical features of electrocyclization enhanced the utility of the reaction and, in addition, stimulated the development of a photochemical variant.



Scheme 4

6.3.1.2 Organization and Scope

It is the structural variety of the precursors which lends versatility to the Nazarov cyclization and which also serves as the organizational framework for this chapter. To facilitate presentation the reaction is divided into five categories: (i) (Lewis) acid-promoted and photochemical cyclization of divinyl and allyl vinyl ketones; (ii) silicon- and tin-directed Nazarov cyclizations of divinyl ketones; (iii) *in situ* generation/cyclization of divinyl ketones; (iv) solvolysis to produce divinyl ketone equivalents; (v) coupling reactions to form and cyclize divinyl ketones. The logic of this sequence follows from the order of decreasing structural similarity of the precursors to divinyl ketones. The last three subgroups encompass considerable structural diversity which will be discussed in each section.

The coverage is intended to be comprehensive in the presentation of structural variation in precursors. Within each category the issues of scope, limitations and, where appropriate, stereochemistry will be addressed with representative examples. The Nazarov cyclization was most recently reviewed in 1983.[56] Prior to that the reaction had been reviewed in the context of pentannulation.[57,58] The related electrocy-

clic closure of the less oxidized pentadienylic cations is discussed where mechanistically relevant. Extensive discussion of the chemistry of these species is available.[59]

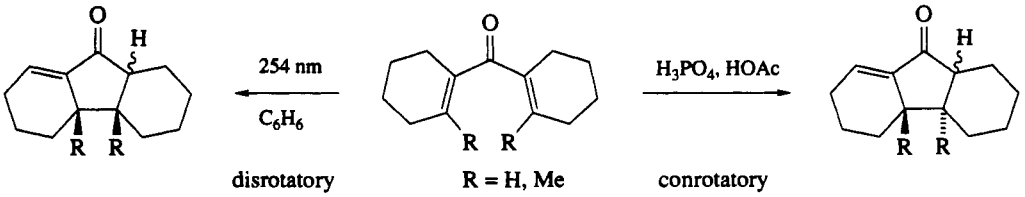
6.3.2 MECHANISM AND STEREOCHEMISTRY

6.3.2.1 Mechanism and Stereospecificity

The first modern thinking about the mechanism of the Nazarov cyclization is due to Braude and Coles,[48] who suggested the intermediacy of a β-keto carbocation from either divinyl or allyl vinyl ketones. The ring is formed by intramolecular attack on the enone with concomitant generation of an α-keto carbocation. Loss of a β-proton from this intermediate affords the product. Nazarov[32,35,36] himself provided support for this proposal by demonstrating the incorporation of deuterium from D_3PO_4 in different positions from divinyl or allyl vinyl ketones.

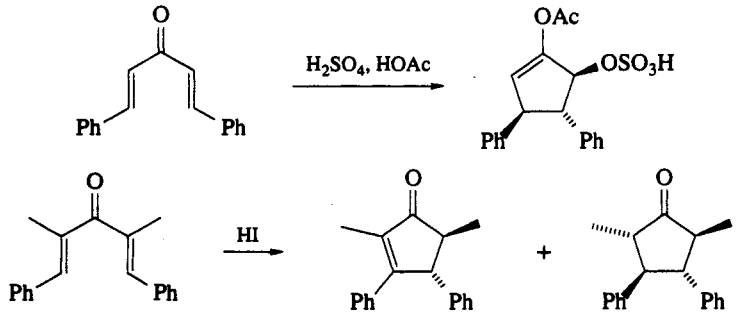
It is now well established that the Nazarov cyclization is a pericyclic reaction belonging to the class of electrocyclizations. As with all pericyclic reactions, mechanism and stereochemistry are inexorably coupled and any discussion of one feature must invoke the other. In this section the stereospecific[60] aspects of the Nazarov cyclization are discussed, the stereoselective[60] aspects of the reaction are dealt with individually in each of the following sections.

The Nazarov cyclization is an example of a 4π-electrocyclic closure of a pentadienylic cation. The evidence in support of this idea is primarily stereochemical. The basic tenets of the theory of electrocyclic reactions[61] make very clear predictions about the relative configuration of the substituents on the newly formed bond of the five-membered ring. Because the formation of a cyclopentenone often destroys one of the newly created centers, special substrates must be constructed to allow this relationship to be preserved. Prior to the enunciation of the theory of conservation of orbital symmetry, Deno[62] and Sorensen[63–66] had observed the facile thermal cyclization of pentadienylic cations and subsequent rearrangements of the resulting cyclopentenyl cations. Unfortunately, these secondary rearrangements thwarted early attempts to verify the stereochemical predictions of orbital symmetry control. Subsequent studies with the pentamethyl derivative were successful.[67,68] The most convincing evidence for a pericyclic mechanism came from Woodward, Lehr and Kurland,[69] who documented the complementary rotatory pathways for the thermal (conrotatory) and photochemical (disrotatory) cyclizations, precisely as predicted by the conservation of orbital symmetry (Scheme 5).



Scheme 5

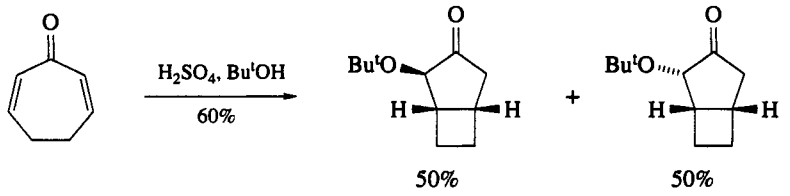
Additional confirmation came from Shoppee who reinvestigated Vorländer's very early work on the thermal cyclization of dibenzylideneacetone[70] and dibenzylidene-3-pentanone[53] in the presence of acid. Careful experimentation revealed the conrotatory electrocyclic pathway for both of these substrates (Scheme 6).



Scheme 6

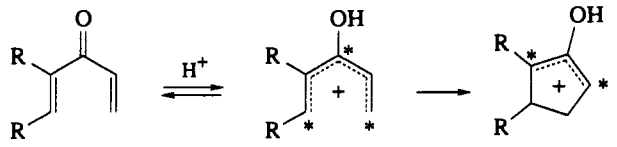
The Woodward–Hoffman rules also predict that in a given cyclization mode a permutation of alkene geometry must be reflected in the configuration of the products. This test is precluded under the normal reaction conditions (acid, light) which would isomerize the dienone double bonds. However, Corey recently reported the formation of a *cis*-disubstituted cyclopentenone from a (*Z*,*E*)-precursor, derived from an allene oxide, which cyclizes *via* the 2-oxido pentadienylic cation (Section 6.3.8).[71]

The predicted photochemical disrotatory closure of protonated divinyl ketones has been documented in several laboratories, most notably by Nozaki,[72] Noyori,[73] and Cerfontain[74] (equation 3). The stereochemical outcome in these reactions was discernible due to secondary processes which preserved the sense of electrocyclization.



(3)

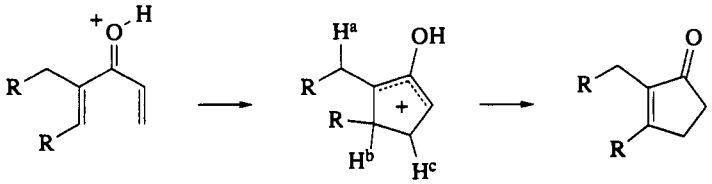
The cationic electrocyclization mechanism also allows predictions of substituent effects. In the rate-determining electrocyclization event, the distribution of positive charge changes as indicated by the asterisks in equation (4). Thus, the effect of substituents which stabilize positive charge should be to either accelerate (α-position) or decelerate (β-position) depending upon location. Further, α-substitution should be greater in magnitude since the charge is less delocalized.



(4)

6.3.2.2 Relative Stereogenesis

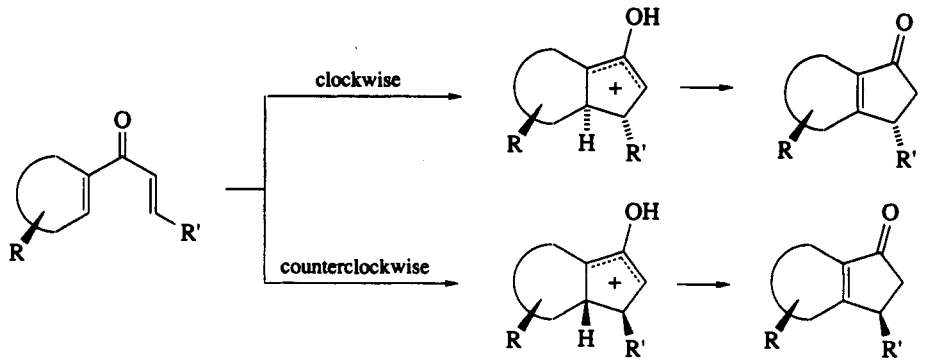
Beyond the disrotatory or conrotatory stereochemical imperative which must accompany all Nazarov cyclizations there exists a secondary stereochemical feature. This feature arises because of the duality of allowed electrocyclization pathways. When the divinyl ketone is chiral the two pathways lead to diastereomers. The nature of the relationship between the newly created centers and preexisting centers depends upon the location of the cyclopentenone double bond. The placement of this double bond is established after the electrocyclization by proton loss from the cyclopentenyl cation (equation 5). Loss of H^a, H^b or H^c in this instance generates three tautomeric products. The lack of control in this event is a drawback of the classical cyclization. Normally, the double bond occupies the most substituted position corresponding to a Saytzeff process. The issue of stereoselection with chiral divinyl ketones is illustrated in Scheme 7. The sense of rotation is defined by clockwise (*R*) or counterclockwise (*S*) viewing down the C—O bond. Thus, depending on the placement of the double bond, the newly created center may be proximal or distal to the preexisting center. If R^1 = H the double bond must reside in a less substituted environment to establish stereoselectivity.



(5)

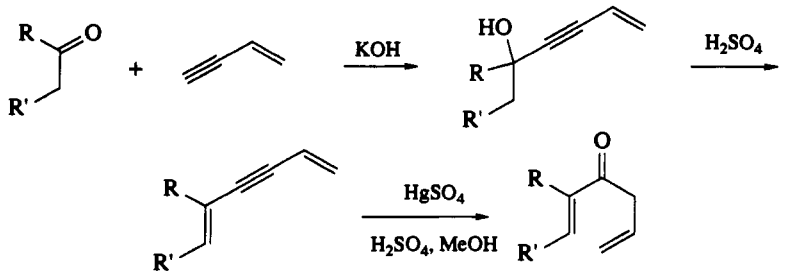
6.3.3 CYCLIZATION OF DIVINYL AND ALLYL VINYL KETONES

The original substrates studied by Nazarov were allyl vinyl ketones. These materials could be obtained easily by mercury(II) ion assisted hydrolysis of dienynes, themselves available from dehydration of vinyl



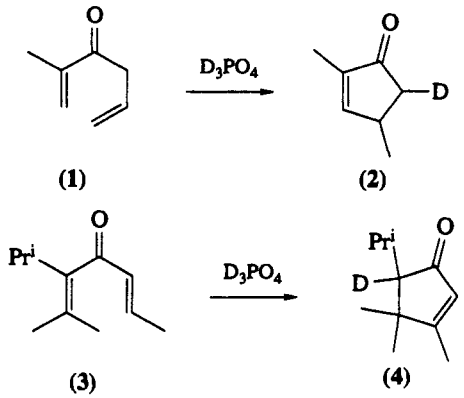
Scheme 7

acetylide adducts of ketones (Scheme 8). This approach allows incorporation of many substitution patterns.



Scheme 8

Following the suggestion of Braude and Coles,[48] Nazarov established the role of the tautomeric divinyl ketones as the true precursors of cyclization. By conducting the cyclization of the allyl vinyl ketone (**1**) in D_3PO_4 it was established that one deuterium is introduced into the cyclic product (**2**; Scheme 9).[35] Direct cyclization of the divinyl ketone (**3**) with D_3PO_4 gave identical results.[36]

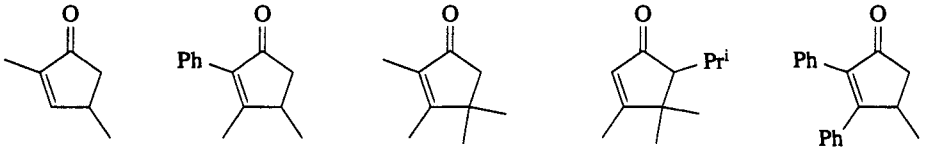


Scheme 9

Thus, in the following section the two different precursors are considered as equivalent and the organization follows structural patterns. In many other variants of the Nazarov cyclization, divinyl ketones are implicit intermediates formed from other precursors. In this section only those cases where a divinyl or allyl vinyl ketone was directly cyclized will be discussed.

6.3.3.1 Acyclic Precursors

The Nazarov cyclization is well suited for the construction of simple cyclopentenones adorned with various substitution patterns. A collection of representative structures prepared from either allyl vinyl or divinyl ketones is shown in Scheme 10. Many different alkyl groups are compatible with the substitution patterns. Aromatic substituents, especially at the α-position, have a beneficial effect on the reaction rate and yield. In all of those cases where a choice is possible, the double bond resides in the thermodynamically most stable position.

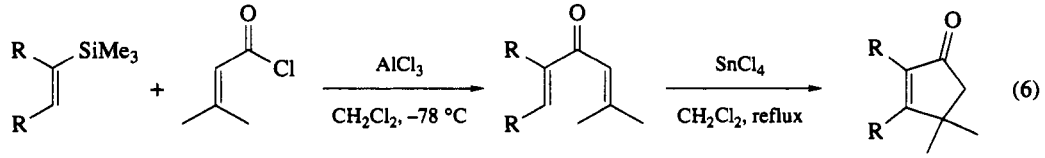


75% (ref. 20) 95% (ref. 17) 60% (ref. 18) 81% (ref. 27) 95% (ref. 30)

Scheme 10

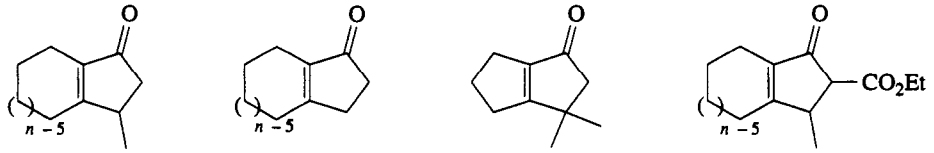
6.3.3.2 Monocyclic Precursors

A useful feature of the Nazarov cyclization is the construction of fused bicyclic systems by annulation of a five-membered ring.[57] This requires one of the vinyl groups to be embedded in a ring. These precursors can be formed easily by vinyl alkyne addition to cyclic ketones followed by dehydration and hydrolysis. This procedure works well for symmetrical ketones but it gives regioisomers from unsymmetrical ketones such as 1- or 2-octalone.[11,22] A superior method, reported by Paquette,[75,76] involves the acylation of cycloalkenylsilanes to provide divinyl ketones (equation 6). The advantages of this protocol are discussed in Section 6.3.7.4.3.



(6)

The preexisting ring may vary in size from 5 up to 12 members. In general the annulation yields are lowest with five-membered rings. A representative sampling of structural types is collected in Scheme 11. The stability of esters under the cyclization conditions is noteworthy.[79]



n = 5, 32% (ref. 75)
n = 6, 70% (ref. 7)
n = 7, 75% (ref. 77)
n = 12, 66% (ref. 75)

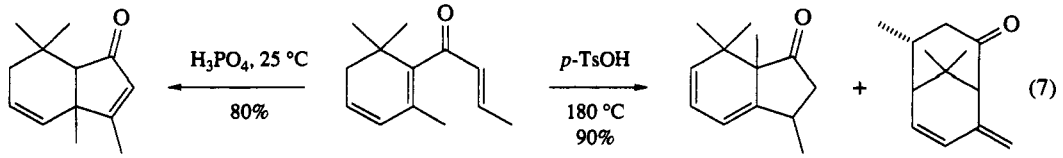
n = 6, 50% (ref. 48)
n = 7, 60% (ref. 77)

62% (ref. 78)

n = 5, 30% (ref. 79)
n = 6, 48% (ref. 79)
n = 7, 35% (ref. 79)

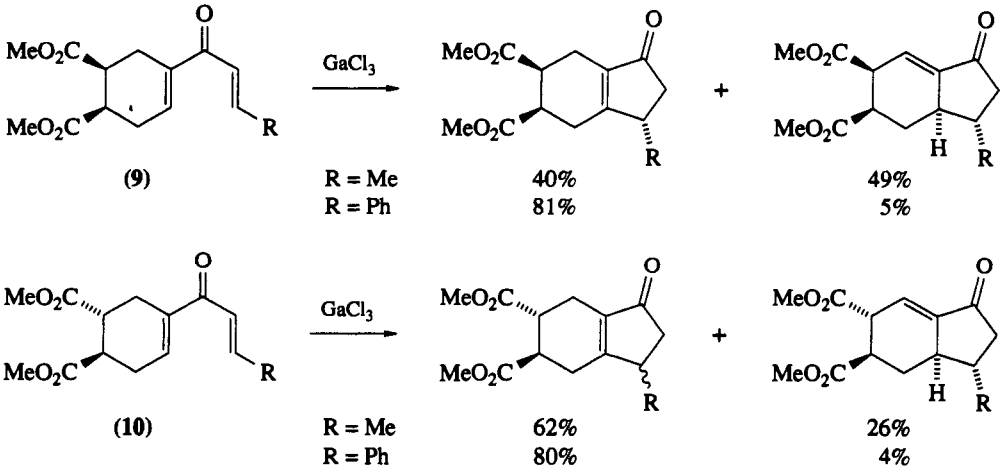
Scheme 11

The intervention of secondary cationic processes has been demonstrated in these systems by Ohloff (equation 7).[80] While cyclization of (**5**) proceeds normally, to (**6**), with H_3PO_4, *p*-toluenesulfonic acid gives products of Wagner–Meerwein rearrangement (**7**) or intramolecular acylation (**8**).



(6) (5) (7) (8)

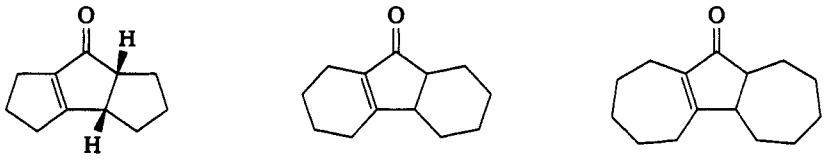
The monocyclic substrates are well suited for discussion of relative stereocontrol. In a recently reported study employing *cis*- and *trans*-disubstituted substrates (**9**) and (**10**), high stereoselectivity could be obtained when gallium trichloride was used as the Lewis acid (Scheme 12).[81] In these reactions new stereocenters can be created at C(3) and C(3a). In the *cis* series both tautomeric products were formed as single stereoisomers while the *trans* series (**10**) produced a mixture of the tetrasubstituted isomers. A *post facto* epimerization was suggested as the cause for the lower selectivity. Discussion of the rotational sense is not warranted here as the configurations of the newly created centers were not rigorously established.



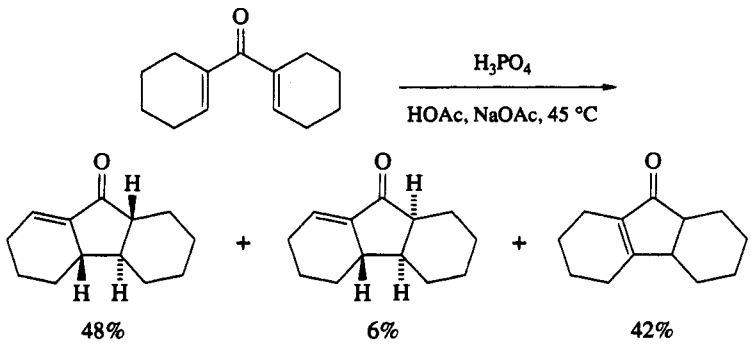
Scheme 12

6.3.3.3 Biscyclic Precursors

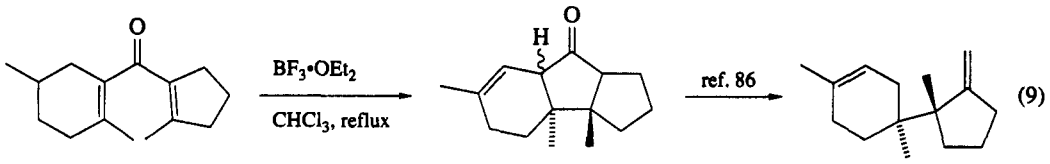
When both vinyl groups of a divinyl ketone are embedded in rings, a linearly fused tricyclic array results from cyclization. Five-,[82] six-[83] and seven-membered[83] rings have been employed in various combinations. In general, the product double bond occupies a ring fusion position. Structures of representative products are collected in Scheme 13. In the classic Woodward–Lehr cyclization (equation 8), the reaction conditions could be modified to allow formation of a significant quantity of the trisubstituted alkene thus permitting the establishment of a conrotatory pathway in the ground state.[69,84] The related substrate bearing two β-methyl groups gave rise to a single trisubstituted ketone possessing the *anti* arrangement of methyl groups.[85] Harding has made good use of the vicinal relationship of these quaternary centers in a synthesis of (±)-trichodiene (equation 9).[86]



Scheme 13

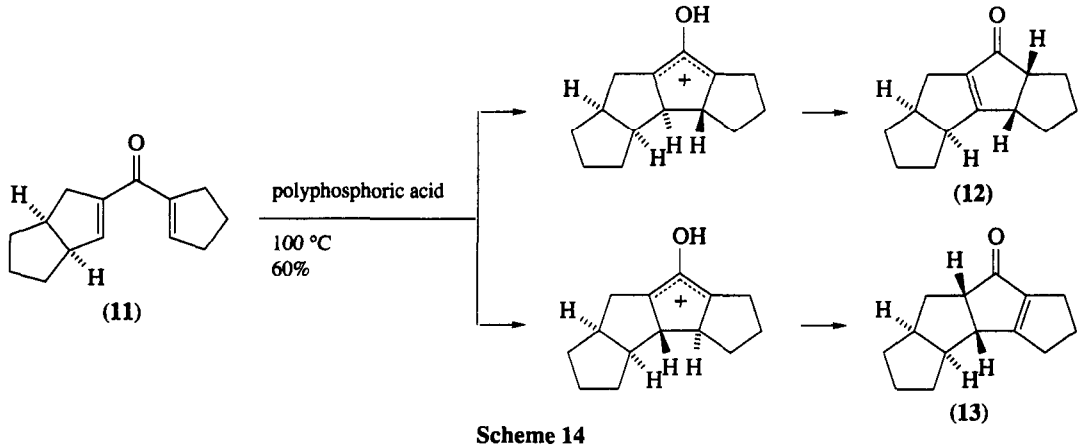


(8)

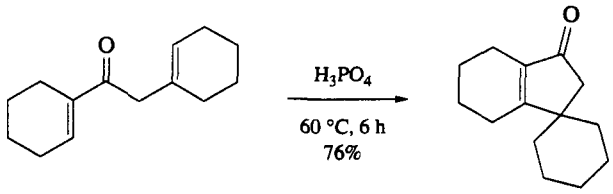


(9)

Mehta has examined relative stereocontrol in an approach to the carbocyclic nucleus of ophiobolins.[87] Cyclization of the triquinane (**11**) gave two products, (**12**) and (**13**), in a 4:1 ratio (Scheme 14). These products arise from opposite rotatory pathways as shown. Surprisingly, the major product arises from conrotation to the concave face of the diquinane unit. Finally, Nazarov has provided an interesting example of both fused and spiro mode annulations in equation (10).[26]



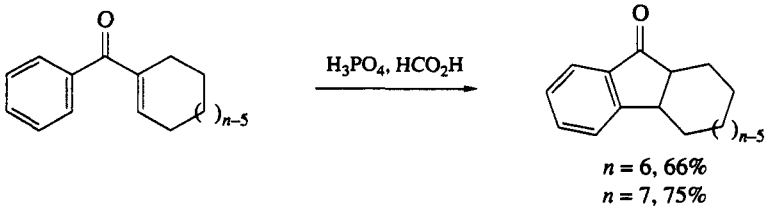
Scheme 14



(10)

6.3.3.4 Aromatic Precursors

Under sufficiently vigorous conditions a benzene ring can be induced to participate in the Nazarov cyclization with both six-[88] and seven-membered[77] rings (equation 11).

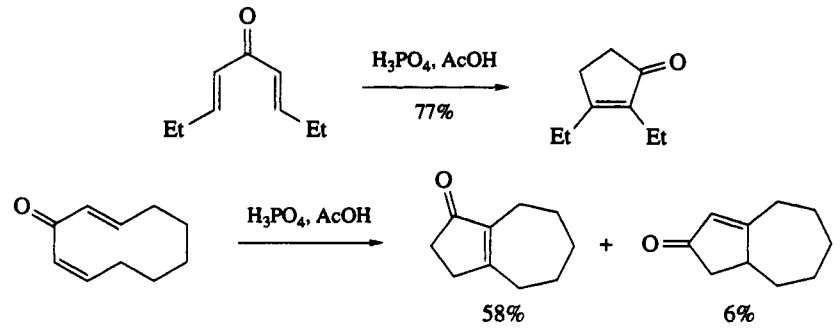


(11)

6.3.3.5 Anomalous Cyclizations

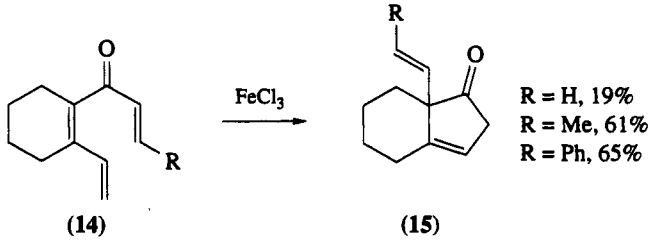
Considering the manifold reaction pathways available for carbocations it is not surprising that unexpected products have been isolated. Capture of the intermediate cyclopentenyl cation by nucleophiles was first shown by Shoppee (Scheme 6).[70] This pathway can become dominant, resulting in a transposition of the enone moiety by tautomerization and dehydration.

The 'abnormal' Nazarov cyclization reported by Hiyama[89,90] leads to transposed cyclopentenones by incorporating carboxylic acids as nucleophiles in the reaction medium. Both acyclic and monocyclic divinyl ketones can be employed, as shown in Scheme 15. Dioxolane acetals have also been used successfully in place of the carbonyl group.



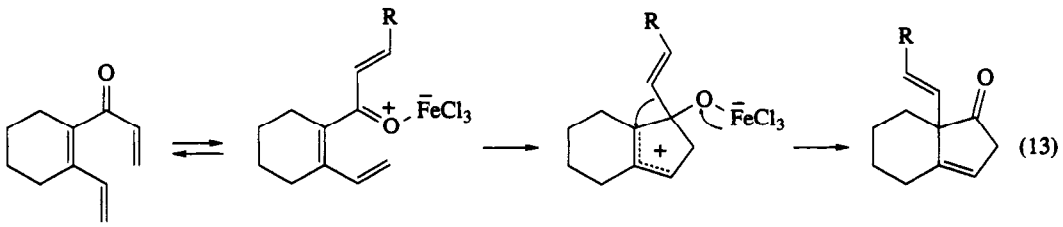
Scheme 15

Although only cross-conjugated divinyl ketones have been considered thus far, in principle conjugated dienones can also undergo the 4π-electrocyclization *via* the 1-oxypentadienylic cation. This pathway was found to dominate in a series of monocyclic dienyl vinyl ketones (**14**) examined by Denmark (equation 12).[91] The angularly substituted indanones (**15**) arise from cyclization of the dienyl ketone followed by a rapid Wagner–Meerwein shift (equation 13). The substituent effects on the migrating double bond are consistent with this mechanism.[91]



(12)

(**14**) (**15**)

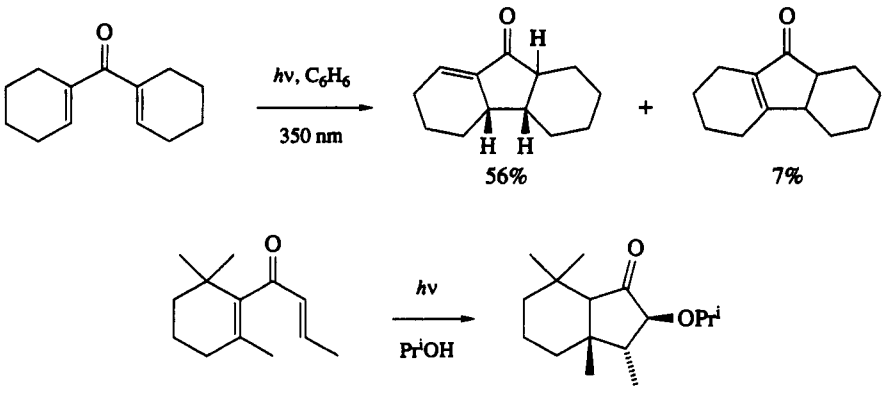


(13)

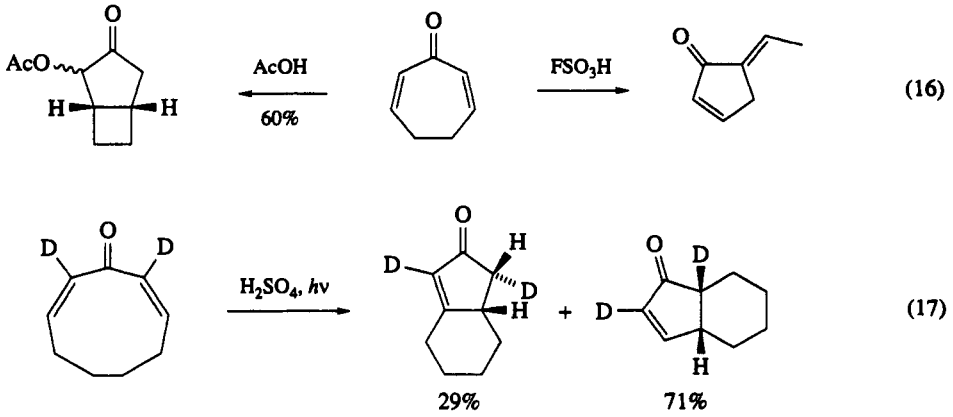
6.3.3.6 Photochemical Cyclizations

The theory of electrocyclic reactions predicts a disrotatory closure of 4π-systems in the excited state.[61] This prediction was verified in fact by Lehr[84] using the same biscyclohexenyl ketone (equation 14). The cyclization proceeded at various wavelengths in pentane as well as in benzene. The reaction could not be inhibited by naphthalene or piperylene. Sensitization with acetophenone did not accelerate the reaction. Finally, no deuterium was incorporated when d_6-benzene was used as solvent. β-Damascone undergoes an apparent disrotatory closure with capture of the zwitterionic intermediate by solvent (equation 15).[74]

The photocyclization of cyclic, cross-conjugated divinyl ketones has been investigated in various ring sizes. The simplest members of this group, 4,4-disubstituted-2,5-cyclohexadienones have been extensively studied,[92] but the subsequent skeletal reorganizations place these reactions beyond the scope of this chapter. The homologous cycloheptadienones give different products depending on reaction conditions (equation 16). The expected disrotatory closure occurs in acetic acid,[72] while a more complex series of

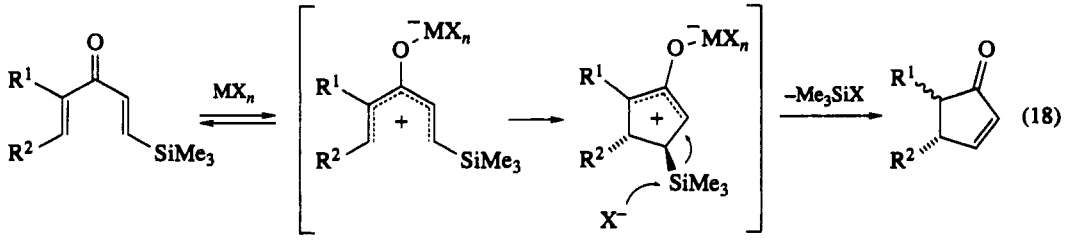


electrocyclizations and openings occurs in FSO_3H.[73] Noyori has further shown that medium ring divinyl ketones give the expected disrotatory closure upon irradiation in 97% H_2SO_4 (equation 17).[73]

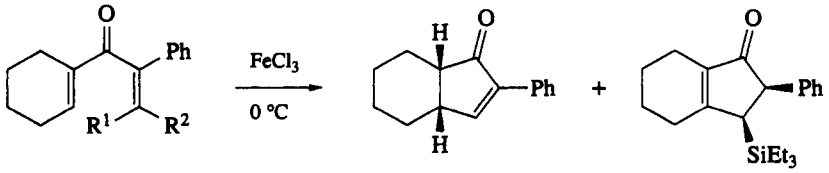


6.3.4 SILICON-DIRECTED NAZAROV CYCLIZATIONS OF DIVINYL KETONES (SDNC)

The recognition that the Nazarov cyclization is a cationic electrocyclization provided a better understanding of the controlling features of the reaction and a rationale for explaining its deficiencies. Among the latter, the most serious are: secondary cationic rearrangements[80] and unselective placement of the cyclopentenone double bond. These problems identify the cyclopentenylic cation (Scheme 4) as the offending intermediate from which these problems arise. By strategic placement of an efficient phantom electrofuge, the collapse of the intermediate cation is accelerated and directed in a preordained sense. By virtue of the β-cation-stabilizing properties of organosilicon groups[93] (the β-effect[94]), these substituents have proven extremely effective in the Nazarov cyclization. Equation (18) illustrates the principle. The β-silyl group acts as a 'spectator' until the crucial electrocyclization at which point it is stereoelectronically aligned[93] to direct collapse of the cation. Two important consequences of the directed collapse as shown are: (i) the placement of the double bond in the thermodynamically less stable position; and (ii) the creation of ring fusion stereocenters which allows the electrocyclic nature of the reaction to be expressed in relative stereogenesis.



The TMS group has been most often employed. In certain circumstances larger alkyl and aryl groups attached to silicon have also been used successfully.[95] With (*Z*)-β-silyl divinyl ketones, Chenard[96] claims that the *t*-butyldimethylsilyl and, in some cases, the triethylsilyl group remain after cyclization (equation 19). That this feature is most likely due to a change in the alkene geometry and not the bulk of the silyl group is shown by the highly silicon-directed transformation of the (*E*)-isomer.[97]

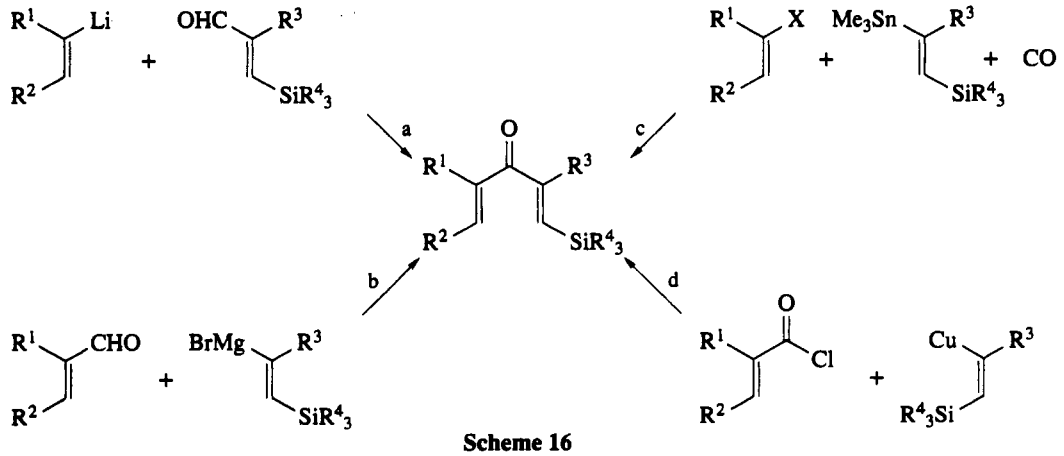


(19)

(*Z*): $R^1 = SiEt_3$; $R^2 = H$ 18% 24%

(*E*): $R^1 = H$; $R^2 = SiEt_3$ 85% 0%

The construction of β-silyl divinyl ketones in many different structural settings has been well developed. The four principal connections outlined in Scheme 16 are as follows: path a,[98] vinyl organometallic addition to 3-trimethylsilyl-2-propenal;[99] path b,[98] 3-trialkylsilylvinyl organometallic[100,101] addition to enals; path c,[102] palladium-catalyzed carbonylation/coupling of 2-trimethylsilylvinyltrimethylstannane;[103] and path d,[104] acylation of a β-silyl copper reagent.[105]

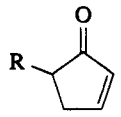


Scheme 16

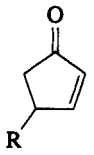
In their initial studies on the SDNC, Denmark and Jones[98,106] demonstrated a Lewis acid dependence, with anhydrous $FeCl_3$ providing optimal results. Subsequently $BF_3{\cdot}OEt_2$ and $ZrCl_4$ have been used successfully where the oxidizing properties of $FeCl_3$ proved deleterious. The SDNC's proceed under much milder conditions than the classical variant. Only with highly substituted substrates or in certain annulations are temperatures above the ambient necessary.

6.3.4.1 Acyclic Precursors

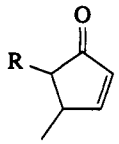
Due to their ready isomerization simple cyclopentenones present a particular challenge in the Nazarov cyclization. In all of the cases studied in α- and β-monosubstituted and α,β-disubstituted systems the cyclopentenone product contained the double bond in the less substituted position, as required by loss of the silicon electrofuge (Scheme 17).[98,104] The relative configuration of substituents in disubstituted cases is controlled by kinetic protonation and weakly favors the *cis* isomers. Substituent effects in rate were particularly noted in these cases where substitution with α- and β-alkyl groups greatly accelerated and decelerated the reactions, respectively.



R = Et, 51%
R =Bu^t, 97%



R = Me, 54%
R = Ph, 27%

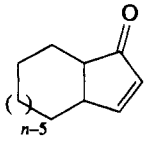


R = Me, 95%, *cis:trans* = 59/41
R = Et, 70%, *cis:trans* = 43/57

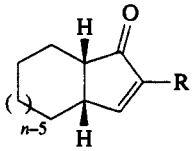
Scheme 17

6.3.4.2 Monocyclic Precursors (Achiral)

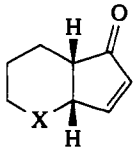
The SDNC is also very useful in the annulation mode with one endocyclic double bond. Various ring sizes, heterocycles and substituent patterns have been examined.[98] In the homologous series of cycloalkenyl groups the rate increases 5 < 6 < 7 ≈ 8 ≈ 12 (Scheme 18). The ring fusion stereochemistry is established by kinetic protonation of the cross-conjugated iron enolate. This tends to favor the *cis* ring fusion. The accelerating effect of α-substitution is seen in the low temperature, high yielding cyclizations to form 2-substituted enones. Oxygen- and nitrogen-containing heterocycles also participate successfully.[104] Ring unsaturation is compatible with the reaction and shows the expected rate effects.[104]



n = 5, 52%
n = 6, 84%
n = 7, 74%
n = 12, 78%



n = 5; R = Ph; 86%
n = 6; R = allyl; 76%



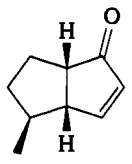
X = O, 60%
X = NCO_2Me, 76%

Scheme 18

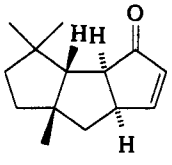
6.3.4.3 Monocyclic Precursors (Chiral)

The stereochemical course of SDNC with ring-substituted monocyclic precursors has been studied in detail. The choice between the two allowed conrotations is influenced by: (i) ring size; (ii) substituent location; (iii) substituent size; and (iv) silyl group size.

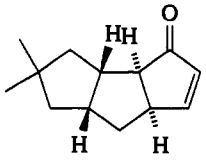
In the cyclopentenyl series the relative stereoselection is variable.[95] With a simple methyl substituent vicinal to the newly forming bond the selectivity is poor. This may be remedied with bulkier silyl groups (Scheme 19) but in unacceptable yields. In the synthesis of (±)-$\Delta^{9(12)}$-capnellene, Stille[107] reports the formation of a single *cis,anti,cis*-triquinane (**16**) in the final SDNC. By contrast in an approach to hirsutene, the SDNC produced triquinane (**17**) as a 2.7:1 mixture favoring the desired *cis,anti,cis* isomer.[108]



Me_3Si: 54/46, 50%
Pr^i_3Si: 79/21, 13%



(16)



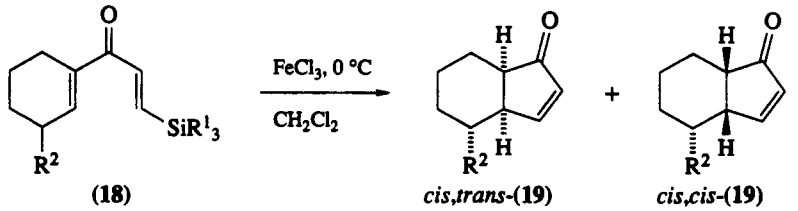
(17)

Scheme 19

The cyclohexenyl system shows generally higher levels of selectivity. Substitution at the enone γ-carbon (**18**) has the strongest effect. The selectivity is sensitive to the size of the substituent as well as the size of the silyl groups. In all cases the major isomer contains a *trans* relationship between the hydrogens at the ring fusion and substitution position (Table 1).[109] Larger silyl groups (Pr^i_3Si) also enhanced the selectivity even in the simplest case of a methyl substituent. Substitution at other positions in the ring (**20**) and (**21**) led to less selective (*ca.* 3:1) cyclizations again favoring the *cis,trans* isomer for all positions

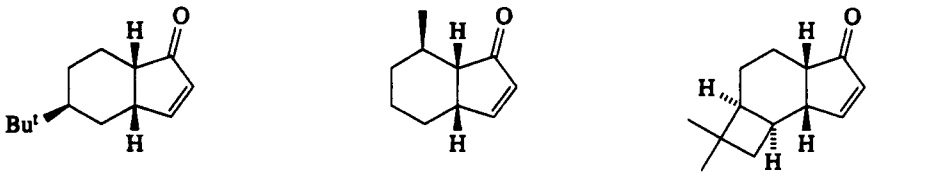
(Scheme 20). Finally, the tricyclic system (**22**) was formed selectively with the *cis,trans* isomer again preferred.[104]

Table 1



(**18**) *cis,trans*-(**19**) *cis,cis*-(**19**)

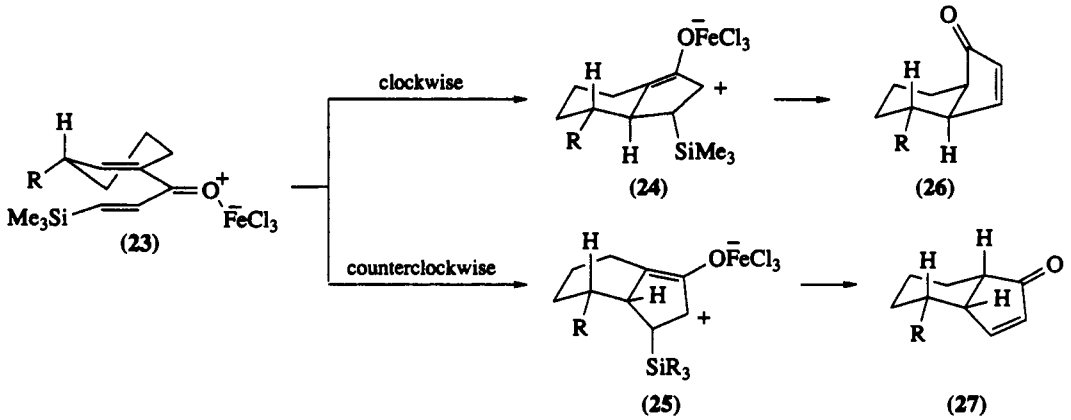
R^1	R^2	*Cis,trans-(19) (%)*	*Cis,cis-(19) (%)*	*Yield (%)*
Me	Me	78	22	99
Me	Vinyl	70	30	66
Me	Ph	94	6	76
Me	Bu^t	94	6	63
Me	OBn	90	10	76
Pr^i	Me	91	9	70



(**20**) 76/24, 82% (ref. 109) (**21**) 72/28, 85% (ref. 109) (**22**) 87/13, 70% (ref. 104)

Scheme 20

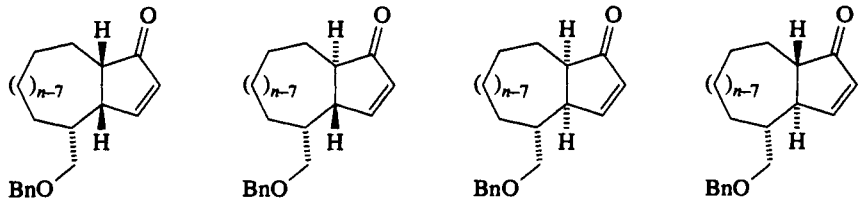
These trends are explained by analysis of the structures of the reactive conformations of the enones and the structures of the cyclopentenylic cations. Considering the γ-substituted series (**18**) the reactive half-chair conformation (**23**) places the substituent in an equatorial position (Scheme 21). In the cations resulting from conrotation (**24** and **25**) all atoms in the five-membered ring must lie in a plane, thus precluding an equatorial hydrogen. Thus the two conrotations, clockwise to (**24**) and counterclockwise to (**25**), lead directly to chair or boat conformations of the six-membered rings, respectively. The size of the substituent then plays two roles: first to fix the ring conformation and second to enhance opposite face approach.



Scheme 21

These studies have been extended to include cycloheptenyl and cyclooctenyl systems using the benzyloxymethyl substituent. In these cases the analysis is complicated by the appearance of the *trans* ring fu-

sion family of isomers. The results of extensive chemical correlation and molecular mechanics studies (Scheme 22)[97] show that the sense of relative stereogenesis changes (*cis* family) with remarkable degrees of selectivity (92:8 and 93:7). This switch is explained by a similar conformational analysis.

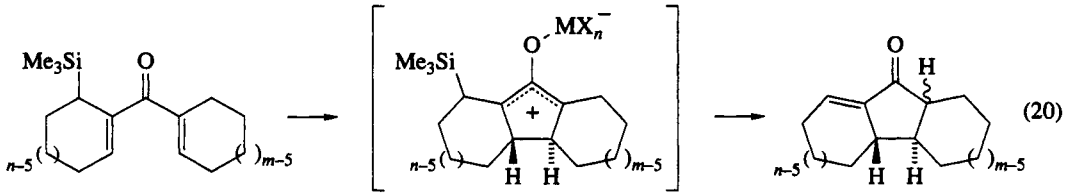


	cis,cis (%)	*trans,cis* (%)	*cis,trans* (%)	*trans,trans* (%)	*Yield* (%)
$n = 7$	78	14	5	3	84
$n = 8$	90	3	4	3	78

Scheme 22

6.3.4.4 Biscyclic Precursors

The formation of linearly fused tricycles serves to illustrate a variant of the SDNC. In these systems (**28**) the double bond must be directed away from both ring fusions. This was accomplished by placing the silyl group at a ring position again poised to direct the collapse of the intermediate cation (**29**; equation 20).



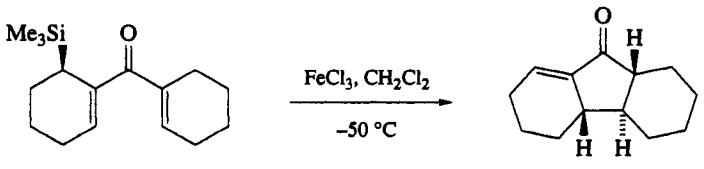
(20)

(**28**) (**29**) (**30**)

a: $n = m = 6$; 79%, *trans*
b: $n = 6$; $m = 5$; 88%, *cis*
c : $n = m = 5$; 77%, *cis*

These cyclizations occur much faster than the original SDNC since the electron-donating silyl group is in continuous overlap throughout the cyclization. The yields are generally good and the ring fusion stereochemistry well controlled.[110]

Since these substrates are chiral there exists the possibility of relative stereogenesis. However, since the original silicon-bearing stereocenter is destroyed in the process, the products of opposite conrotations are enantiomers. Thus, an optically active sample of (**28a**; 88% *ee*) was cyclized and provided (**30a**) with the same enantiomeric excess. This near perfect stereochemical coupling proceeds in the expected *anti* sense, as shown in equation (21).[111]



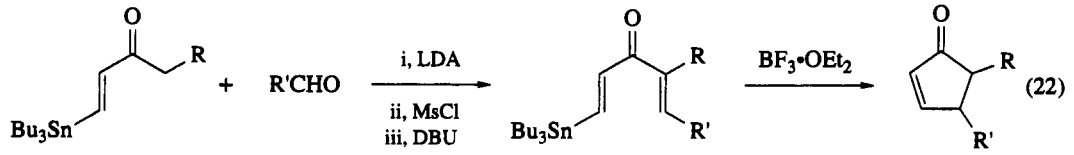
(21)

(**28a**) 88% *ee* (**30a**) 88% *ee*

6.3.4.5 Tin-directed Nazarov Cyclizations (TDNC)

Extension of the SDNC concept to include tin has been reported.[112] The cyclizations of various acyclic precursors proceeded under mild conditions in fair to excellent yields. As expected the less substituted

cyclopentenone is formed in each case. This variant offers a different construction of the divinyl ketone by an aldol condensation (equation 22).



R = H; R' = Ph; 44%

R = Bu^n; R' = Me; 93%, 1.7:1

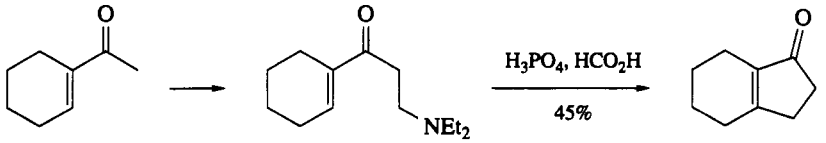
R = Bu^n; R' = styryl; 83%, 1.5:1

6.3.5 CYCLIZATION OF DIVINYL KETONES FROM *IN SITU* GENERATION

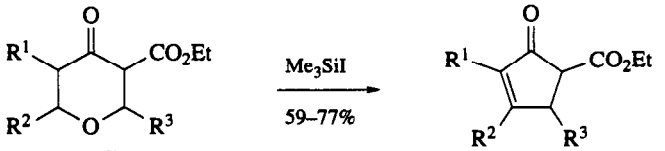
Access to the necessary divinyl ketones has been approached from many different directions. In this section those precursors which contain the carbon skeleton of the divinyl ketone will be discussed.

6.3.5.1 Cyclization of Divinyl Ketones from β′-Substituted Enones

The facile elimination of β-heterosubstituents in ketones allows for the ready construction of α,β-enones. Three different heteroatoms have been employed, chlorine, nitrogen and oxygen. The β′-chloro enones (products of Friedel–Crafts acylation) suffer Nazarov cyclization under standard conditions.[113,114] Jacquier has prepared a series of β′-amino enones (**31**) from Mannich condensations.[115] These substrates undergo cyclization in modest yields under standard conditions (equation 23). Takeda has found that the readily available[116] tetrahydro-4-pyranones (**32**) produce 2-cyclopentenone-4-carboxylates upon treatment with TMS-I (equation 24).[117] It is noteworthy that the putative α-carboalkoxy divinyl ketones have been independently cyclized by Marino using TMS-I.[79]



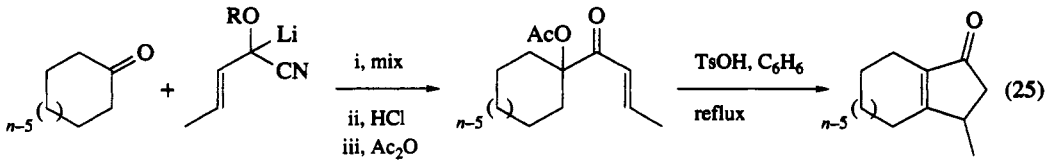
(31)



(32)

6.3.5.2 Cyclization of Divinyl Ketones from α′-Hydroxy Enones

Addition of acyl anion equivalents (propenal d^1 reagents) to ketones provides general access to α′-hydroxy enones. In an application of this method to pentannulation, the trimethylsilyl- or ethoxyethyl-protected cyanohydrins of α,β-enals were used.[118] The derived tertiary acetates undergo elimination (*p*-TsOH/benzene) to the divinyl ketones which cyclize in the acidic reaction medium (equation 25).[118] In some cases the α′-hydroxy or α′-silyloxy enones underwent cyclization but in much lower yields. Substitution in the ring and on the double bonds is compatible.



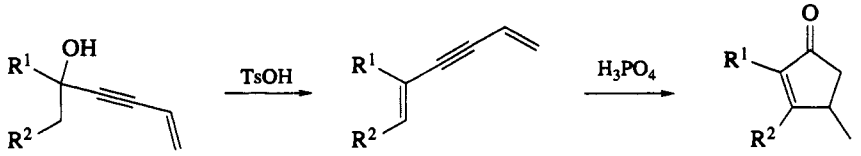
$n = 6$, 53%
$n = 7$, 60%
$n = 12$, 91%

6.3.5.3 Cyclization of Divinyl Ketones from Dienynes

The use of these precursors is due almost entirely to Nazarov[4,6,9,10,13–15,19,22–25,31] in work prior to 1950. The construction of dienynes from condensation of ketones and vinylalkynes followed by dehydration (Scheme 8) provides access to a broad range of structural types. Generally the dehydration occurs in a Saytzeff sense with unsymmetrical ketones.[119] The reagents most commonly used are phosphoric acid (occasionally with added formic acid) or concentrated hydrochloric acid. The conditions are rather harsh (50–80 °C) to accomplish both hydration of the alkyne and cyclization.

6.3.5.3.1 Acyclic precursors

The great majority of substrates employed are derived from vinylacetylene itself thereby providing 4-methyl-2-cyclopentenones, the 1- and 2-substituents arising from the ketone (equation 26). With α-branched ketones, 4,4-disubstituted-3-methylcyclopentenones are formed.[24,25]

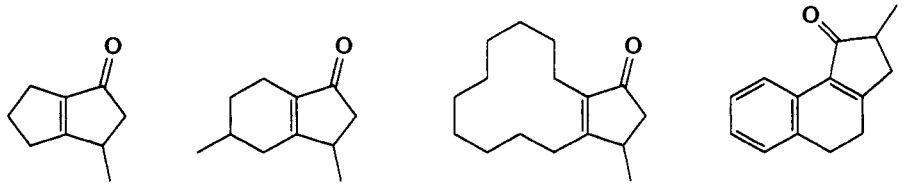


(33) (34)

$R^1 = R^2 = Me$; 71%
$R^1 = Ph$; $R^2 = Me$; 70%
$R^1 = Bu^t$; $R^2 = H$; 49%

6.3.5.3.2 Monocyclic precursors

The dienynes (**34**) derived from cyclic ketones also undergo cyclization to accomplish a cyclopentenone annulation.[8,11,13,14,22,26,31,120] Scheme 23 contains representative structures. The cyclododecyl system was derived from a silyldienyne prepared by a novel condensation route shown in equation (27).[120]

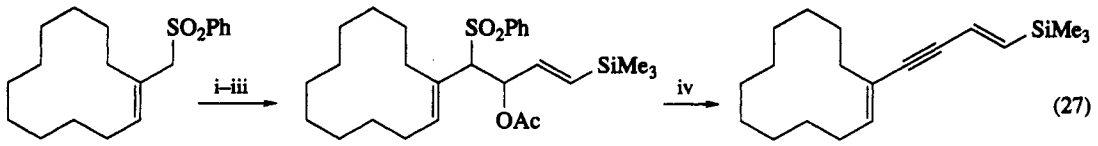


31% (ref. 8) 70% (ref. 13) 64% (ref. 120) 48% (ref. 22)

Scheme 23

6.3.5.4 Cyclization of Divinyl Ketones from Alkynic Alcohols

Moving one step further back in the synthetic sequence towards cyclopentenones identifies the alkynic alcohols as viable precursors. Since the subsequent dehydration–hydration–cyclization steps are all acid-



(27)

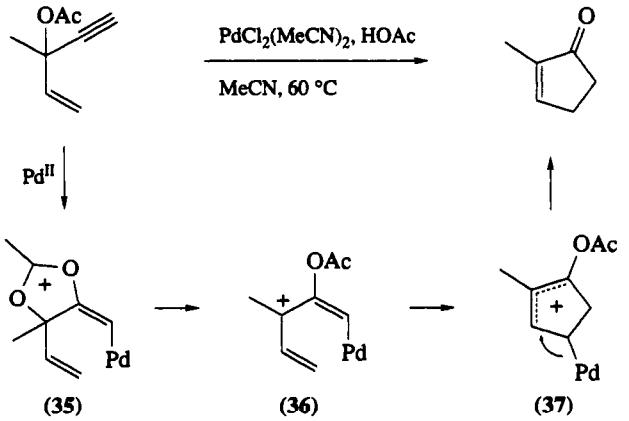
i, Bu^{n}Li; ii, 3-trimethylsilyl-2-propenal; iii, Ac_2O, Py; iv, KOBu^t

catalyzed processes, suitable conditions are easily identified. An alternative pathway may involve direct formation of an allyl vinyl ketone by Rupe rearrangement.[121] This approach has been applied exclusively to monocyclic substrates. The variation in precursor structure derives from the functionality present on the alkynic unit.

6.3.5.4.1 Enynol precursors

Treatment of the vinylacetylene–ketone addition products (**33**; equation 26) with hot phosphoric acid or methanolic sulfuric acid induces the cascade to the ring fused systems.[11,25,31,122] With unsymmetrical ketones a mixture of regioisomers results.[34]

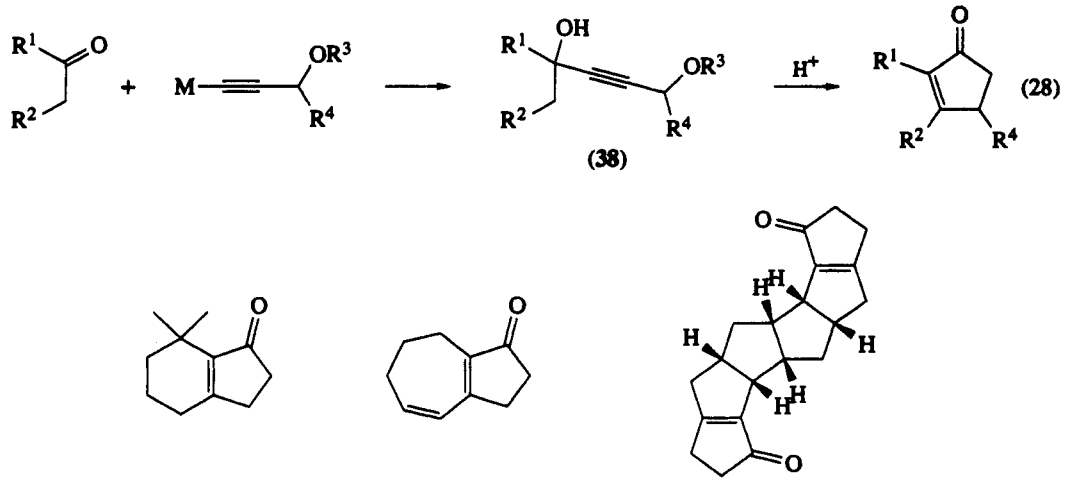
A interesting variation on this theme employing the isomeric enynol acetates (Scheme 24) has been developed by Rautenstrauch.[123] The cyclizations are induced by a Pd^{II} catalyst in warm acetonitrile. The proposed mechanism is intriguing. Reaction is initiated by an anchimerically assisted palladation to (**35**) followed by opening the dioxolenium ion to a pentadienylic cation (**36**). The closure of (**36**) is analogous to the silicon-directed Nazarov cyclization in the ejection of the Pd^{II} electrofuge from (**37**). Both secondary and tertiary acetates can be employed as well as both acyclic and monocyclic systems.



Scheme 24

6.3.5.4.2 Ynediol precursors

For many years the preferred method for cyclopentannulation involved the acid-catalyzed transformation of ynediols (**38**) derived from addition of propargylic alcohol derivatives to ketones (equation 28). This strategy likely involves Rupe rearrangement to the β′-hydroxy enone followed by facile β-elimination to the requisite divinyl ketone. The conditions employed for this variant are generally milder, rarely requiring elevated temperatures. For acid catalysts, methanolic sulfuric acid, phosphoric acid and formic acid are generally employed. Eaton[124,125] has recommended the P_2O_5–$MeSO_3H$ system for this transformation, which has been used successfully by others.[126,127] A representative sampling of structures obtained from the many examples of this reaction is collected in Scheme 25. Acyclic and monocyclic precursors of five-,[129] six-,[126,128,130–132] seven-,[128] eight-[128] and twelve-membered rings[128,133–135] have been employed. Eaton[124] and McKervey[127] have reported double annulation of symmetrical tetraols in their approaches to dodecahedrane. The hexaquinacene in Scheme 25 was prepared by two sequential double annulations.[127]

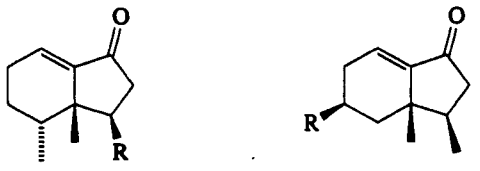


(38)

53% (ref. 126) 49% (ref. 128) 45% (ref. 127)

Scheme 25

The issue of relative stereogenesis has been studied in the context of this variant by Hiyama.[128] The preferred mode of electrocyclization is independent of substitution position but sensitive to the nature of the substituent. Thus conrotation produces the *trans* isomer of 1,2-disubstituted systems (**39**) and the *cis* isomer of 1,3-disubstituted systems (**40**) albeit with lesser selectivity (Scheme 26). The divergence of the stereochemical outcome here from that described in the SDNC (Section 6.3.4.3) arises from the consequences of the β-methyl group on ring conformation and avoidance of eclipsing interactions.



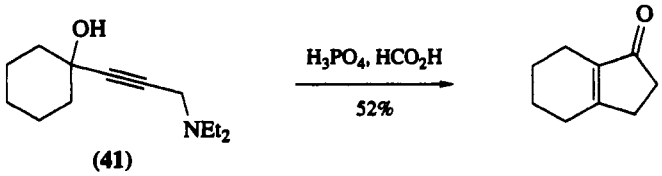
(39) (40)

R = H, 60% R = Pr^i, 64%, *cis*/*trans* = 83/17

R = Me, 67% R = CO_2Me, 60%, *cis*/*trans* = 60/40

Scheme 26

The first example of this general process is due to Raphael[55] who, inspired by the mechanistic thinking of Braude,[48] suggested that alkynic amino alcohols (**41**) should serve to produce the desired divinyl ketone intermediates (equation 29). The reaction was found suitable for five-, six- and seven-membered ring monocyclic precursors, but the yields were low.

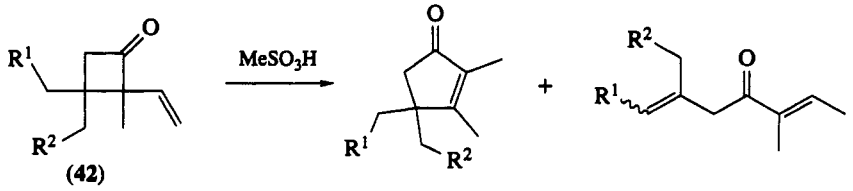


(41) (29)

A higher oxidation state product is obtained by the analogous cyclization of propargylic acetals.[136] Unfortunately, the location of the additional unsaturation cannot be controlled.

6.3.5.5 Cyclization of Divinyl Ketones from α-Vinylcyclobutanones

In 1983 Dreiding reported a general synthesis of α-vinylcyclobutanones (**42**) by the direct cycloaddition of vinylketenes and simple alkenes.[137] These strained compounds are prone to various rearrangement reactions. In the β,β-disubstituted series, treatment with catalytic amounts $BF_3{\bullet}OEt_2$ or $MeSO_3H$ results in the formation of divinyl ketones. If a full equivalent of $MeSO_3H$ is used the major product is the cyclopentenone arising from Nazarov cyclization (equation 30). The reaction is very sensitive to substitution pattern as four different classes of products arising from different pathways have been identified.[138,139]



(30)

(**42**)

$R^1 = Pr^n$; $R^2 = H$	65%	11%
$R^1 = R^2 = CH_2$	71%	3%

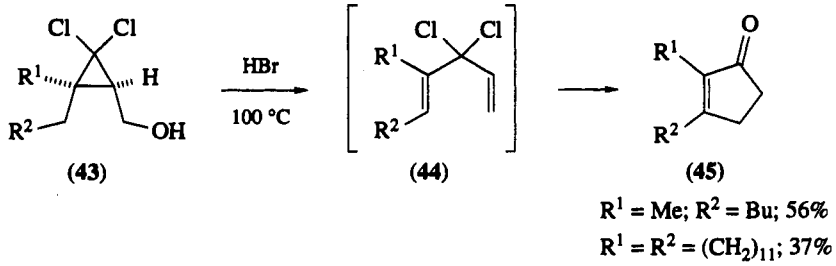
6.3.6 CYCLIZATION OF DIVINYL KETONE EQUIVALENTS FROM SOLVOLYSIS

A variety of different precursors have been shown to rearrange to divinyl ketones or equivalent species under highly ionizing acidic conditions. Equivalents of both cross-conjugated and linear dienones have been generated and cyclize to cyclopentenones *in situ*. The structural diversity of substrates in this class is remarkable and testifies to the utility of these ring-forming reactions which are unified by the propensity for cationic electrocyclization.

6.3.6.1 Solvolysis of Geminal Dichlorides

6.3.6.1.1 Dichlorocyclopropylcarbinols

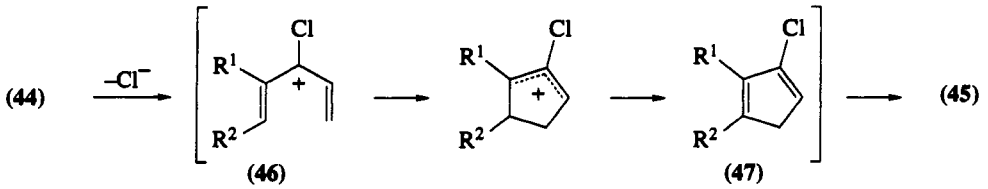
The development of phase transfer catalysis greatly improved the generation of dichlorocarbene and increased the availability of dichlorocyclopropanes for synthesis.[140] Dichlorocyclopropanation of trisubstituted allylic alcohols proceeds cleanly. Heating the dichlorocyclopropylcarbinols (**43**) in 47% hydrobromic acid at 100 °C produces cyclopentenones in good yields (Scheme 27).[141,142] The reaction is proposed to proceed by cyclopropylcarbinyl cation ring opening to the divinyl geminal dichloride (**44**). Chloride ionization to the pentadienylic cation (**46**) initiates the electrocyclization to a chlorocyclopentadiene (**47**) which hydrolyzes to a cyclopentenone *in situ*.



(**43**) (**44**) (**45**)

R^1 = Me; R^2 = Bu; 56%

$R^1 = R^2 = (CH_2)_{11}$; 37%

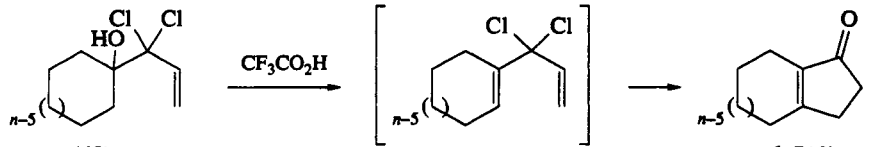


(**46**) (**47**)

Scheme 27

6.3.6.1.2 Geminal dichloro homoallylic alcohols

As a test of the intermediacy of the divinyl dichloride (**44**) in the solvolysis of dichlorocyclopropylcarbinols, Hiyama[143] prepared the homoallylic alcohols (**48**) by addition of 1,1-dichloroallyllithium to cyclic ketones. Treatment of (**48**) with trifluoroacetic acid produced the cyclopentenones in very good yield (equation 31).[143] This reaction presumably proceeds by dehydration to the divinyl dichloride followed by a similar ionization–cyclization sequence. Interestingly the regioisomeric dichloride also underwent closure to a cyclopentenone.[142]

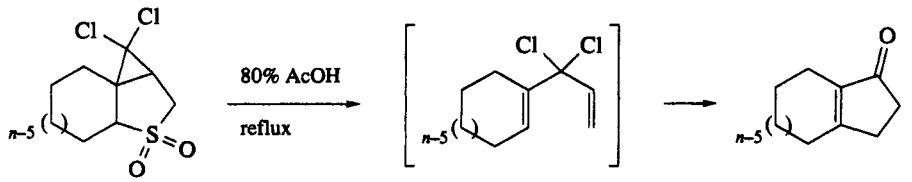


(48)

$n = 6$, 71%
$n = 7$, 87%
$n = 12$, 90%

(31)

In a related study Gaioni[144] generated the divinyl dichloride by cheletropic extrusion of sulfur dioxide from the dichlorocarbene/3-sulfolene adduct (**49**). Under the reaction conditions the divinyl dichloride solvolyzes to the cyclopentenone as outlined previously (equation 32).



(49)

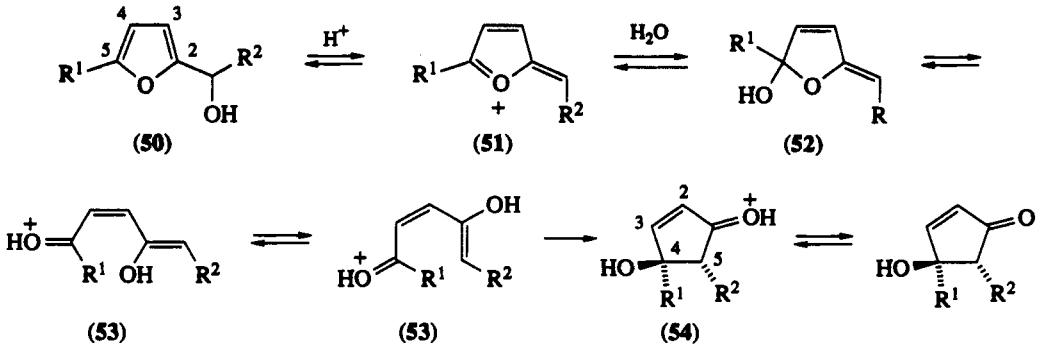
$n = 6$, 26%
$n = 7$, 80%
$n = 10$, 60%

(32)

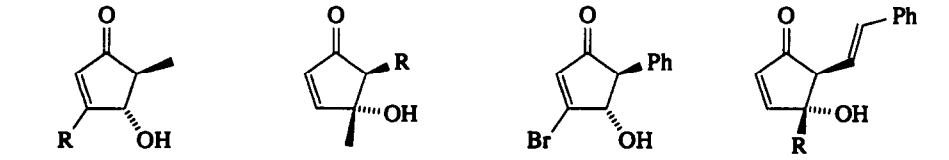
6.3.6.2 Solvolysis of 2-Furylcarbinols

The acid-catalyzed rearrangement of 2-furylcarbinols to 4-hydroxy-2-cyclopentenones was first described by Piancatelli[145] and subsequently investigated by him in detail.[146–152] The precursors are readily available from either Grignard synthesis with furfural or addition of 2-furyllithium to aldehydes. The facility of rearrangement is dependent upon ring substitution and differing reagents are recommended.

For bromo or unsubstituted furans, sulfuric acid is used, while for alkyl-substituted furans, zinc dichloride is most effective. The mechanism for this conversion is depicted in Scheme 28. Acid-catalyzed rearrangement of (**50**) to (**52**) provides access to the open oxocarbenium ion (**53**). This cation is seen as a 1-hydroxypentadienylic cation. Conrotatory closure of (**53**) generates a 1-hydroxycyclopentenylic cation (**54**) which is deprotonated to form the final product. A key feature of this reaction is the creation of the *cis* double bond in (**53**) from the opening of (**52**). The thermodynamically more stable *trans* isomers cannot cyclize. A representative assortment of structures prepared by this route is found in Scheme 29. The furyl carbinyl substituent (R^2) becomes the 5-substituent in the product. Substituents on furan positions 3,4 and 5 reside on cyclopentenone positions 2,3 and 4, respectively. The 4-hydroxy group and the 5-substituent are always *trans* in the product. Assuming the reactions are under kinetic control, this is a reflection of the preferred configuration of the 1-hydroxypentadienyl cation (**53**). Extension of this reaction to furfurylidenecarbinols in an approach to prostanoids was only moderately successful as other electrocyclic processes involving the furan ring intervened.[151]



Scheme 28



R = H, 30% (ref. 145); R = Br, 81% (ref. 150)

R = Bu^n, 18% (ref. 148); R = Ph, 70% (ref. 148)

85% (ref. 150)

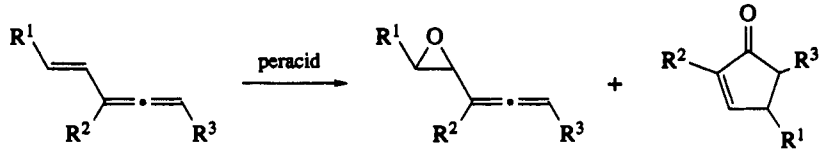
R = H, 65% (ref. 151); R = Me, 30% (ref. 151)

Scheme 29

6.3.6.3 Solvolysis of Vinylallenes and Derivatives

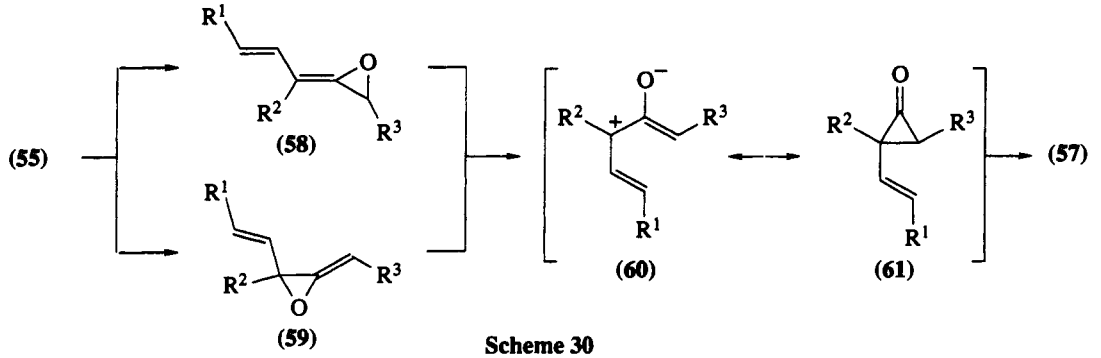
6.3.6.3.1 Epoxidation of vinylallenes

Treatment of vinylallenes (**55**) bearing no allylic substituents with peracids results in epoxidation of the vinyl group. However, if the allene is substituted, the major product is a cyclopentenone (**57**; equation 33).[153,154] The mechanistic details of this transformation are still obscure. It is well known that allenes generally react with epoxidizing agents at the more substituted double bond.[155] In this case, however, it is difficult to distinguish the two possible pathways since the regioisomeric epoxides (**58**) and (**59**) can lead to the same zwitterionic intermediate (**60**) or cyclopropanone (**61**; Scheme 30). A concerted pericyclic process directly converting (**59**) to (**57**) was also put forward in the original work. Experimental support for the concerted pathway was forthcoming in the transformation of optically active (*R*)-allene (**62**) to optically active (*S*)-2,5-dimethyl-2-cyclopentenone (**63**; 15% *ee*; equation 34).[156] Unfortunately the enantiomeric purity of (**62**) was not determined. Nevertheless, this is not consistent with the intermediacy of achiral intermediates such as zwitterion (**60**), but rather with a thermally allowed $[\pi 2_s + \sigma 2_a + \pi 2_a]$ process. Goré has also described a photooxygenation procedure to achieve the same net transformation.[157] A collection of representative structures prepared by this method is found in (Scheme 31).[153,158–162] Both simple and fused cyclopentenones are available in modest yield. The precursor vinylallenes are obtained in various substitution patterns by hydrolysis of vinyl allenic Grignard reagents[163] or S_N2' substitution on propargylic sulfonate or halides.[164]



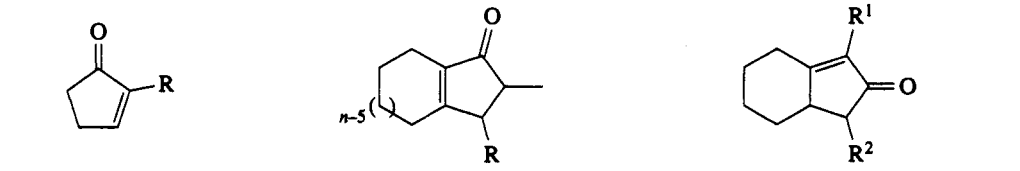
(55) (56) (57) (33)

$R^1 = Pr^n$; $R^2 = R^3 = H$	55%	0%
$R^1 = R^3 = H$; $R^2 = Pr^i$	0%	60%
$R^1 = R^2 = H$; $R^3 = Pr^n$	3%	57%



Scheme 30

(34)



R = Me, 60% (ref. 153)
R = Bu^n, 60% (ref. 157)

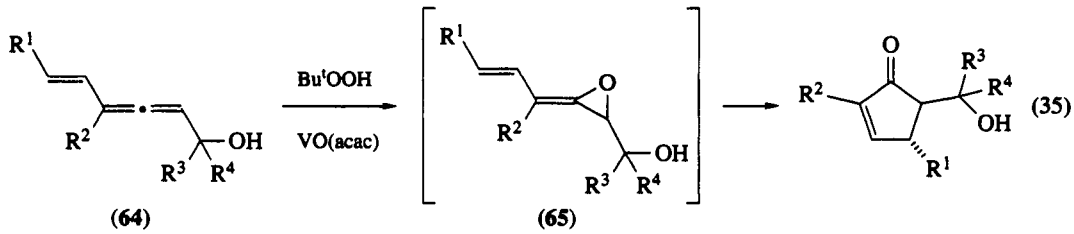
R = Me; n = 6; 50% (ref. 158)
R = H; n = 12; 52% (ref. 161)

$R^1 = R^2$ = Me; 50% (ref. 158)
R^1 = n-C_5H_{11}; R^2 = H; 40% (ref. 157)

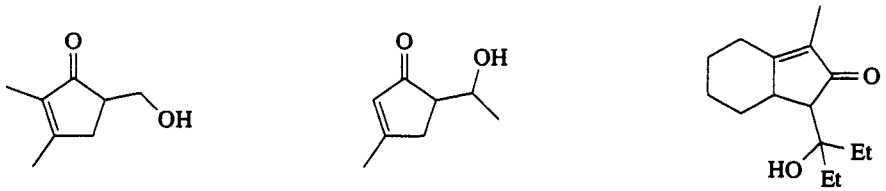
Scheme 31

6.3.6.3.2 Epoxidation of vinyl allenic alcohols

Since epoxidation at the vinyl double bond is unproductive, it is desirable to direct reaction on the allene moiety. This can be accomplished by taking advantage of the hydroxy-directed epoxidation of allylic alcohols using the *t*-butyl hydroperoxide/vanadium(V) system.[165] The directing effects of both allylic and homoallylic type hydroxy groups have been examined at both positions of the vinylallene unit.[166–168] At the 1-position (**64**), primary, secondary and tertiary allylic alcohols are effective, while only primary homoallylic alcohols have been examined (equation 35). Presumably the directing effect of the hydroxy groups favors formation of the intermediate allene oxide (**65**). A sample of the compounds prepared by this route is shown in Scheme 32.[166]



(35)



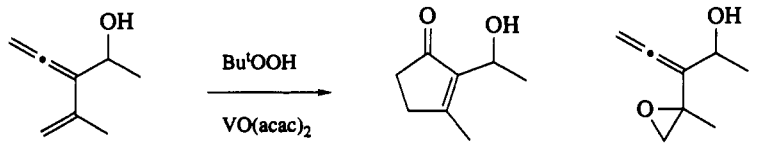
50%

55%

45%

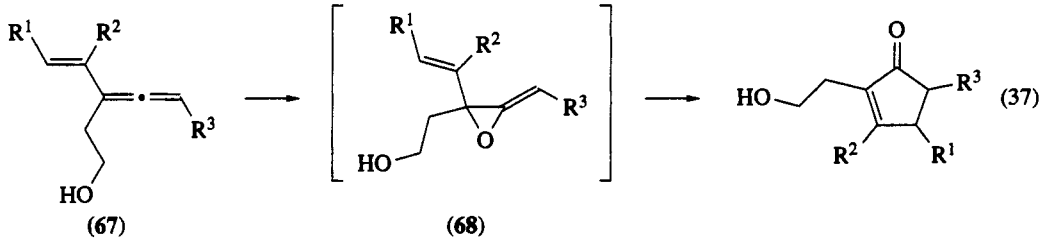
Scheme 32

Placement of the directing function at the 3-position (**66**) is also effective but regiochemistry of epoxidation is dependent upon the substitution of the hydroxy-bearing carbon. With secondary allylic alcohols the major product is the cyclopentenone with the allenyl epoxide as a minor by-product (equation 36). Tertiary alcohols give allenyl epoxides exclusively.[167]

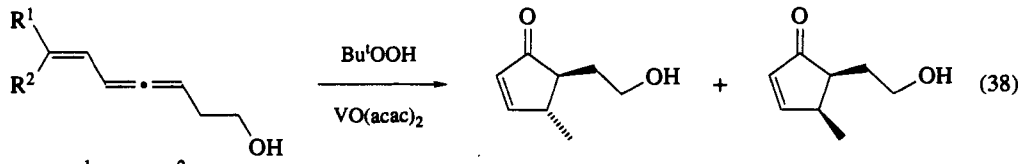


(**66**) 65% 15% (36)

Homoallylic type alcohols (**67**), on the other hand, give predominantly cyclopentenones independent of substitution (equation 37). In the 3-hydroxyalkyl-substituted systems, presumably allene oxide (**68**) is the intermediate. Thus it would appear that the initial site of allene oxidation is not critical to the success of the reaction. Either precursor (**58**) or (**59**) is expected to give the observed stereochemical relationships of the newly formed stereocenters by the concerted mechanism.[169] Finally, Cha has noted that the two intermediates may lead to different stereochemical relationships by the zwitterionic mechanism.[168] This assumes a specific pathway for breakdown of (**58**) or (**59**). That stereochemical information is preserved in the reaction is shown by the selective transformations in equation (38).



(**67**) (**68**) (37)



R^1 = Me; R^2 = H — major — minor

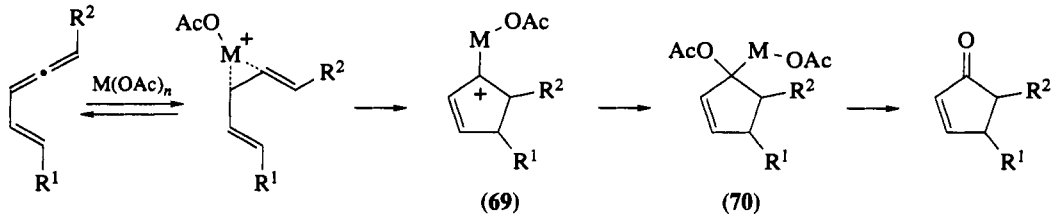
R^1 = H; R^2 = Me — minor — major (38)

6.3.6.3.3 Solvometallation of vinylallenes

A similar electrophilic activation of the vinylallene to 2-cyclopentenone cyclization is possible using either mercury(II) acetate or thallium acetate.[170,171] Solvometallation of allenes is a well studied process[155] following expected Markovnikov attack at the central carbon by the metal salt. The yield of cyclopentenones was generally higher with acetoxymercuration (49–79%) compared to acetoxythallation (25–68%). Compounds of similar substitution pattern as were investigated with epoxidation (Scheme 31) were prepared. Mechanistically the reaction is remarkable for the facility of solvodemercuration (Scheme 33). Intermediates such as (**69**) or (**70**) lose elemental mercury spontaneously in the acetic acid medium to give the 2-cyclopentenones.

6.3.6.3.4 Solvolysis of alkoxyallenyl alcohols

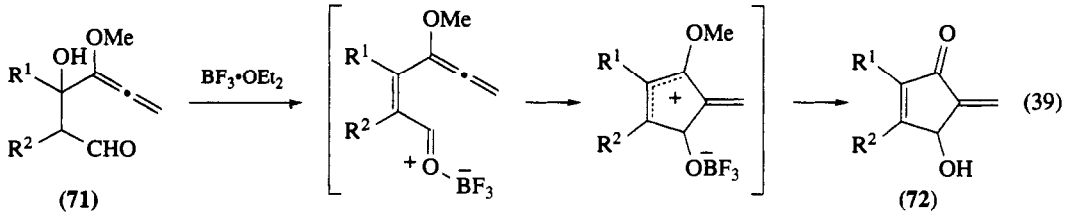
A serendipitous discovery by Tius[172] has been developed into a useful α-methylenecyclopentene annulation procedure.[173,174] In an attempted synthesis of orthoquinones, Tius treated the allenyl alcohols (**71**), derived from addition of 1-lithio-1-methoxyallene to α-silyloxymethylene ketones, with BF_3·Et_2. The product α-methylenecyclopentenones (**72**) were obtained in good yield (equation 39). The process can be



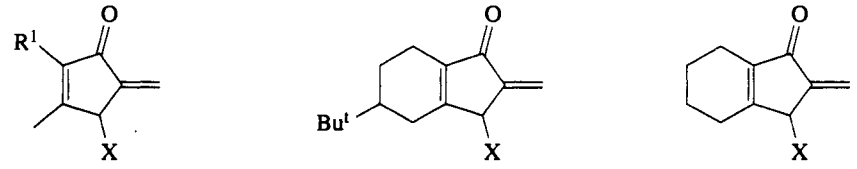
(69) (70)

Scheme 33

seen as a 1-oxypentadienyl cation cyclization (Section 6.3.6.2). This transformation has been generalized to incorporate functionalized α-methylene ketones. Scheme 34 contains a collection of the structures prepared by this route.[172] This method is extremely well suited for the synthesis of α-methylenecyclopentenone natural products.



(71) (72) (39)



R^1 = Me; X = OH; 68%
R^1 = Et; X = OH; 72%

X = OH, 76%
X = H, 56%

X = Ph, 78%
X = SPh, 82%

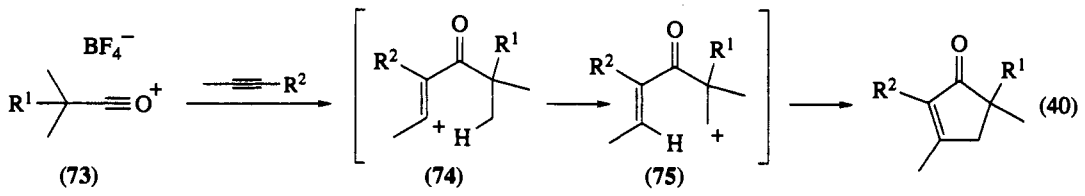
Scheme 34

6.3.7 CYCLIZATION OF DIVINYL KETONES FROM *IN SITU* CONSTRUCTION

In all of the cases in the foregoing sections the substrates employed in the cyclization reactions contained all of the requisite carbon atoms to construct the ring. The subsequent transformations primarily involved functional group manipulations to produce the divinyl ketone or its equivalent for cationic cyclization. This final section includes those processes in which the divinyl ketone is constructed by a carbon–carbon bond forming reaction followed by cyclization under the reaction conditions. With one exception these carbon–carbon bond forming reactions involve an acyl derivative and an alkene or alkyne. The categorization is by acyl derivative.

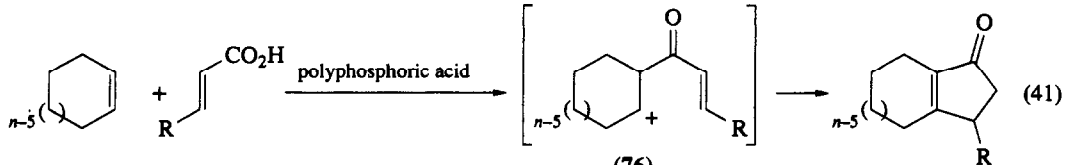
6.3.7.1 Aliphatic Acid Halides

In 1974 Schegolev[175] reported the surprising isolation of 2-cyclopentenones from reaction of *in situ* generated acylium ions (**73**) and alkynes (equation 40). Evidence for the 1,5-hydride transfer to a vinyl cation (**74**) was secured from a study of cyclohexylacylium tetrafluoroborate with alkynes. Remarkably, in this system only products derived from fluoride capture of (**75**) were isolated.[176] The reaction was pursued by Jadhav[177] using propionyl chloride/silver tetrafluoroborate and long-chain internal alkynes. The yields were poor and regioselectivity ambiguous. While structurally similar to the Nazarov cyclization, these reactions are probably not mechanistically related.



6.3.7.2 Alkenic Acids

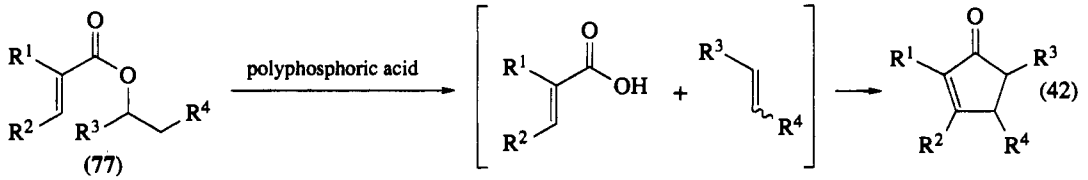
Unsaturated acylium ions generated from alkenic acids or anhydrides react with alkenes to produce cyclopentenones (equation 41).[88,178–181] With cycloheptene the major products arise from ring contraction. Again, it is unclear whether these reactions proceed *via* direct cyclization of (**76**) or a Nazarov cyclization.



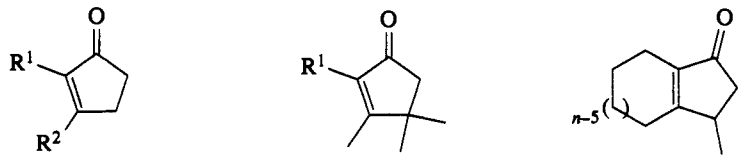
R = Me; n = 6; 60%
R = Ph; n = 6; 26%
R = Me; n = 5; 22%

6.3.7.3 Alkenic Esters

These substrates, studied exclusively by Conia,[182] are a hybrid in that they contain all of the requisite carbon atoms for the ring but still require a coupling reaction. The action of hot polyphosphoric acid on alkenic esters (**77**) may begin by cracking the alkyl carbon–oxygen bond to produce an alkene and the parent acid. This new composition is in principle identical to the Dev mixture just described, and likely proceeds similarly by acylium ion generation and electrophilic attack on the *in situ* generated alkene (equation 42).



Regiochemical ambiguities arise when R^3 and R^4 are similar groups. Another ambiguity arises due to the mobility of the cyclopentenone double bond. Thus, the same indenone (Scheme 35) is obtained by reaction of either isopropyl cyclohexenecarboxylate or cyclohexyl crotonate. The ease of preparation of the precursors allowed a broad survey of structural types. Scheme 35 contains representative structures of compounds prepared by this method.



R^1 = H; R^2 = Me; 20%
R^1 = R^2 = Me; 20%

R^1 = H, 60%
R^1 = Me, 60%

n = 5, 20%
n = 6, 60%

Scheme 35

6.3.7.4 Alkenic Acid Chlorides and Bromides

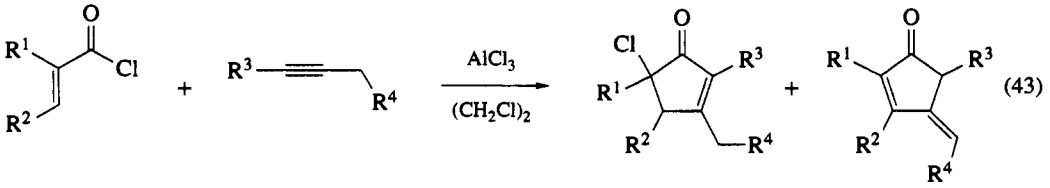
Friedel–Crafts acylation of alkenes (Darzens–Nenitzescu reaction[183]) with unsaturated acylium ions generated from acid halides and Lewis acids constitutes a general synthesis of divinyl ketones.

6.3.7.4.1 Alkenes

As in the foregoing systems, a regiochemical ambiguity arises unless the alkene is either symmetrical or highly biased toward Markovnikov-type addition. Both acid chlorides and bromides can be employed. Aluminum trichloride is the preferred reagent.[113,184] Frequently the divinyl ketone or β′-chloro enone intermediates are isolable as by-products which can be subsequently cyclized. Representative structures are similar to those collected in Scheme 35.

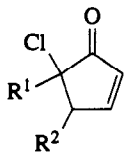
6.3.7.4.2 Alkynes

A thorough and systematic study of the reaction between unsaturated acid chlorides and alkynes has been carried out by Martin.[185–188] The major cyclic products are 5-chloro-2-cyclopentenones (**78**) and 4-alkylidene-2-cyclopentenones (**79**; equation 43). Chlorinated divinyl ketones were also isolated. Nearly all substitution patterns have been investigated with regard to their effect on the distribution of cyclic and acyclic products. Obviously with acetylene only products of the type (**78**) are formed. The yields range from 30–70% with various alkyl groups R^1 and R^2. The use of terminal alkynes results in good regiocontrol, electrophilic attack always occurring in Markovnikov fashion. The alkylidenecyclopentenones (**79**) are generally the major products with highest overall yields for α,β-disubstituted acrylates. Internal alkynes have also been studied. In these reactions the 5-chloro-2-cyclopentenones (**78**) are the major products constituting 75–100% of the cyclic material in 30–60% overall yield. These systems present a stereochemical ambiguity in unsymmetrical alkynes where both possible regioisomers are formed. Representative structures prepared by this approach are found in Scheme 36.

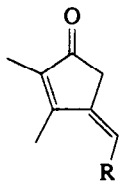


(43)

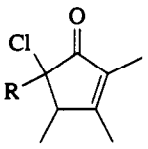
(**78**) (**79**)



$R^1 = R^2 = H$; 40%
R^1 = Me; R^2 = H; 72%
R^1 = H; R^2 = Me; 60%



R = H, 40%
R = Me, 68%

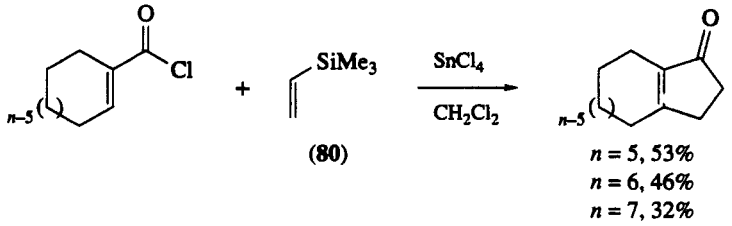


R = H, 30%
R = Me, 40%

Scheme 36

6.3.7.4.3 Trialkylsilylalkenes (vinylsilanes)

A significant advance in the use of Friedel–Crafts acylation of alkenes to prepare divinyl ketones was the employment of vinylsilanes to control the site of electrophilic substitution.[189] Two groups have developed this approach to cyclopentenone annulation using slightly different strategies. In the method described by Magnus[190,191] the reagent vinyltrimethylsilane (**80**) is used primarily as an ethylene equivalent (equation 44). The construction of bicyclic systems followed readily as Nazarov cyclization proceeded under the reaction conditions. Tin(IV) chloride was found to be the most effective promoter of the overall transformation. As expected the position of the double bond is thermodynamically controlled.

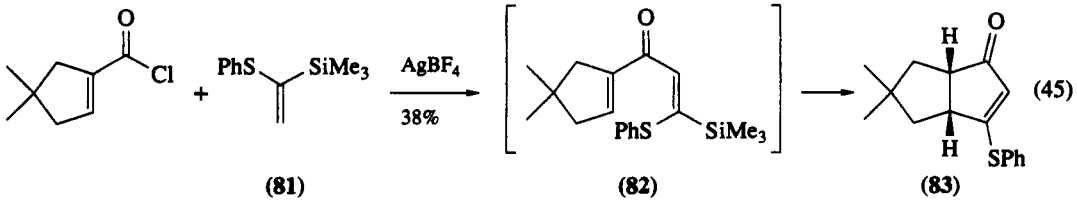


(80)

$n = 5$, 53%
$n = 6$, 46%
$n = 7$, 32%

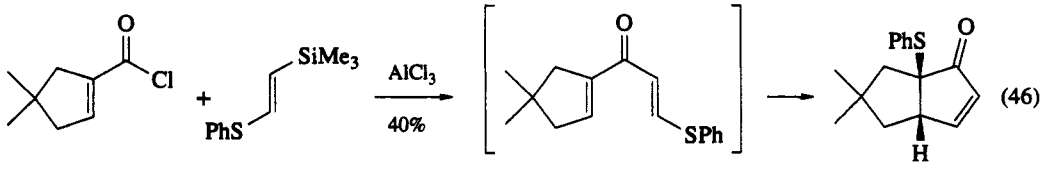
(44)

Magnus has also made use of 1-phenylthio- and 2-phenylthio-vinylsilanes to introduce additional functionality in the cyclopentenone.[192–194] These reagents behave very differently. The 1-phenylthiovinylsilane (**81**) reacts with unsaturated acid chlorides in the presence of silver tetrafluoroborate to afford 3-phenylthio-2-cyclopentenone annulated products (**83**) in modest yields. It is suggested that a silicon-directed Nazarov cyclization of (**82**) intervenes to control the placement of the double bond (equation 45). No transformations of (**83**) were reported. The 2-phenylthiovinylsilane (**84**) also reacts with unsaturated acid chlorides ($AlCl_3$ catalyst) but to afford 5-phenylthio-2-cyclopentenone annulated products (**86**; equation 46). The surprising migration of the phenylthio group is seen to result from enolate capture of the electrofugal sulfenium ion expelled in the Nazarov cyclization.



(81) (82) (83)

(45)

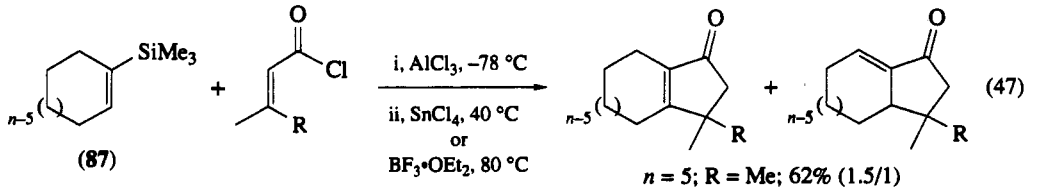


(84) (85) (86)

(46)

Vinyltrimethylsilane also reacts with substituted acryloyl chlorides to produce simple cyclopentenones in modest yield.[195] This reaction requires aluminum trichloride and 1,2-dichloroethane for optimal results.

A complementary approach, developed by Paquette,[75,76] uses substituted acryloyl chlorides as addends in reaction with structurally embellished vinylsilanes. A general route to the vinylsilanes (**87**) was found in the silylation of vinyllithiums generated by the Shapiro reaction.[196] The acylation with acryloyl chlorides takes place readily with aluminum trichloride to afford the divinyl ketones which are subsequently cyclized with tin tetrachloride. The Nazarov cyclization products were formed as a mixture of double bond isomers (equation 47). The best results were obtained with β,β-dimethylacryloyl chloride. Crotonyl chloride could be employed, but acryloyl chloride proved impractical. This method owes much of its utility to the regiocontrolled synthesis of the vinylsilanes, thereby clearly establishing the loci of cyclopentannulation.



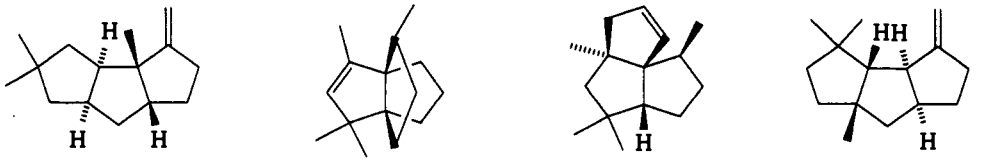
(87)

(47)

$n = 5$; R = Me; 62% (1.5/1)
$n = 5$; R = H; 58% (1/0)
$n = 6$; R = Me; 70% (1.5/1)
$n = 6$; R = H; 44% (1/0)
$n = 7$; R = Me; 57% (1/3.5)

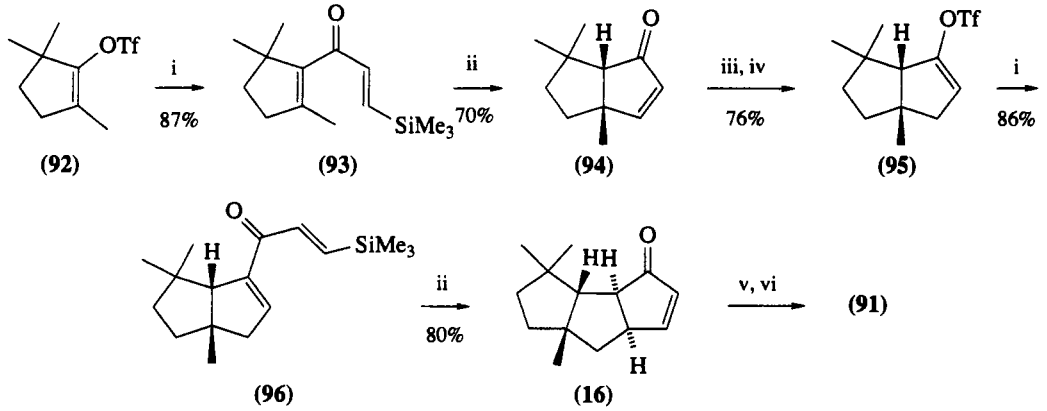
6.3.8 APPLICATIONS IN SYNTHESIS

The Nazarov cyclization has been featured in a variety of synthetic endeavors involving both natural and unnatural[124,125] products. In the area of polyquinane natural products (±)-hirsutene (**88**),[194] (±)-modhephene (**89**),[197,198] (±)-silphinene (**90**),[129] (±)-$\Delta^{9(12)}$-capnellene (**91**)[107] and (±)-cedrene,[199] have all been prepared (Scheme 37). The synthesis of (**91**) is noteworthy in the iterative use of the silicon-directed Nazarov cyclization. The divinyl ketones were constructed by the carbonylation–coupling of enol triflates (**92**) and (**95**) with the β-silylvinylstannane (Scheme 38). The diquinane (**94**), obtained from Nazarov cyclization of (**93**), was transformed into enol triflate (**95**) which was coupled with the β-silylvinylstannane as before. Silicon-directed Nazarov cyclization of (**96**) was highly diastereoselective to provide the *cis,anti,cis* isomer of (**16**). The synthesis was completed by routine manipulations.



(**88**) (**89**) (**90**) (**91**)

Scheme 37

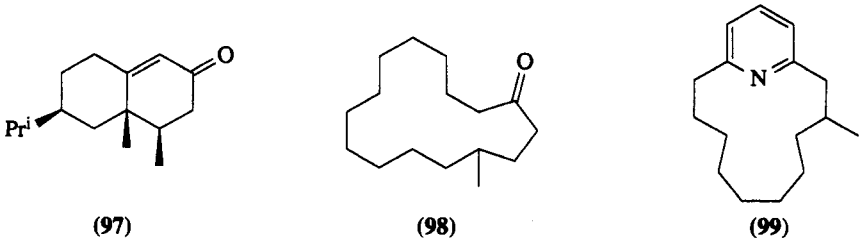


(**92**) (**93**) (**94**) (**95**) (**96**) (**16**)

i, 3-trimethylsilylvinyltrimethylstannane, $Pd(Ph_3P)_4$, CO; ii, $BF_3{\cdot}OEt_2$; iii, $LiBu^s{}_3BH$; iv, Tf_2O; v, H_2; vi, $Ph_3P{=}CH_2$

Scheme 38

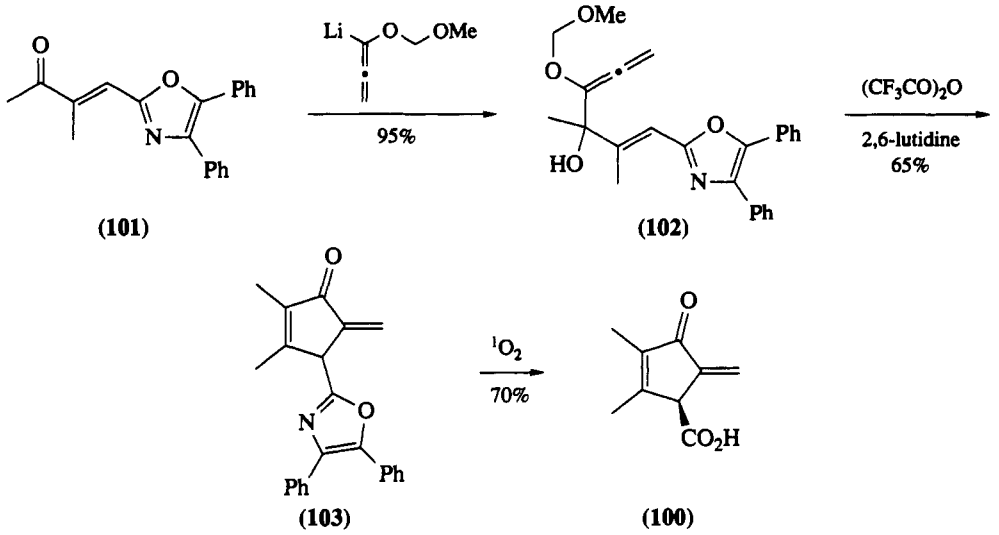
The acetylene-based route (Raphael–Nazarov cyclization) has been used successfully to construct the five-membered rings in (±)-strigol[126] and (±)-norsterepolide.[131] This variant has also been used to perform a cyclopentenone annulation towards the construction of other sized rings in (±)-nookatone (**97**),[128] (±)-muscone (**98**)[133,184] and (±)-muscopyridine (**99**)[128] (Scheme 39). In the nookatone synthesis, the Nazarov cyclization served to set the stereochemical relationship between the isopropyl group and the ring fusion. A carbenoid ring expansion completed the synthesis. Since cyclododecanone is inexpensive, three-carbon ring expansion methods have been developed for the synthesis of (±)-muscone and (±)-muscopyridine.



(**97**) (**98**) (**99**)

Scheme 39

For the construction of simple cyclopentanoid natural products, the Nazarov cyclization has been employed in the synthesis of *cis*-jasmone[141] and prostaglandin analogs[148,149,177] and (±)-vallerenal.[162] Tius has made good use of his cationic α-methylenecyclopentene forming process in the synthesis of the related natural products (±)-methylenomycin B, (±)-deepoxy-2,3-didehydromethylenomycin A (**100**)[173] and (±)-xanthocin.[174] The facile construction of (**100**) illustrates the utility of the method (Scheme 40). Addition of 1-lithioallenylmethoxymethyl ether to enone (**101**) produced the allenyl alcohol (**102**). Cationic cyclization of (**102**) was induced by treatment with trifluoroacetic anhydride to afford the α-methylenecyclopentenone (**103**) in 65% yield. Photooxidative removal of the isoxazole[200] revealed the carboxy group and completed the synthesis.

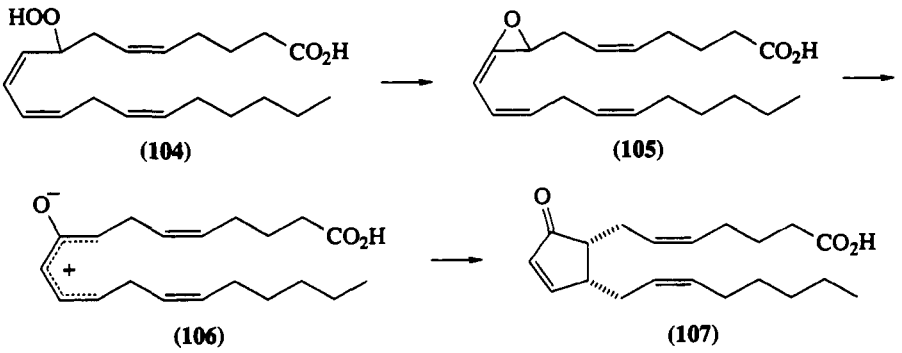


(**101**) (**102**) (**103**) (**100**)

Scheme 40

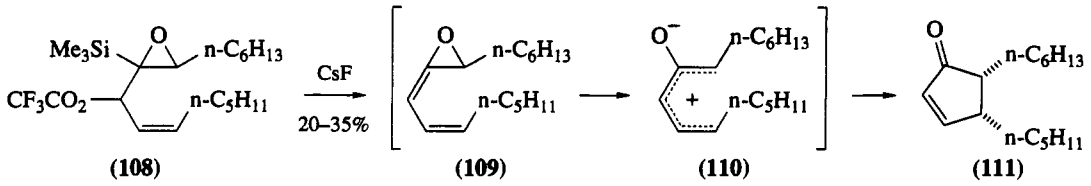
The Nazarov cyclization has also been used industrially. In the Merck synthesis of (+)-indacrinone the indanone unit is formed by an aromatic Nazarov cyclization.[201]

Finally, there has been speculation and recent experimental support for the involvement of a Nazarov-type cyclization in the biosynthesis of *cis*-jasmonic acid[202,203] and marine-derived prostanoids.[204] Radiolabel tracer studies have demonstrated the intermediacy of 8-HPETE (**104**) in the biosynthesis of prostanoid intermediate preclavulone A (**107**).[204] This remarkable conversion was proposed to proceed by formation of allene oxide (**105**) followed by isomerization to (**107**) *via* the 2-oxidocyclopentadienyl cation (**106**; Scheme 41). To demonstrate the chemical feasibility of this proposal, Corey reported the transformation of epoxysilane (**108**) to, *inter alia*, the cyclopentenone (**111**; Scheme 42).[71] The reaction is presumed to involve formation of the allene oxide (**109**)[205] followed by isomerization to the 2-oxidopentadienylic cation (**110**). Conrotatory closure of (**110**) is expected to produce the *cis* isomer of (**111**) as observed.



(**104**) (**105**) (**106**) (**107**)

Scheme 41



(108) (109) (110) (111)

Scheme 42

Strong experimental support for the biochemical pathway is provided by the isolation and characterization of the allene oxide (**105**) by Brash.[206] Further, solvolysis of (**105**) produced (**107**) along with α-ketols.[207,208] The biochemical mechanism for formation of an allene oxide from 8-HPETE remains to be clarified.

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7.1
Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements

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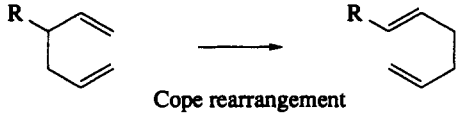
7.1.1 INTRODUCTION

The Cope rearrangement,[1] discovered in 1940 by Arthur C. Cope early in his outstanding career, comprises the thermal rearrangement of 1,5-dienes to isomeric 1,5-dienes (equation 1). Today it is recognized as the prototype all-carbon member of a large family of related rearrangements which include the Claisen, aza-, thia- and phospho-Claisen rearrangements, rearrangements of allylic esters, and a number of other variations collectively classified as 3,3-sigmatropic rearrangements.



Cope rearrangement (1)

The special value of the Cope rearrangement in modern organic synthesis is due to the following characteristics, which provide a remarkable degree of specificity.

(i) The parent Cope rearrangement is effected thermally, without any requirement for acid or base catalysis, and can thus accommodate a wide variety of functional groups.

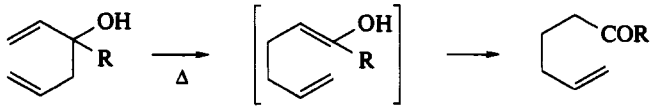
(ii) In creating a new C—C single bond at the expense of an existing bond in the substrate, the rearrangement generates 1,5-dienes in which the location of the new single bond and two double bonds is fixed unambiguously and predictably. The Cope rearrangement produces not only acyclic dienes but also cyclic dienes in rings of seven or more members, and is one of the most powerful methods of synthesis of medium rings.

(iii) Due to the highly ordered cyclic transition state the reaction is extremely stereospecific with respect both to the formation of unsymmetrical double bonds and to the creation of stereogenic centers. The substrate may have as many as four elements of stereochemistry in the six-carbon framework (two unsymmetrical double bonds and two asymmetric centers at the saturated carbons), and these are translated to four new elements, usually with near quantitative asymmetric transmission.[2]

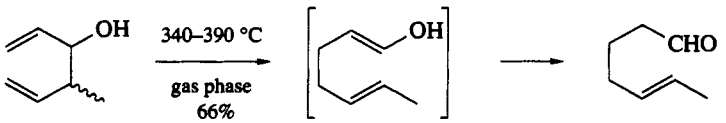
(iv) The development of the oxy-Cope and anionic oxy-Cope reactions has greatly extended the utility of the Cope rearrangement by allowing easier access to diene substrates, lowering the temperature required for rearrangement, and producing carbonyl products irreversibly.

7.1.1.1 Oxy-Cope Rearrangement

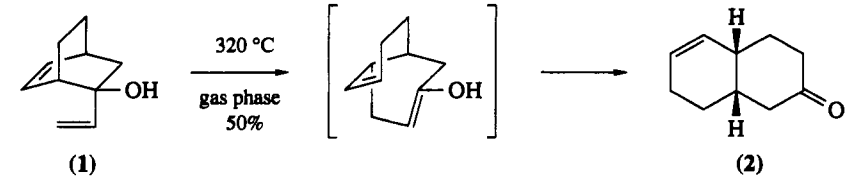
Infrequent synthetic application of the Cope rearrangement was made in the first two decades following its discovery, probably for obvious reasons: the general methods available for the preparation of the 1,5-diene substrates could often be applied just as easily to the direct synthesis of the Cope product, making the rearrangement superfluous. This situation changed drastically with the discovery of the oxy-Cope rearrangement in 1964. Berson and Jones[3] pointed out that substitution of a hydroxy group at carbons C-3 or C-4 of a 1,5-diene resulted, after rearrangement, in an enol whose tautomerization led irreversibly to a δ,ε-unsaturated carbonyl compound (equation 2). Examples of oxy-Cope rearrangement are shown in equations (3)–(5). As these equations illustrate, several advantages accrue from carrying out the rearrangement as the oxy-Cope variation: (i) the Cope substrate is easily prepared by Grignard-type addition, either of a vinyl organometallic reagent to a β,γ-unsaturated carbonyl compound or of an allylic reagent to an α,β-unsaturated carbonyl compound; (ii) the oxy-Cope rearrangement is irreversible; (iii) the product of oxy-Cope rearrangement has two different functional groups, easily manipulated for further synthetic purposes.



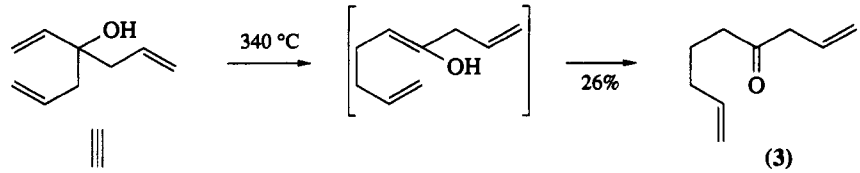
oxy-Cope rearrangement (2)



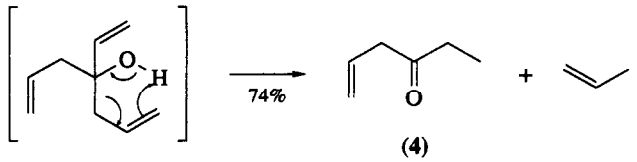
(ref.4) (3)



(1) (2) (ref.3) (4)

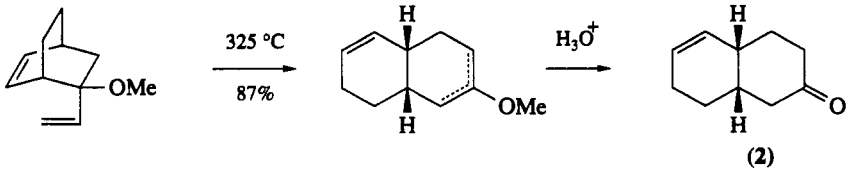


(3) (ref.5) (5)



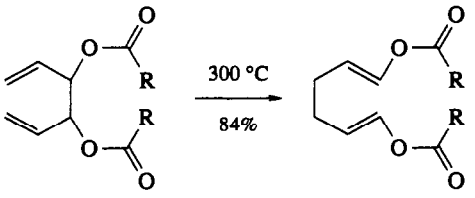
(4)

The principal drawback of the oxy-Cope rearrangement is the competing fragmentation of the substrate *via* a thermal retro-ene reaction, as seen in equation (5), where the Cope product (**3**) is overshadowed by the retro-ene product (**4**), an almost inevitable competitor whenever geometrically possible. In simple substrates fragmentation is frequently the major thermal pathway. One logical solution to this problem is to protect the hydroxy group as an ether or ester. Examples of the oxy-Cope rearrangement of methyl ethers and esters are shown in equations (6)[6] and (7),[7] which illustrate the good yields possible with protected alcohols.



(6)

(2)



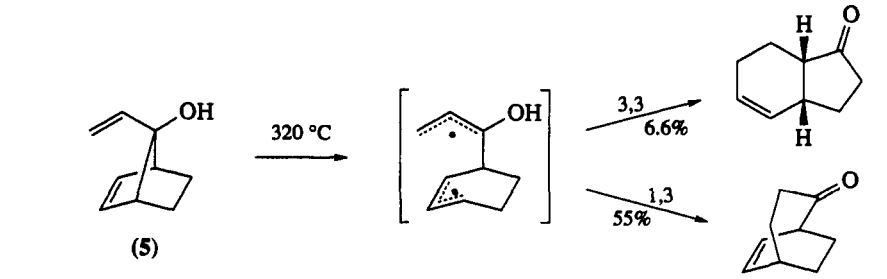
(7)

$R = CHMe_2$

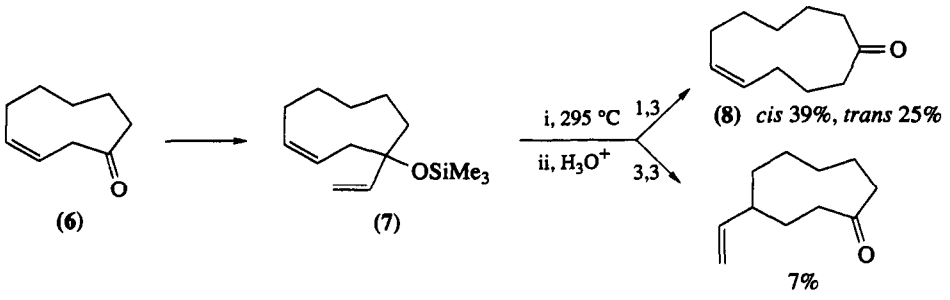
It has also been observed that higher yields of oxy-Cope products are often obtained when *N*-methylpyrrolidone is added to the solvent,[8] probably interfering with inter- or intra-molecular hydrogen bonding.

The oxygen substituent has another important effect on the oxy-Cope process: Berson and Walsh[9] have shown that, at least in bridged bicyclic substrates of type (**5**), the hydroxy group lowers the bond dissociation energy by 24 kcal mol^{-1} (1 cal = 4.18 J). This is sufficient to change the mechanism from a concerted one to a stepwise diradical process, which in turn may lead to significant amounts of 1,3-rearrangement as well as 3,3-rearrangement (equation 8).[9]

Thies[10] has shown that the 1,3-oxy-Cope rearrangement can be used to advantage as a two-carbon ring expansion method (equation 9).[10] Addition of vinyllithium to a cyclic β,γ-unsaturated ketone (**6**), followed by pyrolysis of the TMS ether (**7**) of the resulting alcohol, gives predominantly the 1,3-rearrangement product (**8**).



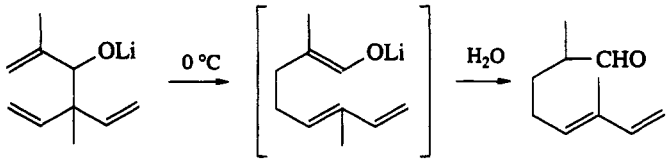
(8)



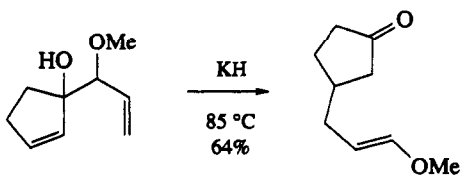
(9)

7.1.1.2 Anionic Oxy-Cope Rearrangement

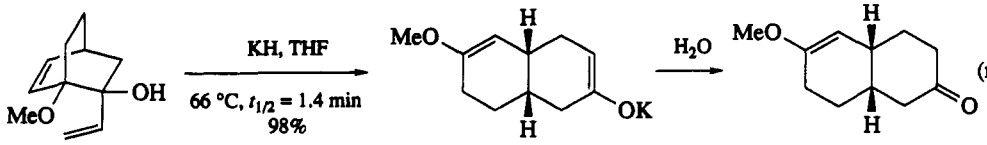
A major advance in synthetic applications of Cope rearrangements occurred in 1975, when Evans and Golob[11] reported their remarkable finding that rate enhancements of 10^{10}–10^{17} in oxy-Cope rearrangements can be achieved by using the 1,5-diene alkoxide as substrate. Sodium and, especially, potassium alkoxides were found most effective. Some examples of anionic oxy-Cope rearrangements are shown in equations (10)–(12), where the relatively mild reaction conditions required to induce rearrangement are indicated.



(ref.12) (10)



(ref.13) (11)

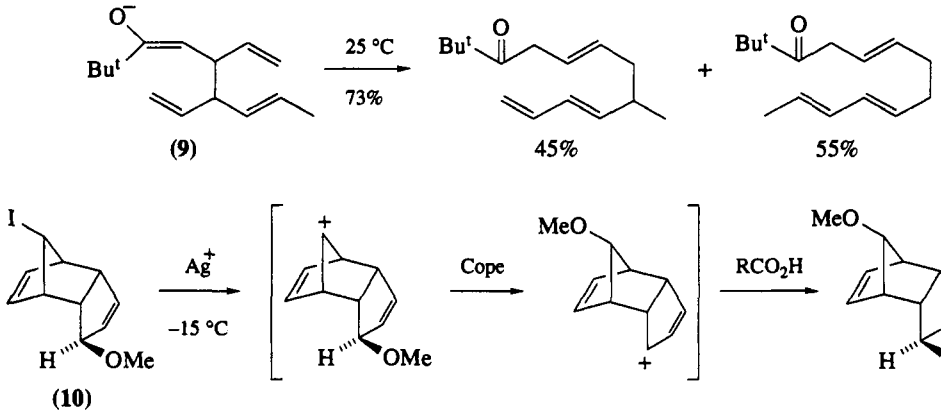


(ref.11) (12)

A simplistic explanation of the rate acceleration provided by the alkoxide ion is that in the product, as an enolate, the negative charge is much more delocalized than in the alkoxide substrate. Theoretical calculations, however, show that the primary effect of the alkoxide is to weaken the carbon–carbon single bond,[14] rather than an effect on the transition state. The oxy-anion effect is seen in the gas phase as well as in solution.[15]

A simple model of substituent effects[16] predicts that both donor and acceptor groups substituted on the saturated carbons of a Cope substrate should increase the rate. Interesting examples have been published

in which either an enolate ion (**9**)[17] or a carbocation (**10**)[18] in that position does indeed dramatically accelerate a Cope rearrangement.



7.1.2 POSITION OF EQUILIBRIA IN COPE REARRANGEMENTS

Characteristic of all sigmatropic rearrangements, the Cope rearrangement is reversible; the starting and product 1,5-dienes exist at equilibrium at rearrangement temperature through a cyclic transition state. In the Claisen rearrangement the gain in energy which accompanies the conversion of a a vinyl ether double bond into a carbonyl double bond is usually sufficient to shift the equilibrium completely toward the carbonyl product, but the Cope rearrangement of the parent 1,5-hexadiene is degenerate, and so the position of equilibrium is determined by such other factors as the substitution pattern, conjugation, strain, or irreversible conversion of one diene to a more stable product. These factors are outlined below.

7.1.2.1 Alkyl Substitution

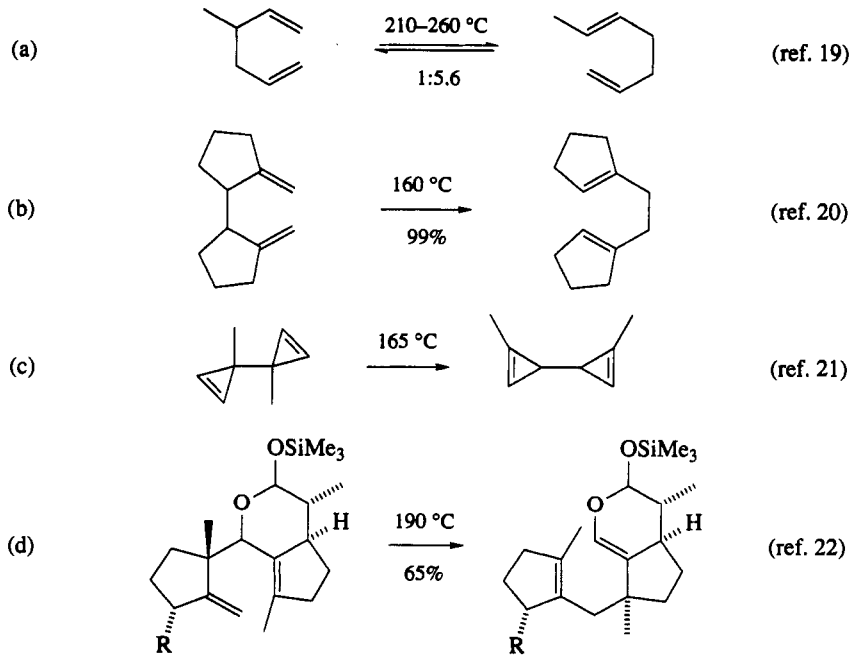
In the absence of conjugating substituents the equilibrium between isomeric 1,5-dienes will generally lie on the side of that with more-substituted double bonds, reflecting the relative stability ranking of tetra- > tri- > di- > mono-substituted alkenes. Some examples of this preference are given in Scheme 1. In each case the product contains a higher degree of alkyl substitution on the double bonds than does the starting 1,5-diene.

7.1.2.2 Conjugating Substituents

A second important factor is conjugation of one or both of the double bonds with π-substituents such as ketone, ester, cyano, or phenyl. Some examples are shown in Scheme 2. In each case the conjugated isomer heavily predominates at equilibrium.

The reactions in which Cope initially discovered this rearrangement exploit this factor and represent a strategy still useful in synthesis today, illustrated in Scheme 3. An α,β-unsaturated carbonyl compound (or cyanoacetic ester, *etc.*) is converted to the anion and alkylated with an allylic halide; alkylation of the ambident anion takes place next to the carbonyl group(s), creating a 1,5-diene. Heating then initiates the Cope rearrangement which brings the double bond back into conjugation. In equation (13) the condensation product of cyclohexanone with ethyl cyanoacetate is alkylated with allyl bromide to give the 1,5-diene (**13**); distillation at atmospheric pressure effects Cope rearrangement[28] to the conjugated isomer (**14**). Conia has used this technique extensively with α,β-unsaturated ketones. As seen in equation (14), alkylation of 2-benzyl-3-methylcyclohexenone with allyl bromide gives diene (**15**), which again rearranges[29] on heating to the isomeric conjugated ketone (**16**).

A recent variation of this strategy is due to Ziegler,[30] who used TMS ethers of cyanohydrins of α,β-unsaturated aldehydes as substrates. Alkylation with an allylic halide, such as crotyl bromide in equation (15), gave diene (**17**), which underwent Cope rearrangement on heating to afford the conjugated isomer (**18**). Work-up with KF in methanol afforded the ester (**19**) by way of an intermediate acyl cyanide.



Scheme 1 Cope equilibria in nonconjugated dienes

Equation (16) shows a practical application of this sequence to steroid synthesis; the ester (**20**) was converted by carbocation cyclization to estrone or 11-ketoprogesterone.

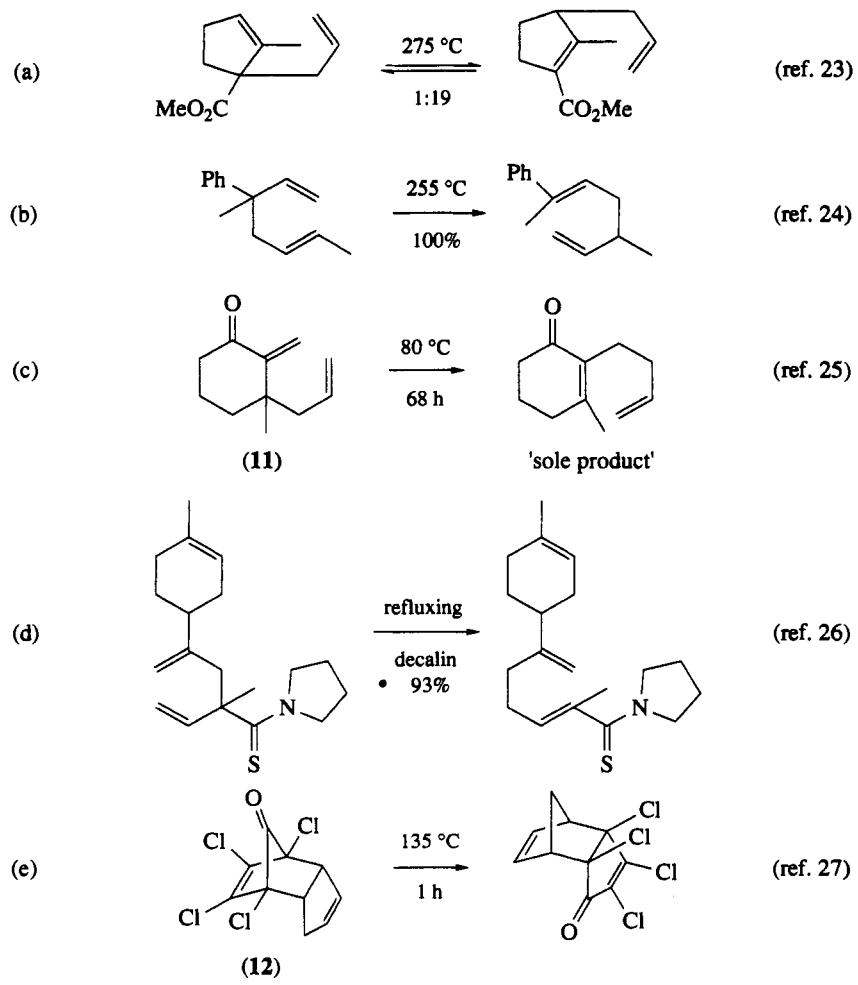
It should be noted that occasionally the preference for polyalkyl substitution of double bonds will outweigh conjugation with electron-withdrawing groups, and the Cope equilibrium then lies on the side of the nonconjugated isomer. In equation (17) the unconjugated ester (**21**) is favored by a 3:1 ratio,[23] and in equation (18) the conjugated sulfone (**22**) is converted in high yield to the unconjugated isomer.[31] In both cases the equilibrium position is apparently due to the greater degree of alkyl substitution in the nonconjugated isomers.

7.1.2.3 Aromatization of Cope Products

In some cases the driving force for Cope rearrangement may be the incorporation of one of the double bonds into an aromatic ring system. Equations (19) and (20) show two examples of generation of a five-membered aromatic nitrogen heterocycle by Cope rearrangement.[32] Indoline (**23**) rearranges readily to the indole isomer, while (**24**) rearranges, after tautomerization to the enamine (**25**), to the aromatic pyrazole (**26**).

Alternatively, a Cope product may be able to tautomerize to an aromatic ring, driving the equilibrium toward the aromatic product. A classic example is the second step in the '*para*' Claisen rearrangement of aryl allyl ethers. This step can be seen in isolated form in equation (21) in the rearrangement of 5-allyl-2,4-cyclohexadienones such as (**27**), which rearranges readily[33] to phenol (**28**). A useful modification of this principle is Evans' method[34] of introducing isoprenyl groups into quinones (equation 22). The dimethylallyl group in (**29**) is inserted by Grignard addition to a protected cyanohydrin of a naphthoquinone. Once the carbonyl group is released from the cyanohydrin TMS ether by treatment with silver fluoride, an oxy-Cope rearrangement occurs readily to give (**30**), and loss of methanol drives the equilibrium toward quinone (**31**).

Is the reverse possible, *i.e.* can a double bond of an aromatic ring participate in Cope rearrangement, destroying (at least temporarily) the aromaticity of the ring? In view of the close parallel between Cope and Claisen rearrangements, one might envision a Cope analog of the allyl aryl ether Claisen which would transfer an allyl group from a benzilic carbon to an *ortho* position on the ring (equation 23). Attempts to realize this possibility with simple benzenes have met with uniform failure, both in the parent case (R = H) or with conjugating substituents.[35] One of the few successful cases of aromatic double bond participation occurs with the thiophene (**32**) to give the rearranged isomer (**33**; equation 24);[36] the unprecedented cyclization to (**34**) which takes place at higher temperatures is also seen with naphthalene and



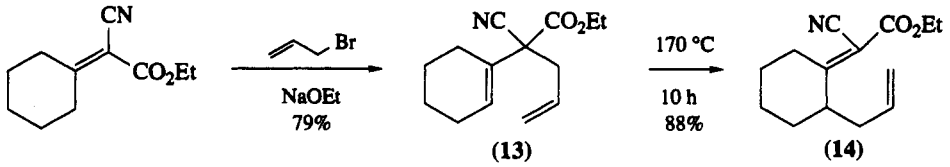
Scheme 2 Effect of conjugation on Cope equilibria

phenanthrene analogs.[37] The only example of a benzene which undergoes Cope rearrangement is phenol (**35**), in which the cyclopropane ring lowers the otherwise high activation energy required for disruption of aromaticity, affording the benzocycloheptene (**36**; equation 25);[38] heteroaromatic analogs of (**35**) rearrange even more readily.[39]

Aromatic double bonds participate somewhat more easily in oxy-Cope rearrangements, where the driving force of tautomerization to a carbonyl compound helps to compensate for loss of aromaticity. Equation (26) shows one example,[40] in which 1,3- and 3,3-oxy-Cope products are formed from naphthalene (**37**). The best cases to date have been provided by Jung and coworkers in bicyclo[2.2.1]heptenols of type (**38**), which take advantage of relief of strain in the bridged ring system as well as the oxy-Cope effect to allow double bonds of furan and naphthalene to participate.[41] Cope rearrangement of (**38**) leads to the steroid skeleton (equation 27), and an imaginative route to coronafacic acid was realized from the benzofuran analog.

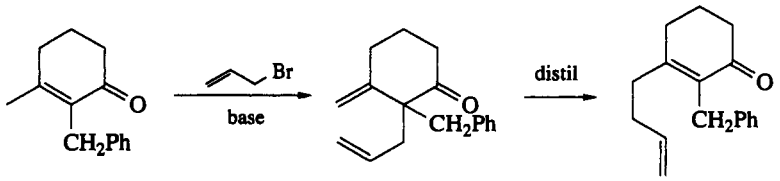
7.1.2.4 Ring Strain

A critical factor in the Cope equilibrium between a 1,2-divinylcycloalkane and cyclic diene partner is the strain associated with the particular ring sizes involved. *cis*-1,2-Divinylcyclopropanes and cyclobutanes are notorious for easy Cope rearrangements to less-strained seven- and eight-membered ring dienes, as shown in Scheme 4. *cis*-1,2-Divinylcyclopropane (**39**) undergoes a spontaneous Cope rearrangement below room temperature[42] to produce 1,4-cycloheptadiene (**40**), and *cis*-1,2-divinylcyclobutane (**41**) rearranges easily[43] to afford 1,5-cyclooctadiene (**42**). The relative strains in these two small rings are pitted against each other in the equilibrium between (**43**) and (**44**), and the equilibrium lies



(13)

(13) (14)



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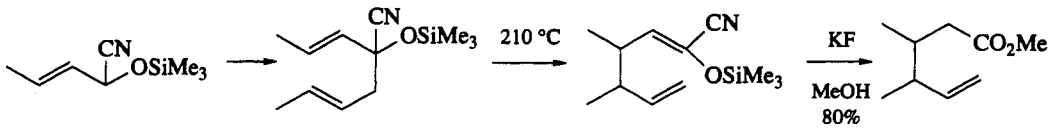
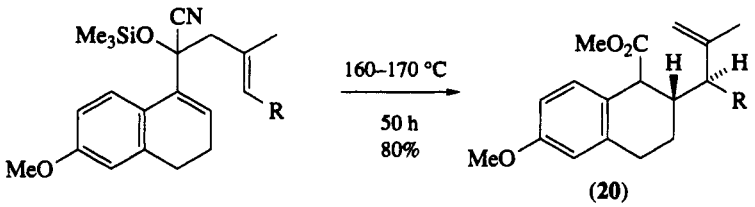
(15) (16)



(15)

(17) (18) (19)



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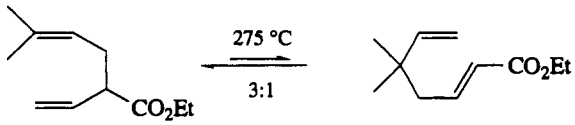

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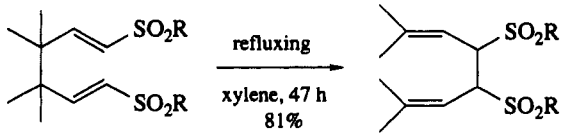
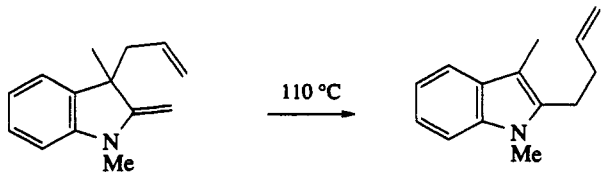


(18)

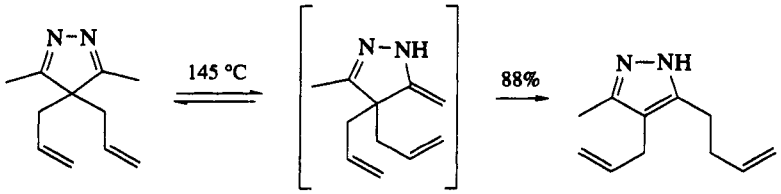
(22)

Scheme 3 Exploiting conjugation in Cope equilibria



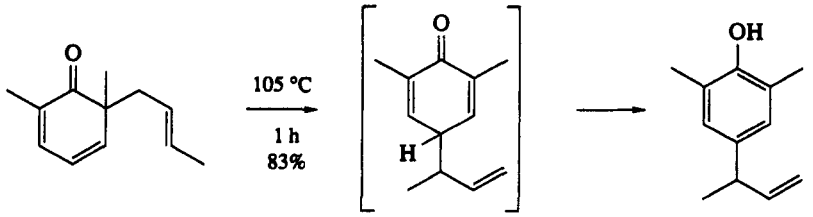
(19)

(23)

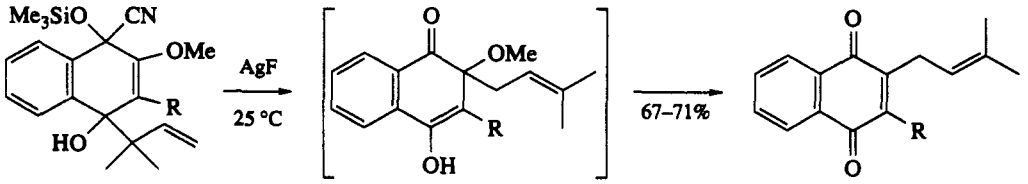


(20)

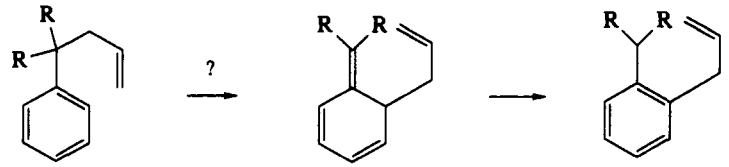
(24) (25) (26)



(27) (28) (21)



(29) (30) (31) (22)



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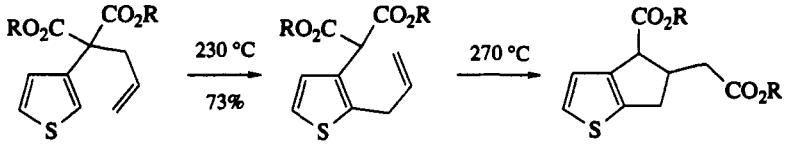
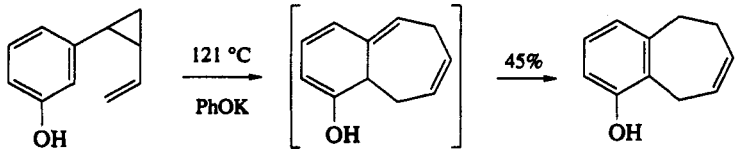
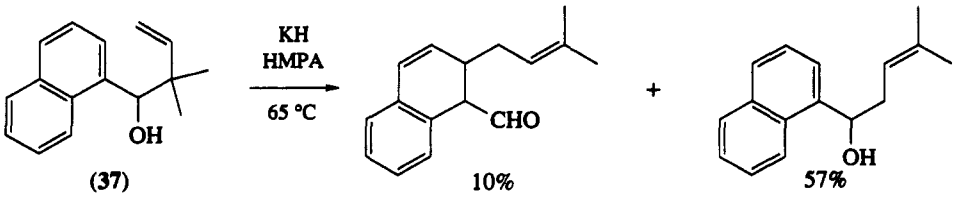


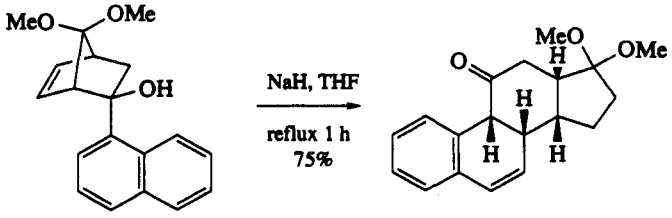
(32) (33) (34) (24)



(35) (36) (25)

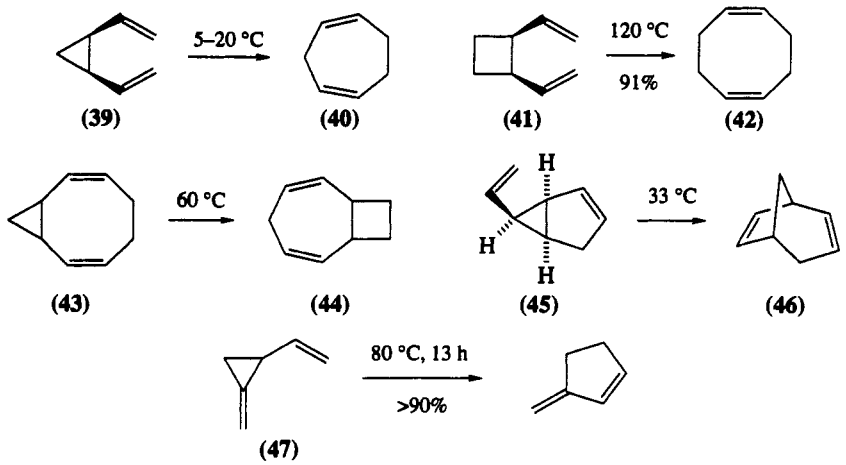


(37) 10% 3,3-shift 57% 1,3-shift (26)



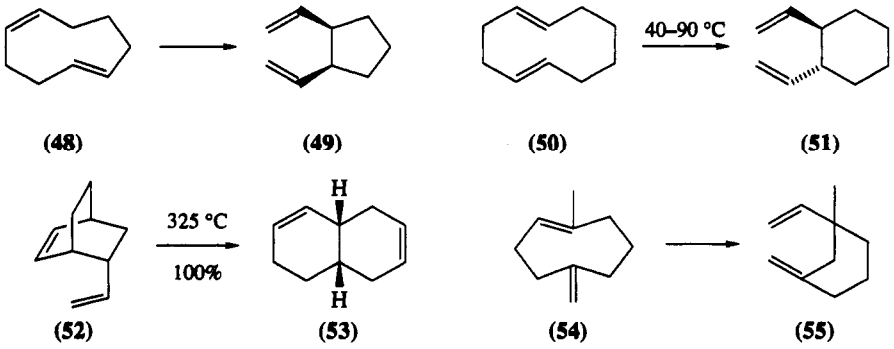
(38) (27)

completely on the side of the fused cyclobutane.[44] Cope rearrangement still occurs readily when the 1,2-divinylcyclopropane arrangement is built into bicyclic ring systems, as in diene (**45**), which rearranges[45] just above room temperature to the bicyclo[3.2.1]octadiene (**46**). Though not a 1,2-divinylcycloalkane, 2-vinylmethylenecyclopropane (**47**) also undergoes a low temperature Cope rearrangement to relieve the ring strain.[46]



Scheme 4 Cope equilibria in cyclopropanes and cyclobutanes

The position of equilibrium is totally reversed when one moves up to 1,2-divinylcyclopentanes and cyclohexanes (Scheme 5). Given relatively strain-free five- and six-membered rings *versus* considerable strain in the medium rings, the balance shifts in the opposite direction, and 1,5-cyclononadiene (**48**)[47] and cyclodecadiene (**50**)[48] rearrange completely to the divinylcycloalkanes (**49**) and (**51**). We will enlarge on the stereochemistry and synthetic applications of these rearrangements subsequently. The Cope rearrangement of the vinylbicyclo[2.2.2]octene (**52**) to diene (**53**) is an example of a 1,2-divinylcyclohexane whose rearrangement product is more stable,[49] but this is undoubtedly due primarily to the release of strain in the bicyclooctene. The rearrangement[50] of the methylenecyclooctene (**54**) to (**55**) is probably favored by the increased stability of a six- *versus* an eight-membered ring.

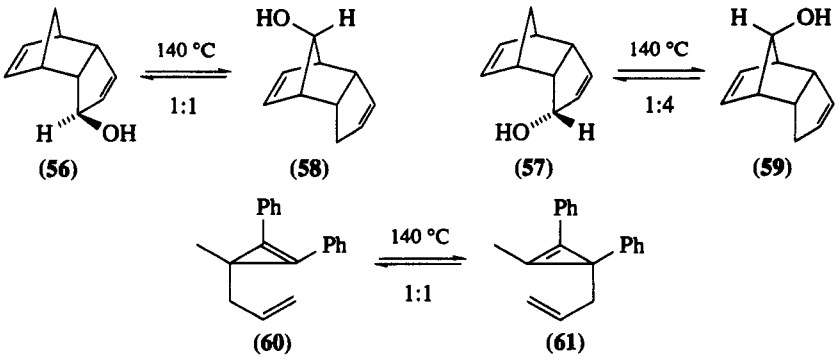


Scheme 5 Cope equilibria in 1,2-divinyl-cyclopentanes and -cyclohexanes

7.1.2.5 Conformational Factors

In addition to the major factors discussed above, a number of Cope equilibria can be interpreted only in terms of more subtle conformational factors which favor one isomer. Consider the two hydroxydicyclopentadienes (**56**) and (**57**) in Scheme 6: at 140 °C each is in equilibrium with its Cope rearrangement product (**58**) or (**59**). For the *exo*-alcohol (**56**), the equilibrium ratio is 1:1, but in the *endo* isomer (**57**), where the hydroxy group suffers steric compression, the rearrangement product is favored by at least 4:1.[51] In the diphenylcyclopropene (**60**), conjugation would appear to favor the starting material, but the

1:1 ratio with its Cope product (**61**) at 140 °C may reflect the nonbonded interactions between the phenyl groups in the *cis*-stilbene starting material, relieved in the product.[52]

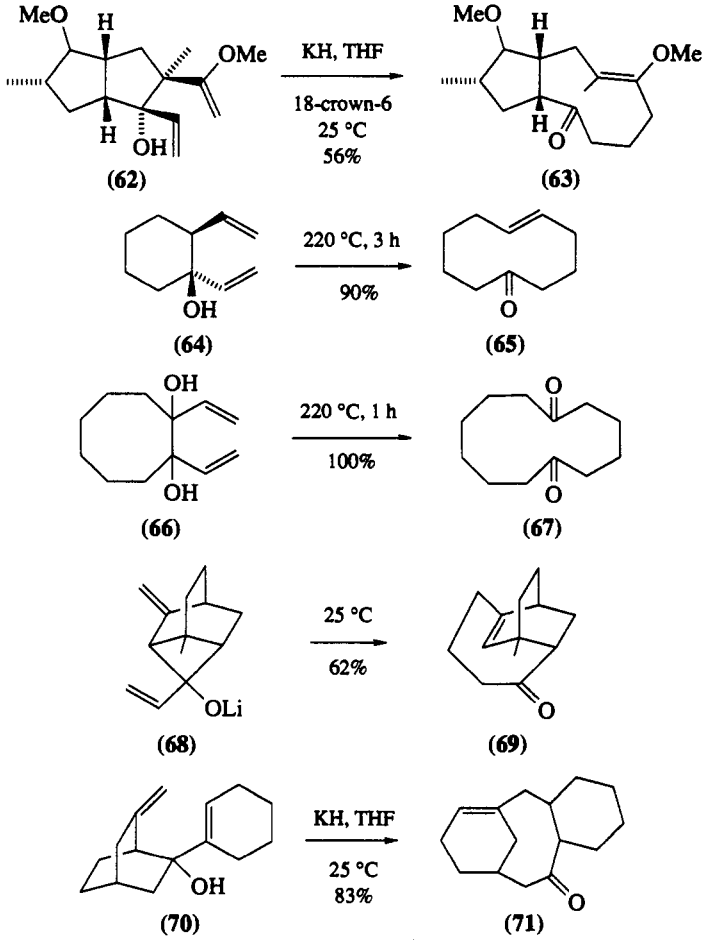


(56) (58) (57) (59) (60) (61)

Scheme 6 Conformational factors in Cope equilibria

7.1.2.6 Irreversibility of Oxy-Cope Rearrangements

As noted earlier, the generation in the oxy-Cope rearrangement of an enol which rapidly tautomerizes to a carbonyl compound effectively removes the Cope product from equilibrium and drives the rearrangement irreversibly; examples have been cited in equations (3)–(5), (10)–(12) and (26) and (27). Scheme 7 lists several additional examples which emphasize the ability of the oxy-Cope rearrangement

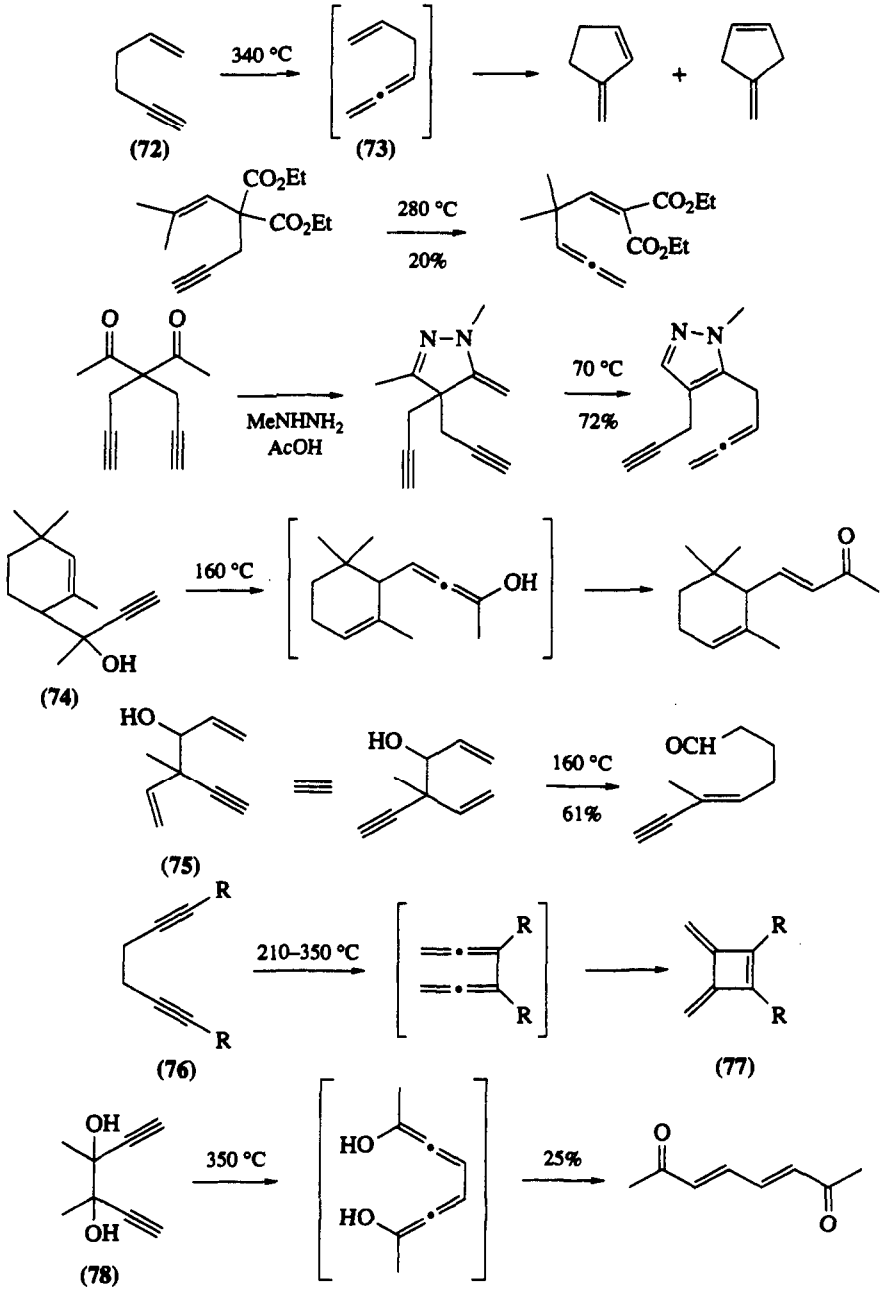


(62) (63) (64) (65) (66) (67) (68) (69) (70) (71)

Scheme 7 Shift of unfavorable equilibria by oxy-Cope rearrangement

to reverse the normal equilibrium or to produce strained products which would not have been possible by the normal Cope process.

1,2-Divinylcyclopentanes, as observed above, are usually the stable products of Cope equilibria, but the rearrangement of diene (**62**) is driven to the cyclononenone (**63**) by making it an irreversible oxy-Cope rearrangement.[53] Similarly 10-membered ring ketones, such as (**65**), can be prepared by oxy-Cope rearrangement of 1,2-divinylcyclohexanols (**64**),[54] and this versatile route to functionalized cyclodecanes has played an important role in the synthesis of germacrane sesquiterpenes. Rings containing 12 or more carbons can be synthesized in good yield by oxy-Cope rearrangement of 1,2-divinyl-1,2-cycloalkanediols, *e.g.* (**66**) to (**67**).[55] Considerably strained molecules such as the tricyclic ketones (**69**) and (**71**), both of which contain bridgehead double bonds, can be assembled in reasonable yields by oxy-Cope rearrangement of hydroxydiene precursors (**68**)[56] and (**70**);[57] the oxy-Cope reaction provides one of the attractive strategies which have been developed to construct the taxane skeleton in (**71**).



Scheme 8 Cope rearrangement of 1,5-enynes and 1,5-diynes

7.1.3 PARTICIPATION OF ALKYNES AND ALLENES IN COPE REARRANGEMENT

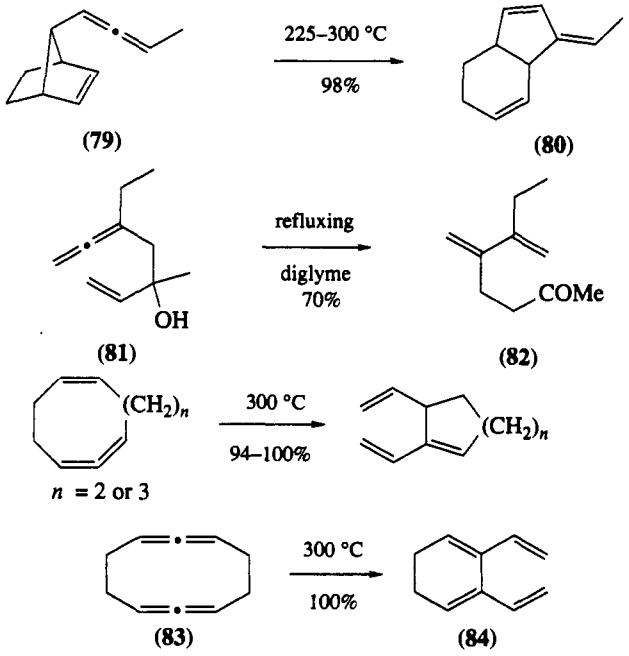
7.1.3.1 Alkynes

While it may seem geometrically unlikely that a linear alkyne bond could fit into the constraints of a six-membered cyclic transition state, Cope rearrangement of 1,5-enynes and even 1,5-diynes works surprisingly well and provides a useful route to allenes. Examples are shown in Scheme 8. Simple cases such as the parent (**72**) do not provide a viable route to allenes because the products (**73**) cyclize at high temperatures,[58] but more highly substituted examples are synthetically useful, and those shown in equations (28)[59] and (29)[60] give isolable allenes. The oxy-Cope rearrangement of (**74**) leads to an allene enol which tautomerizes to an unsaturated ketone, providing a valuable intermediate in the β-ionone series.[61] The rearrangement of (**75**), designed to provide head-to-head competition between a vinyl *versus* an alkynyl group, shows that the normal unstrained Cope rearrangement of a 1,5-diene is preferred.[62]

Huntsman and Wristers have examined the Cope rearrangement of 1,5-diynes (**76**); these appear to rearrange normally to bisallenes, but the products undergo ready electrocyclization to bismethylenecyclobutenes (**77**) at the temperatures required for rearrangement.[63] Diynediol (**78**) undergoes oxy-Cope rearrangement to a linear dienedione, again by tautomerization of a bisenol.[64]

7.1.3.2 Allenes

One double bond of an allene unit participates readily in Cope rearrangements, leading to the useful result of placing a conjugated diene at that end of the product. Several examples are shown in Scheme 9. Bicyclic allene (**79**) is converted in high yield on heating to the hydroindane (**80**).[65] In an application of the oxy-Cope rearrangement to allenes, alcohol (**81**) is converted to diene (**82**), again in good yield.[66]



(30)

Scheme 9 Cope rearrangement of allenes

When the allene and isolated double bond are both incorporated into a large ring, then Cope rearrangement affords 2,3-divinylcycloalkenes, as seen in equation (30).[67] The cyclic bisallene (**83**) affords 2,3-divinyl-1,3-cyclohexadiene (**84**), again in excellent yield.[67] These examples illustrate just how useful the allene variation of the Cope rearrangement is in the synthesis of interesting 1,3-dienes.

7.1.4 EXPERIMENTAL CONDITIONS; CATALYSIS

7.1.4.1 Experimental Conditions

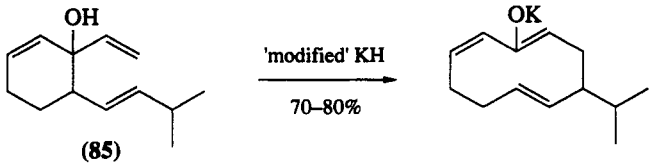
The experimental simplicity of the Cope rearrangement is one of its most attractive features. As thermal reactions, the Cope and oxy-Cope rearrangements can be carried out in either of two basic ways.

(i) Heating the substrate neat or in a high boiling solvent (*e.g.* decalin, xylene, diphenyl ether) under reflux or in a sealed tube is the most common method. The rates of most Cope rearrangements show little response to solvent polarity, so that a variety of solvents are acceptable. Substrates of moderate molecular weight frequently undergo Cope rearrangement during distillation at atmospheric pressure.

(ii) Vapor-phase rearrangement in a flow apparatus is often used for volatile substrates; passing the vapors at low concentration through a heated tube with short contact time helps to minimize decomposition.

Descriptions of both techniques may be found in the 1975 *Organic Reactions* review[1] and in representative articles.[4]

Typical bases used to generate the alkoxide ion for the anionic oxy-Cope rearrangement include sodium and potassium hydrides and potassium hexamethyldisilazide. Preliminary treatment of commercial KH with iodine, to destroy the putative contaminants potassium and potassium superoxide, is reported[68] to result in reproducibly high yields of anionic oxy-Cope reactions with dienolates such as (**85**). Tetrahydrofuran is the common solvent, although higher boiling solvents (*e.g.* diglyme) may be necessary. Frequently the addition of a complexing agent for the potassium ion (*e.g.* 18-crown-6,[11] HMPT, or TMEDA[69]) is found advantageous.



(**85**)

7.1.4.2 Catalysis

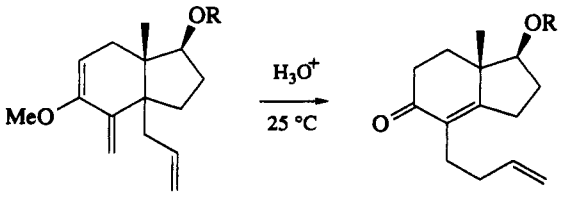
An experimental aspect of the Cope rearrangement particularly important in synthesis is the feature that it is frequently subject to catalysis. We have already seen that in the anionic oxy-Cope rearrangement enormous rate enhancements are realized by the incorporation of an alkoxide ion in the substrate. In many Cope rearrangements similar rate enhancements are achieved by the addition of catalysts, particularly acids and metals.[70]

7.1.4.2.1 Acid catalysis

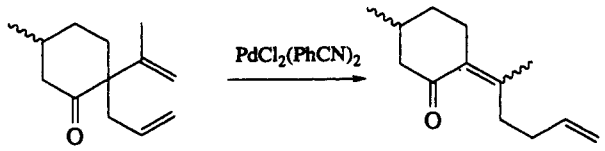
A number of Cope rearrangements of acyl-substituted 1,5-dienes are markedly accelerated by protic or Lewis acids.

(i) 2-Acyl-1,5-dienes

An example of this category is ketone (**11**) in Scheme 2; thermal rearrangement requires several days at 80 °C, but equally good yields are obtained in 15 min at 25 °C if 1 equiv. of trifluoroacetic acid or boron trifluoride etherate is added.[25] A related case is enol ether (**86**), which rearranges to ketone (**87**) at room temperature in dilute acid.[25]



(**86**) (**87**)



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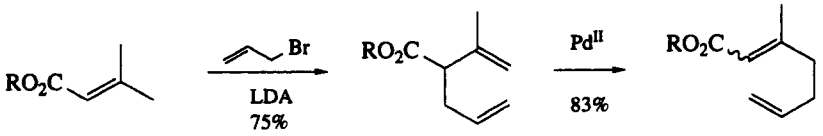

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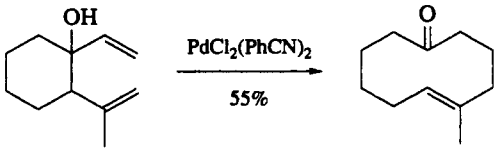
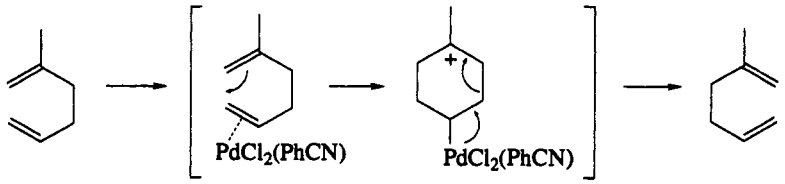


(37)

example of 'cyclization-induced rearrangement catalysis', illustrated in equation (38). In this mechanism the metal coordinates with one of the double bonds, initiating a carbocation cyclization step which forms a transient cyclohexane ring intermediate. Upon loss of the metal, this opens to form the rearranged diene. Support for this mechanism is given by the observation that cyclohexenes are occasionally found as by-products of palladium-catalyzed Cope rearrangements, *e.g.* equation (39).



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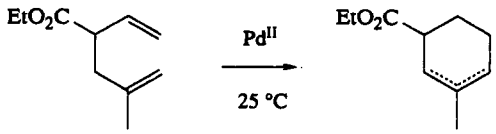


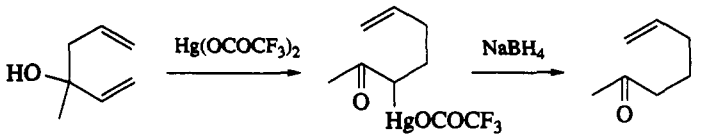
(39)

An alternative view suggests that coordination of the Pd^{II} catalyst with both double bonds of the 1,5-diene promotes dissociation into a bis(η^3-allyl)palladium complex, followed by joining the allyl units together to form the isomeric 1,5-diene (equation 40).[80]

(40)

(ii) Other metal catalysts

Scattered reports exist of catalysis of Cope rearrangements by metals other than palladium. Some amino-substituted 1,5-dienes exhibit weak catalysis by $Rh_2(CO)_4Cl_2$.[81] Gore and coworkers have studied the catalysis of oxy-Cope rearrangements by silver and mercury salts.[82] As shown in equation (41), stoichiometric quantities of mercury(II) trifluoroacetate effect oxy-Cope rearrangement to a mercuriated ketone, from which the mercury is removed by sodium borohydride reduction. The same overall result can be achieved by using a catalytic amount of mercury(II) ion in the presence of excess lithium trifluoroacetate. Silver triflate acts in a similar manner to catalyze the rearrangement of enynols, as illustrated in equation (42). Yields are variable with either silver or mercury(II) ion catalysis.



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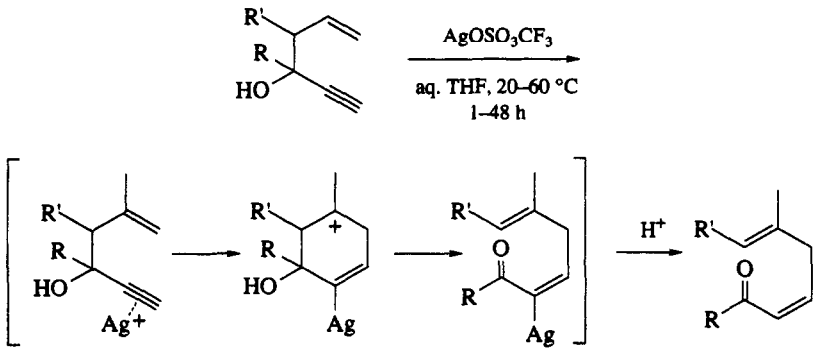
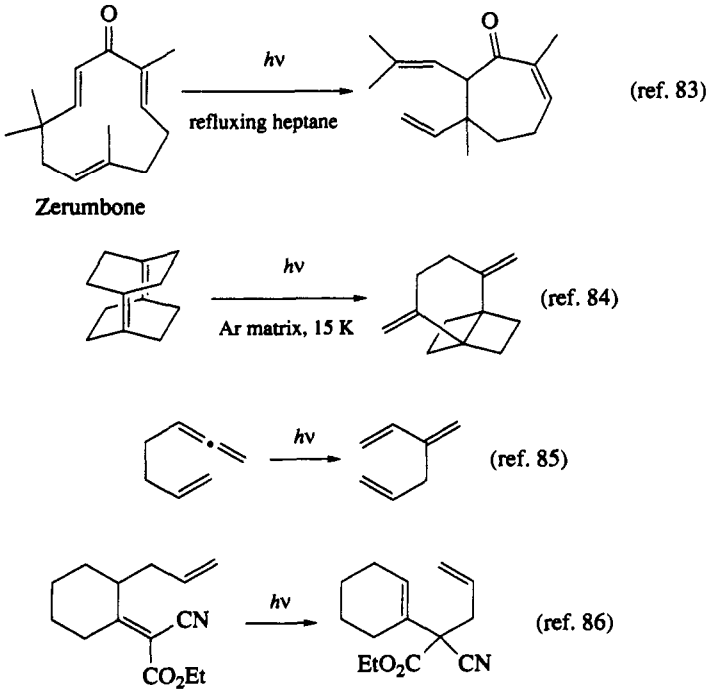


(42)

(iii) Photochemical initiation

A handful of cases are known in which Cope rearrangement has been initiated by photolysis. Some of these are shown in Scheme 10. The examples reported to date are a fairly random collection and it is not

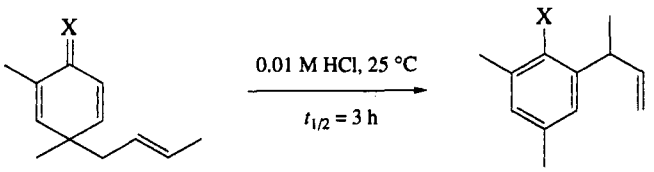


(43)

Scheme 10 Photochemical Cope rearrangement

(ii) 1-Acyl-1,5-dienes

The most commonly encountered examples of this type are the 4-allylcyclohexadienones and their derivatives, such as (**88**), which undergo room temperature Cope rearrangement, followed by aromatization, in the presence of acid.[71,72] It is interesting that the 3,3-Cope rearrangement competes with 1,2-migration (acid-catalyzed dienone–phenol rearrangement).



(**88a**) X = O
(**88b**) X = NNHTs

X = OH
X = NHNHTs

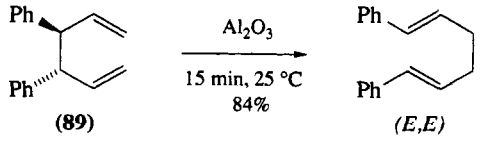
(iii) 3-Acyl-1,5-dienes

The best-known examples of this category are the tricyclic ketones illustrated by (**12**; Scheme 2), which again undergo room temperature Cope rearrangement in the presence of mineral or Lewis acids. The thermal rearrangement of (**12**) requires 1 h at 135 °C, but the rearrangement can be achieved in 3 min at 25 °C if a catalytic amount of sulfuric acid or aluminum chloride is added.[27]

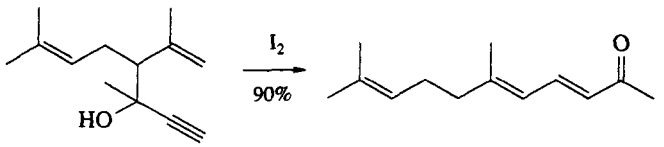
Another example of a 3-acyl-1,5-diene is cyclohexadienone (**27**), which is converted to (**28**) at room temperature in a few minutes by 1% sulfuric acid.[71]

The origin of the catalytic effect of acids in these cases has not been proven definitively. All these reactions cited above could be considered examples of carbocation charge-accelerated rearrangements, seen earlier in substrate (**10**); coordination of the carbonyl group with a proton or Lewis acid creates a carbocation which weakens the nearby single bond in the 1,5-diene. Moreover, in classes (ii) and (iii), Cope rearrangement transforms the initial carbocation into a more stable cation, which would lower the activation energy. An alternative possibility for the 2-acyl-1,5-dienes is that the acid catalyst completely changes the mechanism from a concerted process to a two-step sequence, first a carbocation cyclization to form a new ring, followed by fragmentation. These possibilities remain to be sorted out.[70a]

As an example of what appears to be an acid-catalyzed Cope rearrangement in a simple diene lacking acyl substitution, (±)-3,4-diphenyl-1,5-hexadiene (**89**) rearranges in high yield on treatment with alumina at room temperature; a cyclization-induced rearrangement mechanism was suggested.[73] Catalysis of oxy-Cope rearrangement of (**90**) by weak acids, including ammonium salts and iodine, has been reported.[74]



(**89**) *(E,E)*



(**90**) Pseudoionone

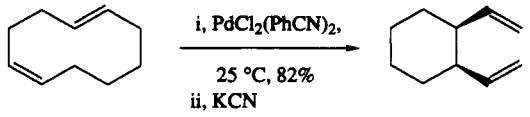
7.1.4.2.2 Metal catalysis

While acid catalysis appears to be largely restricted to 1,5-dienes containing carbonyl substituents (or possibly other Lewis bases), several metal-containing catalysts have been shown to have a broader scope of application to a variety of 1,5-dienes.

(i) Palladium

In the initial discovery, made by Jonassen and coworkers in 1966, a stoichiometric amount of bis(benzonitrile)palladium dichloride was found to effect the rearrangement of (*E,Z*)-1,5-cyclodecadiene into

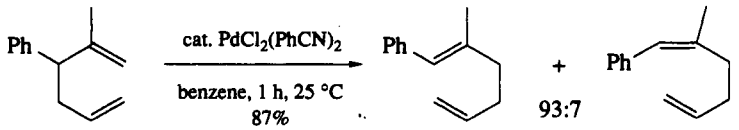
cis-1,2-divinylcyclohexane (as its $PdCl_2$ complex) at room temperature (equation 31).[75] This was a striking contrast to the thermal process, which required a temperature of 150 °C. A series of substituted cyclodecadienes and, later, 1,2-divinylcyclobutanes was studied extensively by Heimbach and coworkers, again isolating the Cope products as palladium complexes.[76]



(31)

In a finding of greater practical significance, Overman and coworkers showed that the reactions could be carried out with catalytic amounts of the palladium(II) complex, and that the catalytic effect was broadly applicable to acyclic 1,5-dienes as well.[70b] In a typical example (equation 32), 2-methyl-3-phenyl-1,5-hexadiene rearranges in 1 h at room temperature in 87% yield in the presence of 0.06 equiv. of bis(benzonitrile)palladium dichloride, in contrast to the thermal rearrangement which has $t_{1/2}$ = 13 h at 177 °C. The catalyst thus provides an estimated rate acceleration of about 10^{10}. The product is a 93:7 mixture of (*E*)- and (*Z*)-isomers, corresponding to the equilibrium ratio. Palladium acetate and tetrakis(triphenylphosphine) were ineffective as catalysts. One serious limitation is that the catalyzed reaction occurs only with those 1,5-dienes which possess an alkyl or aryl substituent at C-2 or C-5 (but not both).

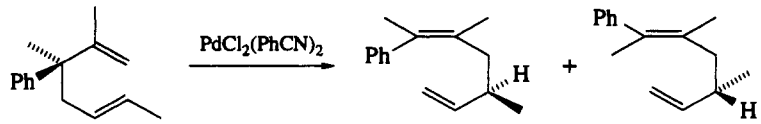
The catalyzed rearrangements generally give stereochemical results analogous to the uncatalyzed,



(32)

thermal reactions. For example, optically active (**91**) rearranges to a mixture of (*E*)- and (*Z*)-isomers of (**92**) with 96–97% *ee*, very similar to the results of thermal rearrangement.[77] The catalyzed rearrangement exhibits the same preference for the chair-like transition state conformation seen in the thermal reactions (see Section 7.1.7).

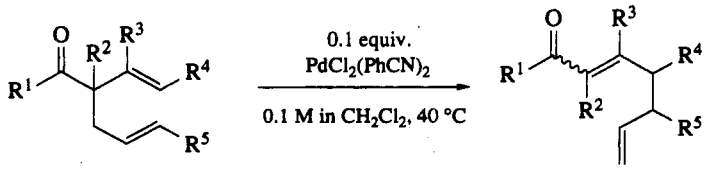
Pd^{II} catalysis is also effective for dienes with electron-withdrawing groups at C-3, *e.g.* acid, ester,



(3*R*,5*E*)-(**91**) (*Z*)-(**92**) 7:3 (*E*)-(**92**)

cyano, ketone, as seen in equations (33) and (34); it was shown that the catalyst equilibrates the geometric isomers around the conjugated double bond.[78] In equation (34) the catalyzed rearrangement occurs in good yield at room temperature, while the thermal rearrangement at 220–300 °C gave significant amounts of the β,γ-unsaturated isomer of the product along with ene cyclization products. The use of Pd^{II} catalysis extends the application of the strategy seen earlier in equations (13) and (14); as illustrated in equation (35), alkylation of an α,β-unsaturated ester with an allyl halide gives a 1,5-diene, which can then be subjected to Cope rearrangement at room temperature.

The same Pd^{II} catalyst is also effective for oxy-Cope rearrangements (equation 36), provided that both



(33)

R^1 and R^3 are alkyl groups.[79] An example of this application, shown in equation (37), is the catalyzed Cope rearrangement to a cyclodecenone.

Several mechanisms have been proposed for palladium catalysis of Cope rearrangements.[70] Overman, who has examined metal ion catalysis of a number of 3,3-sigmatropic rearrangements, considers this an

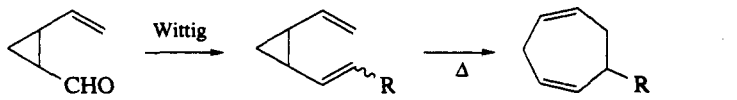
yet clear what factors facilitate the photochemical rearrangement, but it is interesting that at least in one case (equation 43) the normal equilibrium is reversed.

7.1.5 1,2-DIVINYLCYCLOALKANES

This section will focus on the use of the Cope rearrangement of 1,2-divinylcycloalkanes to synthesize carbocyclic rings of seven to ten members and even larger. As noted earlier in Section 7.1.2.4 and Schemes 4 and 5, the Cope equilibrium between divinylcycloalkanes and cyclic dienes is determined primarily by ring size; divinylcyclopropanes and cyclobutanes rearrange to cyclohepta- and cycloocta-dienes, providing one of the best general routes to seven- and eight-membered rings. In 1,2-divinylcyclopentanes, cyclohexanes, and cycloheptanes, on the other hand, the equilibrium lies in the opposite direction, but use of the irreversible oxy-Cope reaction does permit the synthesis of 9-, 10- and 11-membered rings. Finally, when the vinyl groups are attached to medium rings of 8–12 members, the equilibrium shifts once again to favor the larger rings. We examine here each of the ring sizes in turn.

7.1.5.1 1,2-Divinylcyclopropanes

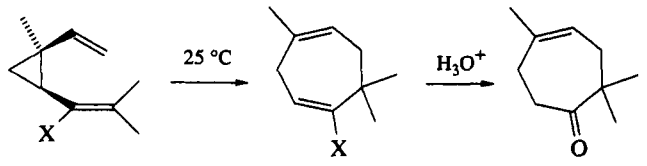
cis-1,2-Divinylcyclopropane (**39**) rearranges spontaneously below room temperature to 1,4-cycloheptadiene (**40**; Scheme 4) so readily that preparation of (**39**) by Hofmann degradation or other pyrolytic reactions[87] leads instead to (**40**), although (**39**) can be isolated[42] by conducting its synthesis by the Wittig reaction at –20 °C. The Cope rearrangement thus offers a straightforward route to simple cycloheptane natural products such as the dictyopterenes (equation 44)[88] and karahanaenone (equation 45).[89]



(44)

Dictyopterene A, R = Bu^n

Dictyopterene B, R = Et



(45)

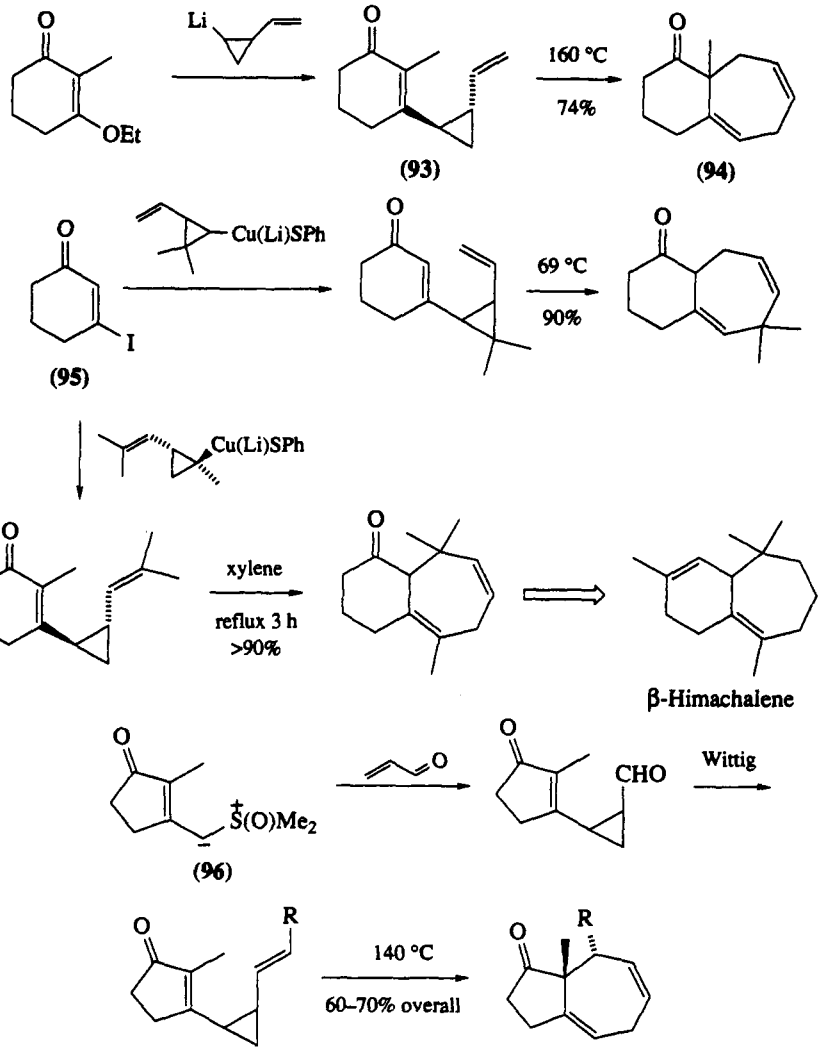
X = SPh or $OSiMe_3$ Karahanaenone

In order to use the divinylcyclopropane rearrangement for the construction of fused cycloheptanes, one of the double bonds must be incorporated in a separate, attached ring. Several practical methods have been developed to prepare the required substrates, as illustrated in Scheme 11.

(a) *Addition–elimination of vinylcyclopropyl organometallic reagents to β-substituted cycloalkenones.* Cyclopentenones and cyclohexenones with a leaving group at the β-carbon are easily prepared from the 1,3-diones, and undergo displacement when treated with organolithium or cuprate reagents derived from 2-vinyl-1-halocyclopropanes. Examples of this strategy are given in equations (46)–(48). In the simplest cases,[90] divinylcyclopropanes of type (**93**), prepared from enol ethers of cyclohexane-1,3-diones, rearrange on heating to bicyclic ketones of type (**94**). More highly substituted cyclopropanes have been prepared by cuprate displacement of 3-iodocyclohexenone (**95**), leading to alkylated bicyclo[5.4.0]undecanes (equations 47 and 48), including the sesquiterpene β-himachalene.[91]

(b) *Construction of cyclopropanes from sulfur ylides.* Sulfur ylides of type (**96**) are easily available by displacement of 3-chlorocyclopentenones by trimethyloxosulfonium ylide, and add to α,β-unsaturated aldehydes and ketones to furnish cyclopropanes (equation 49). Wittig reaction then gives the divinylcyclopropanes, which undergo Cope rearrangement on heating to afford hydroazulenes in good overall yields.[92]

Bridged cycloheptadienes are created when one of the vinyl double bonds is located in a ring fused to the cyclopropane, as seen in the conversion of (**45**) to (**46**); when both double bonds are in fused rings,



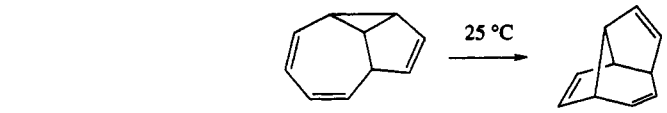
Scheme 11 Fused cycloheptanes by Cope rearrangement

tricyclic skeletons result (equation 50).[93] Several general ways to prepare the necessary starting dienes are shown in Scheme 12.

(a) *Addition of vinylcarbenes to cyclic dienes.* In a noteworthy one-step synthesis developed by Davies,[94] vinylcarbenes are generated by rhodium-catalyzed decomposition of diazo esters in the presence of furan or cyclopentadiene; the initial cyclopropane adducts, derivatives of (**45**), are not isolated but rearrange to bicyclo[3.2.1]heptadienes (equation 51). An intramolecular version of this reaction is illustrated in equation (52).

(b) *Enol derivatives of 6-vinylbicyclo[3.1.0]hexan-2-ones.* Piers has shown that TMS enol ethers of the title ketones, as members of the (**45**) family, undergo Cope rearrangement leading, after hydrolysis of the enol ether, to bicyclooctenones.[95] A simple example is given in equation (53) and an application to the synthesis of quadrone is shown in equation (54).

cis-1,2-Divinylcyclopropanes are constrained to undergo Cope rearrangement through one of the boat conformations (**97**), since only *cis* double bonds are possible in 1,4-cycloheptadiene. *trans*-1,2-Divinylcyclopropanes (**98**) give the same products at higher temperatures, but only after isomerizing *via* a diradical intermediate to the *cis* isomers.[96] Consequently in the synthetic applications discussed above, either stereoisomer (or mixtures) can be used, the only difference being the temperature necessary to effect rearrangement. Terminal substituents on the double bonds retard the rate. Diene (**99**) rearranges to the *meso*-dimethylcycloheptadiene, but the *cis*-propenyl isomer (**100**) fails to undergo Cope rearrangement due to steric interactions between the methyls and the ring in the boat transition state.[97]



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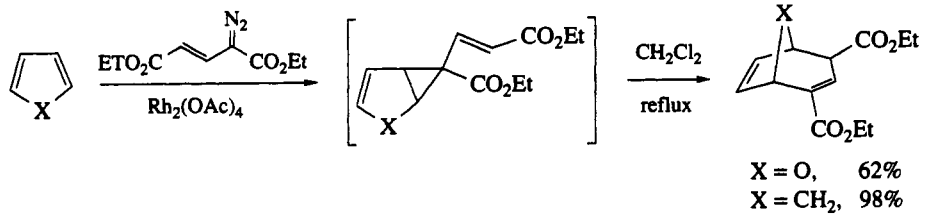

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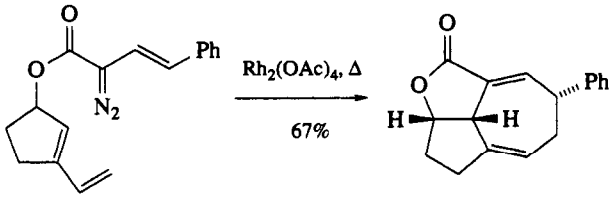

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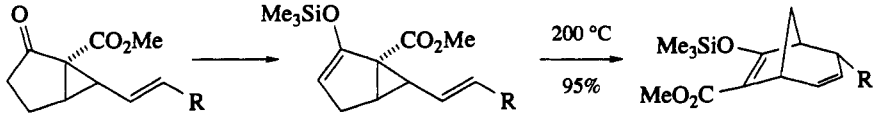

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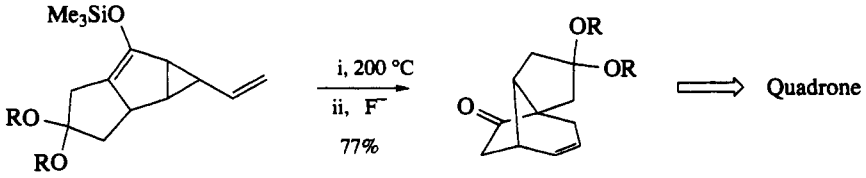
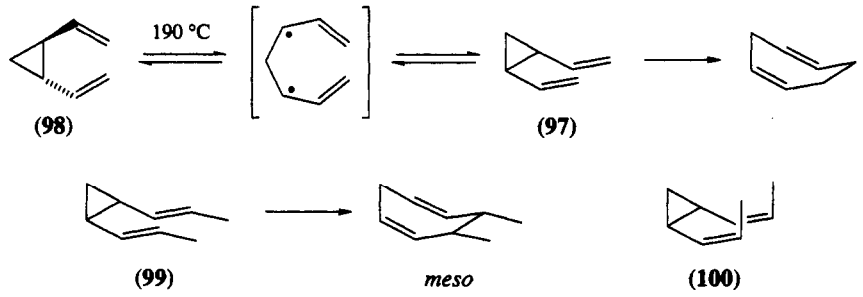


(54)

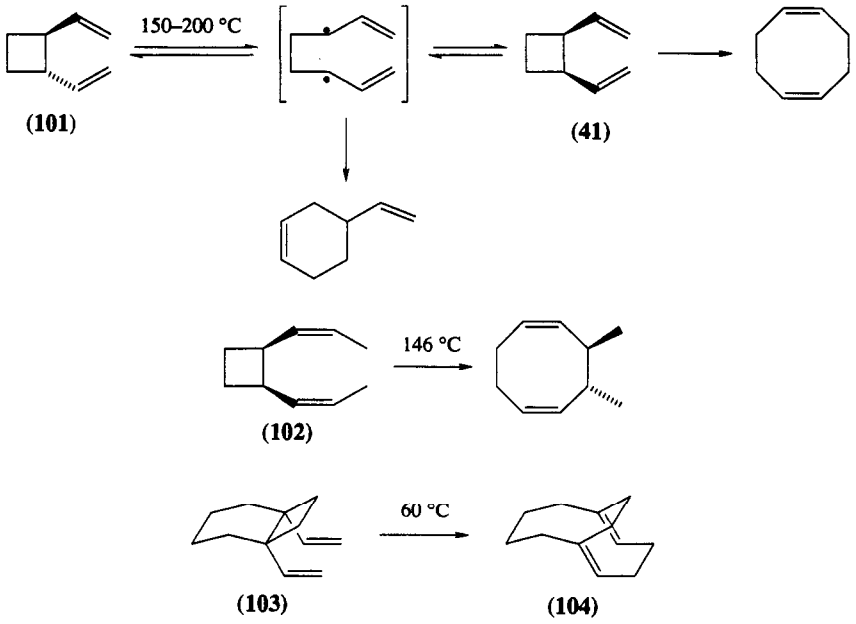
Scheme 12 Bridged cycloheptadienes by Cope rearrangement



7.1.5.2 1,2-Divinylcyclobutanes

The Cope chemistry of this strained-ring substrate class parallels that of the divinylcyclopropanes, and is discussed in detail in Chapter 8.2, this volume. *cis*-1,2-Divinylcyclobutane (**41**) is stable at room temperature but rearranges at 120 °C to *cis,cis*-1,5-cyclooctadiene (equation 55).[43] *trans*-1,2-Divinylcyclobutane (**101**) requires higher temperatures since it must first equilibrate with (**41**) through a diradical intermediate, but the diradical here has other options, particularly closure to a vinylcyclohexene.[98] Substituents on the double bonds again retard the rate, and the two *cis*-methyls in (**102**) cause the transition state to choose a nonboat conformation.[99] Relief of ring strain is an obvious factor in the rearrangement of diene (**103**) to the bridgehead diene (**104**), which occurs at 60 °C.[100] Shea *et al.* have examined a series of Cope rearrangements of this type; when the small ring is a cyclopropane, the Cope rearrangement occurs spontaneously below −10 °C.

Oxy-Cope rearrangements are popular in the divinylcyclobutane series, because several good methods of preparation of 2-vinylcyclobutanones are available. A number of these ketones, such as (**105**), can be



(55)

prepared by ring expansion of cyclopropane intermediates.[101] Addition of a vinyl group to the ketone then affords the divinylcyclobutanol (**106**), ready for oxy-Cope rearrangement (equation 56; Scheme 13).[102] Equation (57) shows an example of this strategy in Gadwood's synthesis of poitediol; addition of lithium acetylide to cyclobutanone (**107**) occurs from the convex face, giving a *cis*-enyne which undergoes oxy-Cope rearrangement to the fused cyclooctadienone.[103]

Another common strategy for construction of fused cyclooctanones is to first build a fused cyclobutanone by [2 + 2] cycloaddition of a vinylketene to a cycloalkene. Equation (**58**) illustrates this approach with Paquette's synthesis of the tricyclic skeleton of the ophiobolins.[104] Cyclobutanone (**108**) is assembled by addition of a vinylketene to cyclopentadiene. Cyclopentenyllithium then adds to the less-hindered face of (**108**), and the lithium alkoxide undergoes a spontaneous anionic oxy-Cope rearrangement to afford the central cyclooctane ring.

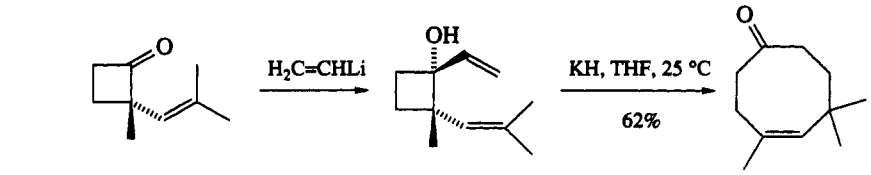
In another approach to fused cyclooctanes, dienone (**109**) rearranges at 180 °C to bicyclic dienone (**110**). Adding fluoride ion in DMF allows the reaction to occur at –30 °C in doubled yield, apparently an 'enolate-assisted' Cope rearrangement. Since Majetich has shown that divinylcyclobutanes of type (**109**) are intermediates in some intramolecular allylsilane Michael additions, this finding permits the novel sequence of steps shown in equation (59) as a route to fused cyclooctanes.[105] Another variation to fused cyclooctanes uses the spiro substrate (**111**) in an anionic oxy-Cope rearrangement (equation 60).[102a]

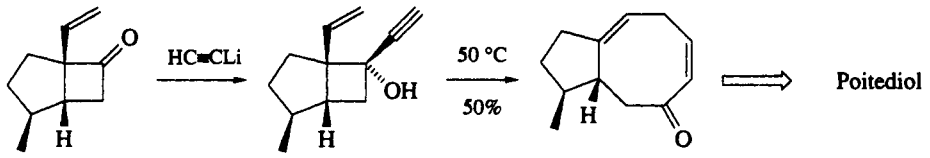
Bridged cyclooctadienes result from Cope rearrangement of fused substrates, following the theme seen in Scheme 12. A general route to the requisite substrates is the [2 + 2] cycloaddition of vinylketenes to cyclic 1,3-dienes, illustrated in equations (61) and (62); the vinylketenes may be formed by dehydrohalogenation of unsaturated acid chlorides or by thermolysis of cyclobutenones.[106]

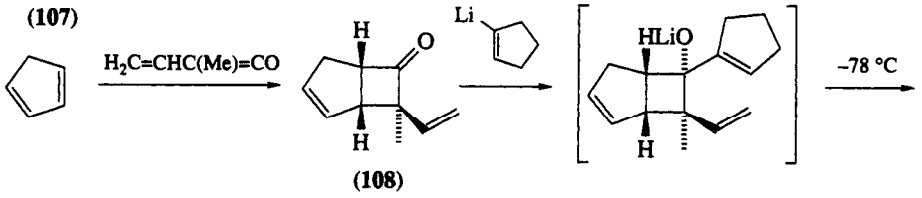
A final useful pattern incorporates one double bond into a spiro ring, leading *via* oxy-Cope rearrangement to bicyclic ring systems with bridgehead double bonds (equation 63).[107]

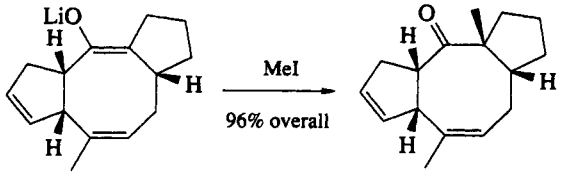
7.1.5.3 1,2-Divinylcyclopentanes

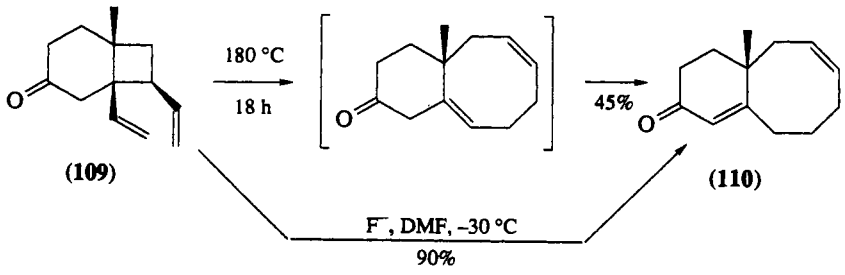
As noted in Section 7.1.2.4 the Cope equilibrium shifts when the ring size of a 1,2-divinylcycloalkane increases to 5–7, favoring the smaller ring. The equilibrium between *cis*-1,2-divinylcyclopentane (**49**) and (*Z,Z*)-1,5-cyclononadiene, reached at 220 °C from either component (equation 64), is 95:5 in favor of (**49**). This rearrangement must utilize a boat transition state, but (*E,Z*)-1,5-cyclononadiene, which also rearranges to (**49**), uses a chair transition state.[47] Rearrangements of substituted cyclononadienes have been little studied because of the inaccessibility of the substrates, but Paquette has examined oxy-Cope rearrangements of a series of cyclononatrienols,[108] two of which are shown in equations (65) and (66). In equation (66) the alcohol fails to undergo a thermal oxy-Cope, giving products of hydrogen shifts instead, but the room temperature anionic oxy-Cope works well, giving an aldehyde used as an intermediate in the synthesis of multifidene, an algae sperm attractant.

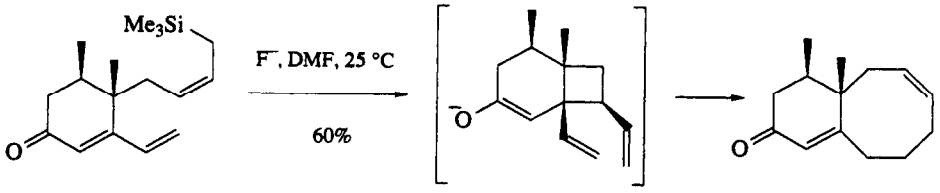


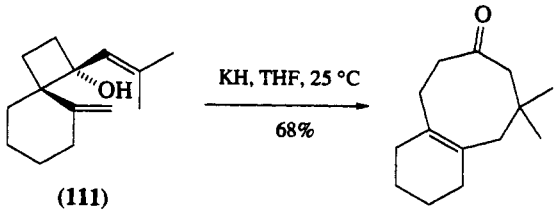


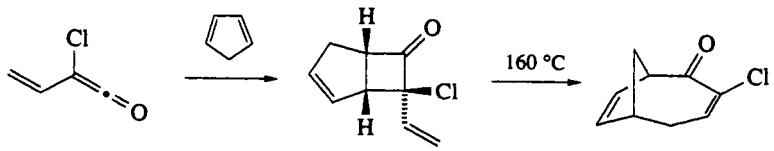




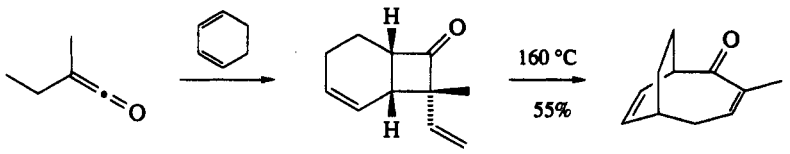








Scheme 13 *(continued overleaf)*



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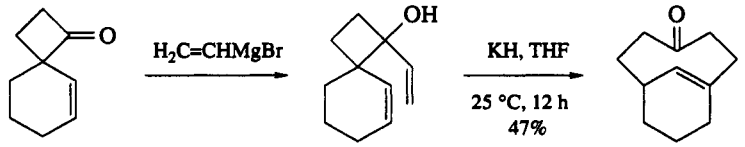
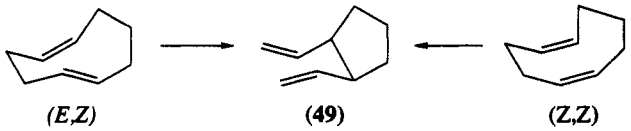
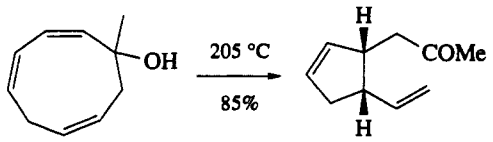


(63)

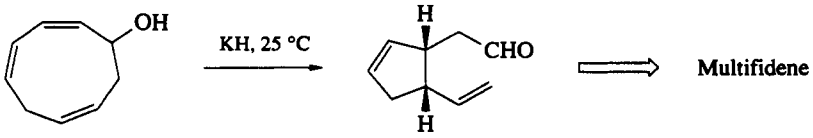
Scheme 13 Cyclooctanones by oxy-Cope rearrangement



(64)

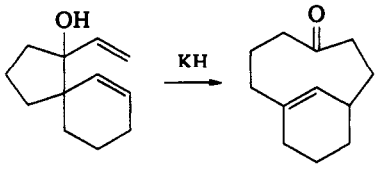


(65)

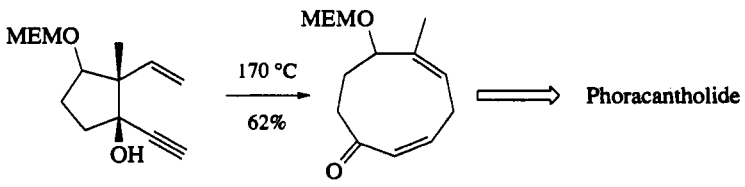


(66)

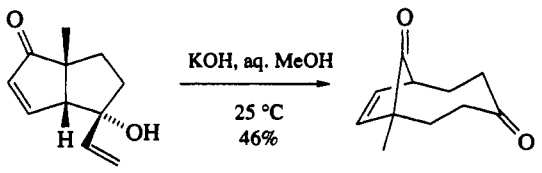
The normal equilibrium can be reversed, of course, by using the oxy-Cope rearrangement of a 1,2-divinylcyclopentanol; one example was shown in Scheme 7 (**62** → **63**) in which irreversible tautomerization of the enol gave a fused cyclononenone. Two additional examples are shown in equations (67)[107b] and (68), the latter a key step in a synthesis of phoracantholide.[109] The fused divinylcyclopentane shown in equation (69) undergoes anionic oxy-Cope rearrangement to a bridged cyclononenone.[110]



(67)



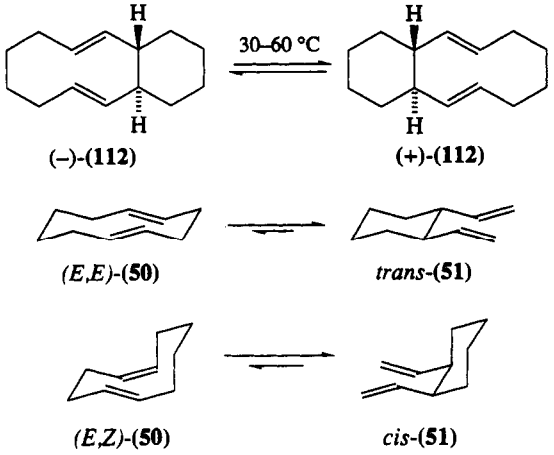
(68)



(69)

7.1.5.4 1,2-Divinylcyclohexanes

The Cope equilibrium between 1,2-divinylcyclohexane (**51**) and 1,5-cyclodecadiene (**50**) lies completely on the side of the six-membered ring (Scheme 5); attempted preparation of (**50**) by Hofmann elimination[111] leads directly to (**51**; mostly *trans*), although the cyclodecadiene can be prepared at lower temperature. Optically active (**51**) racemizes at 200 °C through the Cope equilibrium[48] with (**50**), and optically active (**112**) racemizes on heating, by Cope rearrangement to its enantiomer.[112] The stereochemistry of these rearrangements is best accounted for by assuming that the transition state assumes a chair-like conformation; (*E,E*)-(**50**) rearranges to *trans*-(**51**), while (*E,Z*)-(**50**) affords *cis*-(**51**).[113]

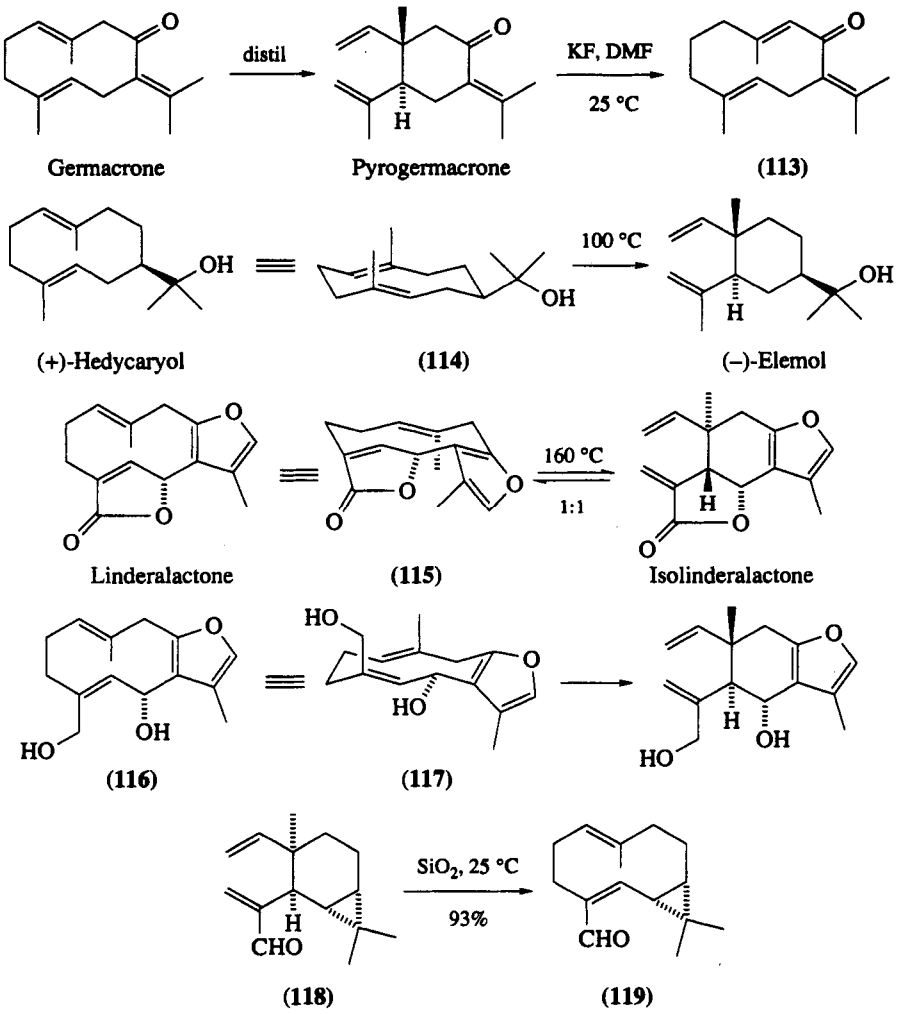


This class of Cope rearrangement is commonly encountered among the germacrane sesquiterpenes, many of which contain a 1,5-cyclodecadiene skeleton. Examples are shown in Scheme 14. Distillation of germacrone (equation 70) effects Cope rearrangement to the divinylcyclohexane isomer pyrogermacrone.[114] Substituents on the cyclodecadiene ring affect the conformation chosen for rearrangement.[115] In hedycaryol for example, the hydroxyisopropyl group occupies an equatorial position in the preferred transition state conformation (**114**), leading to elemol of the configuration shown (equation 71).[116] Comparison of linderalactone and the related diol (**116**) in equations (72) and (73) is particularly instructive; the C—O bond of linderalactone must be axial, forcing the choice of chair conformation (**115**) for rearrangement, but in diol (**116**), the C—O bond is free to be equatorial in the alternate chair conformation (**117**), leading to the opposite configuration at the ring junction in the product.[115]

In highly substituted cyclodecadienes, Cope equilibria do not always lie totally on the side of the divinylcyclohexane. Linderalactone[117] and isolinderalactone, for example, exist in a 1:1 ratio at 160 °C (equation 72); the equilibrium has allowed a synthesis[118] of linderalactone through its isomer. Aldehyde (**118**) is converted in high yield to its cyclodecadiene isomer (**119**) by silica gel at room temperature, though curiously this Cope rearrangement cannot be effected by heating at 200 °C.[119] Pyrogermacrone is converted by fluoride ion at room temperature to the conjugated ketone (**113**; equation 70), apparently by catalyzing the equilibrium with germacrone and then the tautomerization to the more stable conjugated isomer.[105]

In this series, as well as the divinylcyclopentanes, the equilibria can be shifted completely in favor of the 10-membered ring by using the irreversible oxy-Cope rearrangement of 1,2-divinylcyclohexanols; the prototype (**64** → **65**) was shown in Scheme 7. This reaction type has found wide application in the synthesis of cyclodecane natural products, as illustrated in Scheme 15. In equation (74) the starting material was made beginning with (–)-carvone, leading after rearrangement to optically active germacranolides.[120] Equation (75) shows one of the first spectacular successes in this area, the oxy-Cope step in Still's total synthesis of periplanone B, the sex attractant of the American cockroach.[121] These examples illustrate the range of substituents which the low temperature, anionic oxy-Cope rearrangement can tolerate. The synthesis of eucannabinolide (equation 76)[122] is novel in incorporating one of the vinyl groups into a cyclobutene ring, and an even more strained cyclobutene transition state is involved in the rearrangement shown in equation (77).[123]

A final class of oxy-Cope rearrangements leading to cyclodecenones is represented by spirodienol (**120**), which rearranges to a bicyclic ketone (**121**) containing a bridgehead double bond.[107b] The related alkynic alcohols (**122**) behave similarly,[124] but when R is H the initial product undergoes an intramolecular Michael addition to afford (**123**).



Scheme 14 Cope rearrangement of germacranes

A recent modification due to Sworin and Lin is to incorporate an additional functional group into the substrate so that the intermediate enol can cyclize by intramolecular S_N2' or Michael reactions. As shown in equations (78) and (79), this provides a novel route to hydroazulenes.[125]

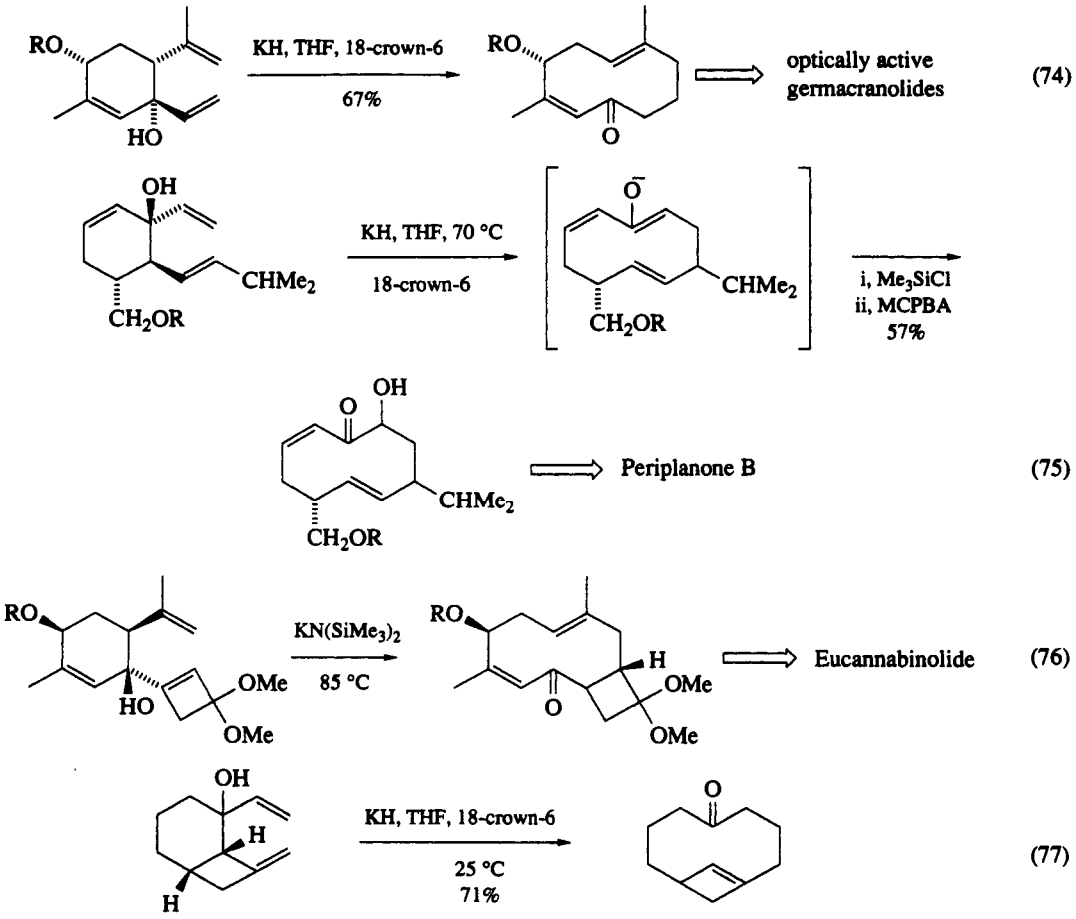
7.1.5.5 1,2-Divinylcycloheptanes

Very few Cope rearrangements of this type have been reported. The reaction shown in equation (80) implies that the divinylcycloheptane is favored in the equilibrium with a cycloundecadiene,[83] but more examples are needed before this generalization is secure.

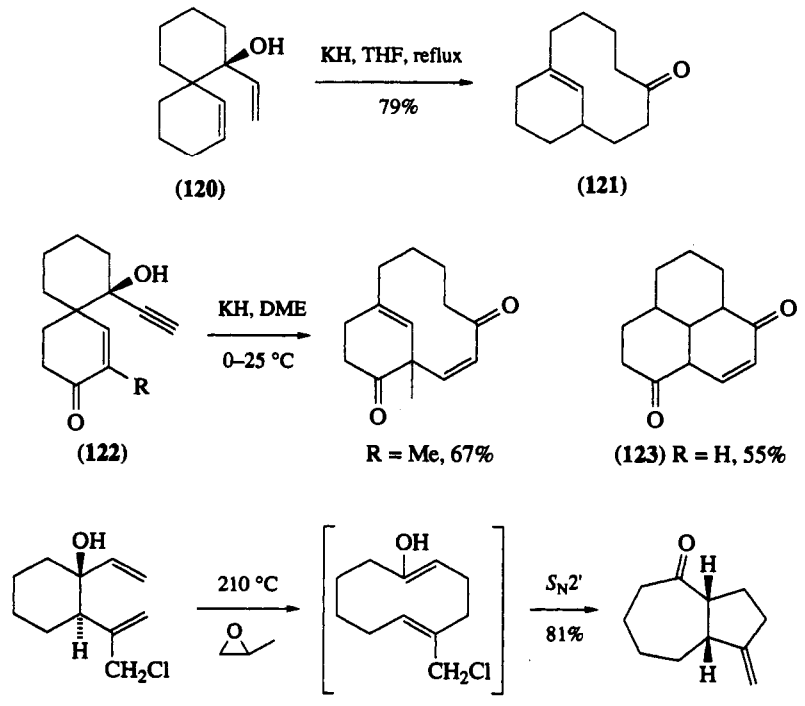
At least one of the general protocols for effecting ring expansion by anionic oxy-Cope rearrangement has been applied to a cycloheptanone, and is shown in equation (81).[126] The 2-vinyl group is inserted by Grignard reaction with the 2-chloro ketone, and additional vinyl Grignard reagent yields the divinylcycloheptanol. Heating then effects oxy-Cope expansion to the 11-membered ketone.

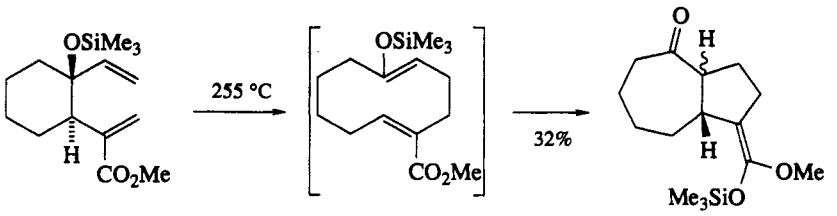
7.1.5.6 1,2-Divinylcyclooctanes and Larger Rings

At this point the Cope equilibrium shifts direction again, and 1,2-divinylcyclooctanes and larger homologs rearrange in good yield to afford 12-membered and larger rings (Scheme 16). The strain present in medium rings (8–11 members) is clearly a determining factor in these equilibria. Equations (82)[127] and (83)[128] show simple examples of divinylcyclooctanes which rearrange to 12-membered rings.

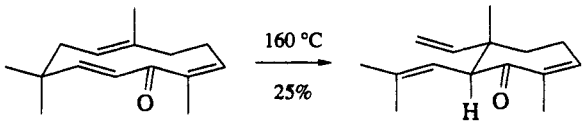


Scheme 15 Cyclodecenones by Cope rearrangement of 1,2-divinylcyclohexanols

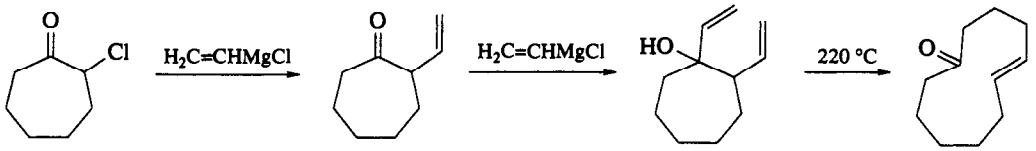




(79)



(80)



(81)

1,2,3,4-Tetravinylcyclobutane undergoes two consecutive Cope rearrangements, through a cyclooctane intermediate (equation 84), to a cyclododecatetraene.[129]

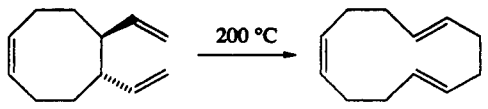
Larger rings participate easily in Cope rearrangements, and again the ring strain of a medium ring may help to induce rearrangement, as indicated by the mild conditions necessary for expansion of the divinylcycloundecane ring system in equation (85).[130] The four-carbon ring expansion which the Cope rearrangement allows offers the strategy of repetitive ring expansions leading to large rings. The most straightforward application is the oxy-Cope reaction, shown in equation (81) and again in equation (86)[126,128] for the cyclododecane substrate. A number of ways[128] have been published for introducing a 2-vinyl group into a cyclic ketone in addition to the method shown in equation (81); vinyl Grignard addition and oxy-Cope rearrangement then afford the enlarged ketone. Another practical repetitive strategy is shown in equation (87): two vinyl groups are inserted into a cyclic β-keto ester (**124**), and Cope rearrangement of the diene (**125**) affords a homologated β-keto ester which can be subjected to the same sequence.[131]

7.1.6 VINYLBICYCLOALKENES AND OTHER BRIDGED DIVINYLCYCLOALKANES

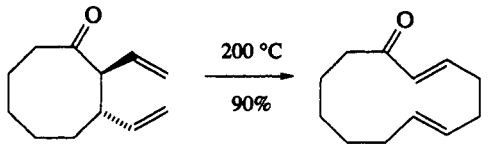
7.1.6.1 Vinylbicycloalkenes

The most popular Cope substrates of this class, represented by (**127**), can be considered relatives of 1,2-divinylcycloalkanes in which an additional carbon–carbon bond (as in **126**) generates a vinylbicycloalkene. Concerted Cope rearrangement of (**127**) is permitted as long as the vinyl group is *endo*, and leads to a fused bicyclic diene (**128**), necessarily *cis*. The ring systems most frequently employed have been bicyclo[2.2.1]heptenes ($x = y = 1$), leading to hydroindenes, and bicyclo[2.2.2]octenes ($x = 2$, $y = 1$), which afford *cis*-decalin skeletons. Examples of the former are shown in equation (88)[132] and the latter is illustrated in Scheme 5 (**52** → **53**).

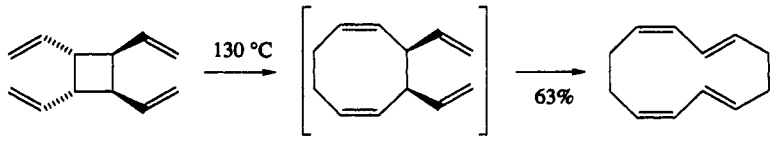
The most common route to these substrates is a convergent one in which the vinyl moiety is joined by Grignard addition to the bicyclic ketone, giving an alcohol which serves directly in the oxy-Cope or anionic oxy-Cope rearrangement. Equation (89) exemplifies this strategy beginning with dehydrocamphor (**129**),[133] and equations (90)[134] and (91)[135] provide additional examples of construction of hydrindenones, as well as the example seen earlier in equation (27). Grignard addition can, of course, give a diastereomeric mixture of *endo*- and *exo*-alcohols, but fortunately the *endo* face of the ketone is usually more accessible and the major product is consequently that with the vinyl group *endo*. This simple two-step sequence is thus a powerful and versatile route to functionalized *cis*-hydrindanones; the rearrangement in equation (90) was used to synthesize dihydronepetalactone and, as illustrated in equation (91), an additional fused ring can be added if the vinyl group is incorporated into a ring.[135] Notice, in equation



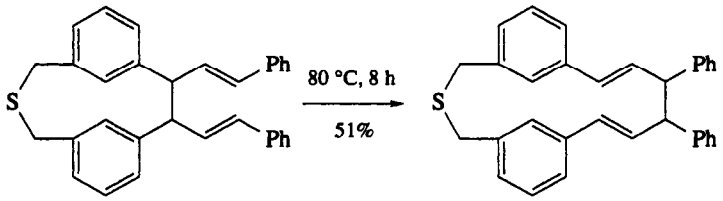
(82)



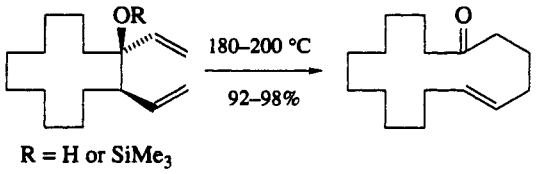
(83)



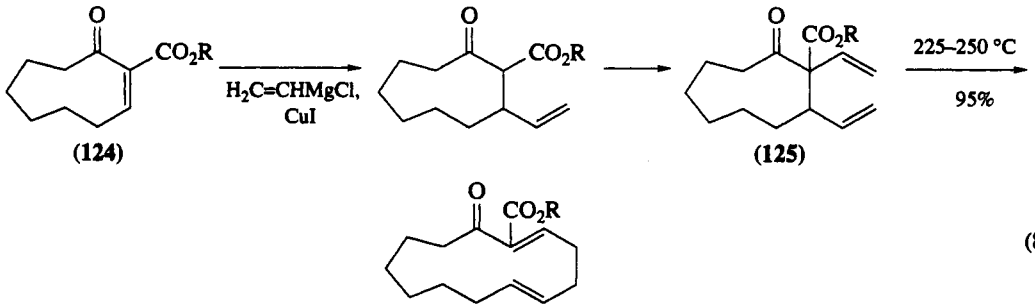
(84)



(85)

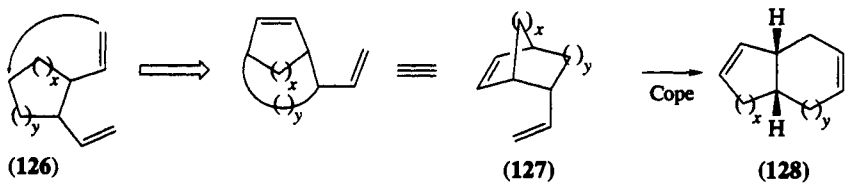


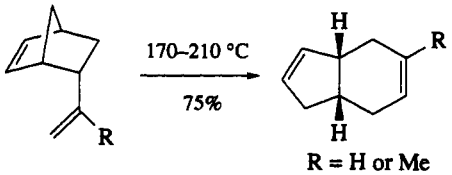
(86)



(87)

Scheme 16 Cope rearrangements of 1,2-divinylcyclooctanes and larger rings

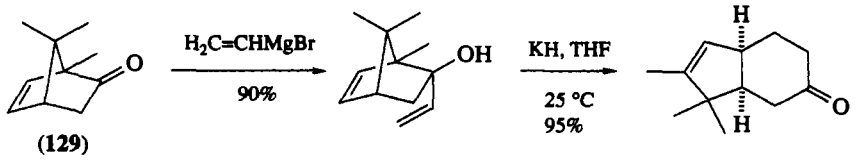




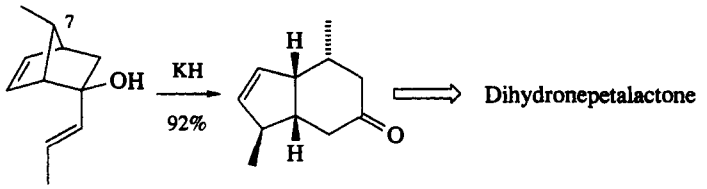
(88)

(90), that a substituent at C-7 in the bicycloheptene becomes attached, in a predictable configuration, to the five-membered ring in the Cope product. Moreover, a *trans* substituent at the β-carbon of the vinyl

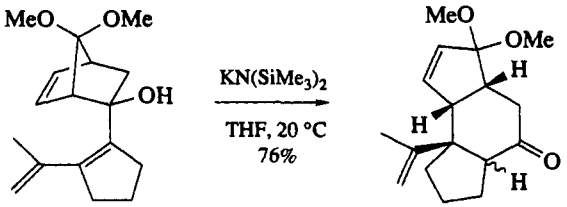
group ends up in the six-membered ring in a predictable configuration, based on the fact that in the transition state (**130**) the group R prefers to lie oriented away from the rest of the molecule.



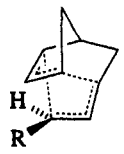
(**129**) (89)



(90)

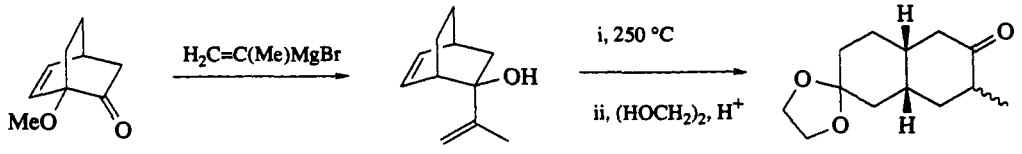


(91)

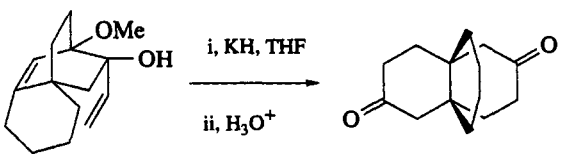


(**130**)

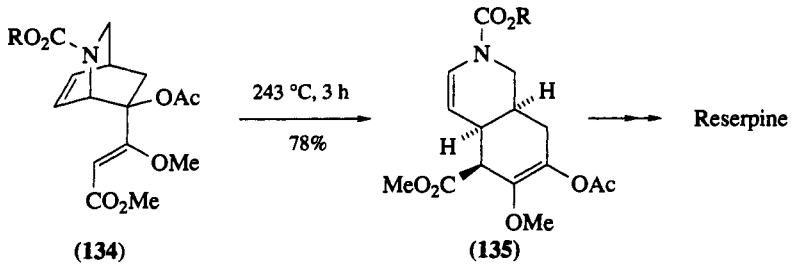
This strategy is equally powerful for the synthesis of *cis*-β-decalones from vinylbicyclo[2.2.2]octanols; examples were seen in equations (4), (6) and (12). Ketone (**2**), prepared in 98% yield by anionic oxy-Cope rearrangement, was the starting material for two syntheses of the alleged 'cannivonine',[136] and ketone (**131**; equation 92) was the key intermediate in Evans' synthesis of luciduline.[137] Propellane (**133**) is readily accessible[138] by oxy-Cope rearrangement of tricyclic alcohol (**132**; equation 93). The bicyclooctane skeleton may also incorporate heteroatoms, as in the aza derivative (**134**), which leads upon Cope rearrangement to a *cis*-hexahydroisoquinoline (**135**), an intermediate in Wender's elegant synthesis of reserpine (equation 94).[139] Again, if the vinyl group is contained in a ring, that ring becomes fused to the decalin skeleton, as in equation (95), showing Paquette's approach to a forskolin model.[140]



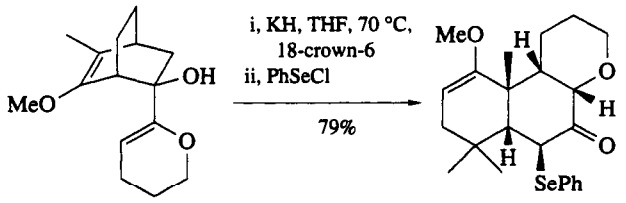
(**131**) (92)



(**132**) (**133**) (93)

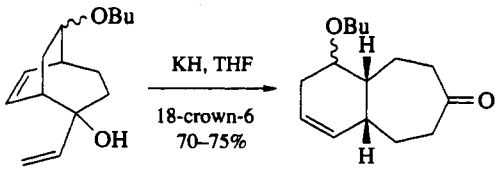


(134) (135) (94)



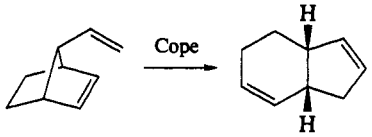
(95)

Still larger rings may be constructed by this general strategy; equation (96) shows the formation of a bicyclo[5.4.0]undecane by oxy-Cope rearrangement of a vinylbicyclo[3.2.2]nonane.[141]



(96)

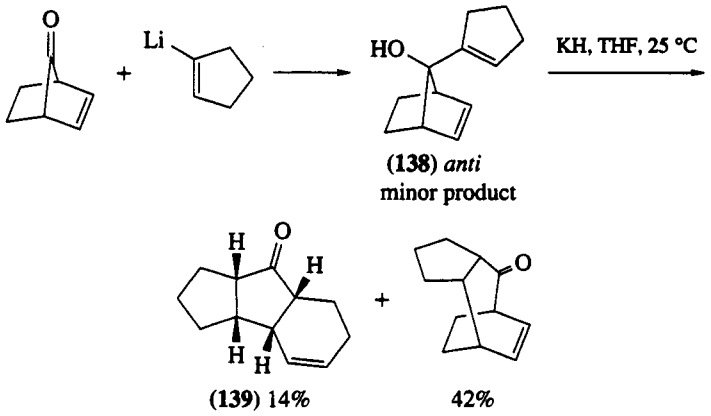
A related substrate group is the 7-vinylbicycloheptenes (**136**), which rearrange to tetrahydroindenes (**137**), double bond isomers of the products shown in equation (88); an example was encountered earlier in Scheme 9 (**79** → **80**). These, too, are usually performed as oxy-Cope reactions, but suffer from two problems in comparison with the oxy-Cope rearrangements of 2-vinylbicycloheptenols (equations 89–91): (i) addition of vinyl organometallic reagents to 7-ketobicycloheptenes is not very selective, and usually gives the *syn*-alcohol as the major product, not the *anti* isomer required for concerted Cope rearrangement[142]; (ii) as noted earlier for alcohol (**5**; equation 8), dienols of this type tend to give mostly 1,3-rearrangement products rather than 3,3-Cope rearrangements. This is also true for cyclic vinyl groups,[143] as shown in equation (97), which illustrates both of these problems. *anti*-Alcohol (**138**) is the minor product of addition, and it rearranges predominantly by a 1,3-pathway, giving only 14% of the Cope product (**139**). Somewhat unexpectedly, Paquette *et al.* have found that replacement of vinyl with dienyl groups markedly increases the extent of Cope rearrangement,[135] making this a practical route to tetrahydroindanones. Examples are seen in equations (98) and (99).



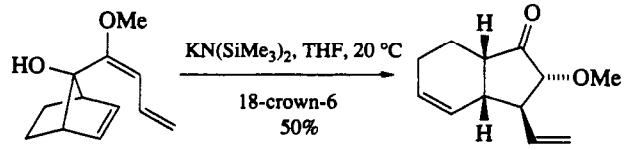
(136) (137)

7.1.6.2 2-*exo*-Methylene-6-vinylbicyclo[2.2.2]octanes

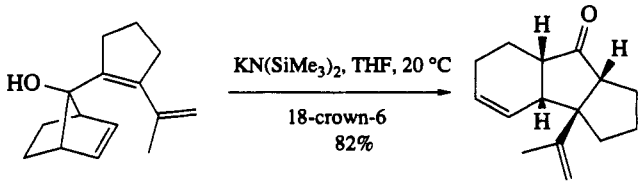
Another member of the divinylcycloalkane family is the title diene (**140**), which can be considered as a 1,2-divinylcyclohexane in which one vinyl group is connected to the ring by an additional carbon. Cope rearrangement of (**140**) is of synthetic interest in leading to a product (**141**) containing a bridgehead double bond. The few examples of this type realized so far all use the oxy-Cope rearrangement to ensure formation of the strained products. The simplest example is (**142**), which undergoes anionic oxy-Cope rearrangement in high yield to (**143**); Martin *et al.* have studied several examples of this type,[57] including the preparation of the taxane model (**71**; Scheme 7). More complex examples in which an additional ring



(97)



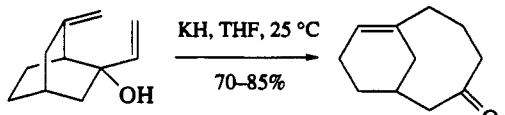
(98)



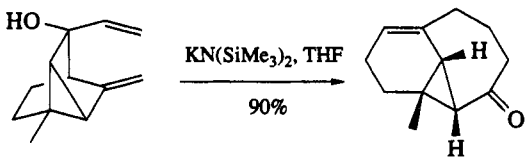
(99)

is present include the conversion of (**68**) to (**69**; Scheme 7) and the rearrangement of (**144**) to (**145**), the key step in Paquette's approach to cerorubenic acid acid-III.[144]

(**140**) (**141**)



(**142**) (**143**)

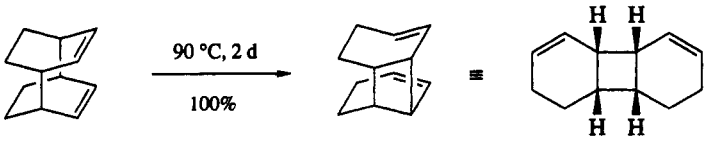


(**144**) (**145**)

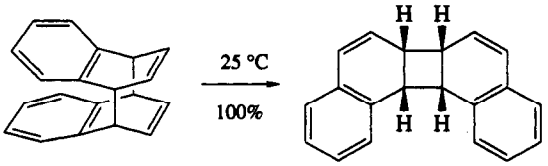
7.1.6.3 Bridged 1,5-Cyclooctadienes

A final variation of bridged divinylcycloalkanes is represented by (**146**), which can be thought of as a doubly bridged 1,2-divinylcyclooctane. Alternatively it can be considered as a bridged 1,5-cycloocta-

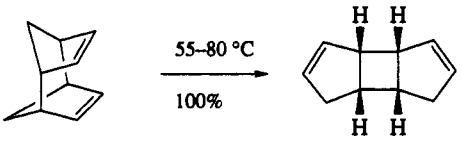
diene which could participate in a Cope equilibrium[145] with the 1,2-divinylcyclobutane (**147**). A handful of rearrangements of this type are known, and in every case not only does the equilibrium lie totally on the side of the cyclobutane, but the rearrangement occurs under unusually mild conditions, sometimes at room temperature (equations 100 and 101).[146] Apparently the strain in the cyclobutane ring is more than compensated by relief of nonbonded interactions in the tricyclic starting materials.



(**146**) (**147**)



(100)



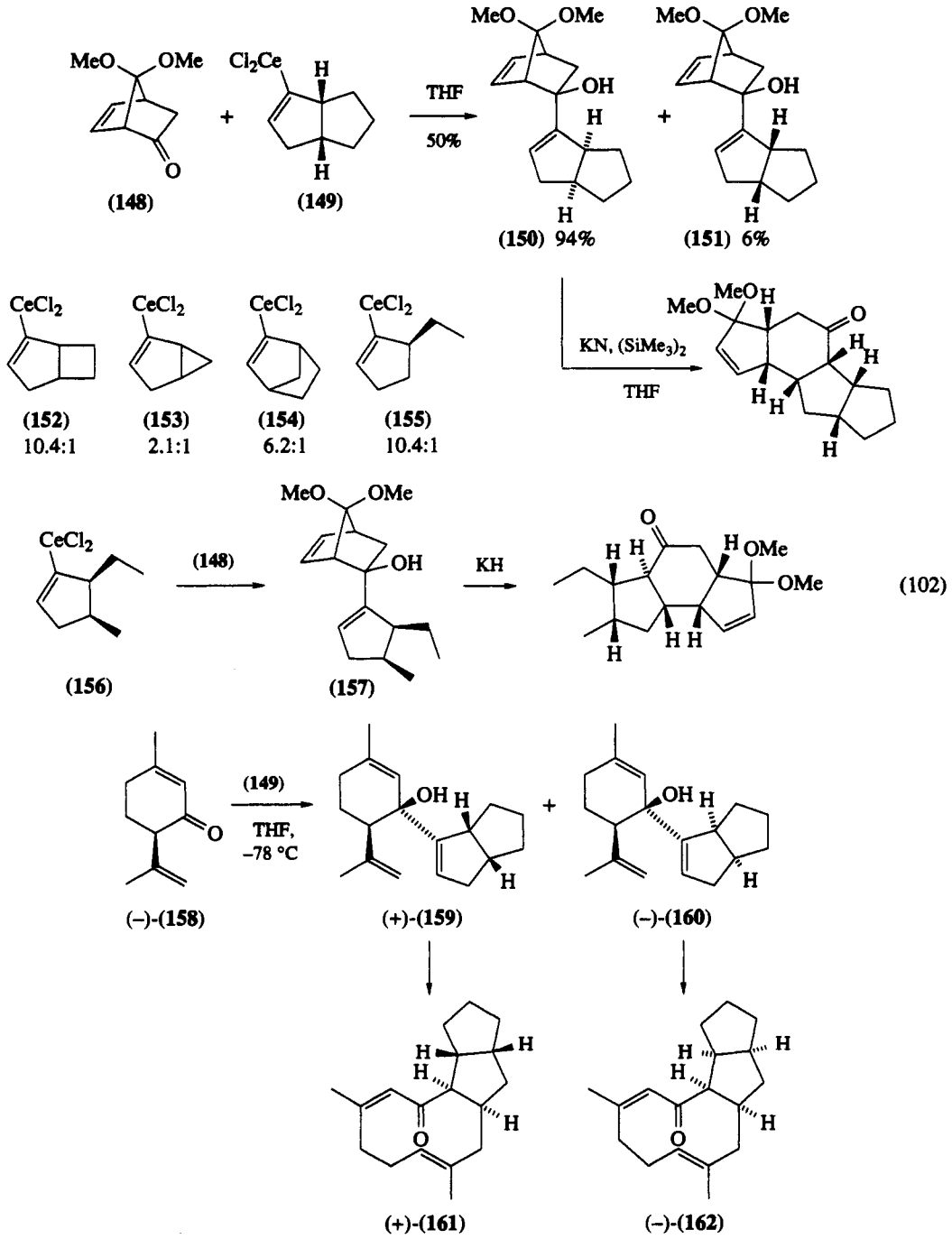
(101)

7.1.6.4 Double Diastereoselection with Chiral Vinyl Substituents

Previous examples in this section (especially equations 90 and 91, and 95–99) have made it clear that the use of substituted vinyl groups in oxy-Cope rearrangements of vinylbicycloalkenes leads to products with at least four stereogenic centers with essentially complete stereocontrol. If the vinyl moiety is not only cyclic but contains one or more chiral centers, then a large number of stereoisomeric products could result. In the search for control over the stereochemical outcome, Paquette *et al.* have investigated a series of chiral cyclopentene organometallic reagents (Scheme 17).[147]

Using the 7,7-disubstituted bicycloheptenone (±)-(**148**) reduces the number of possible stereoisomers, since organometallics add only from the *endo* face of the ketone. Still, when a chiral reagent such as (±)-(**149**) adds, two (±)-pairs (**150** and **151**) may result. The useful result is that one of these heavily predominates, in this case (**150**), by a ratio of 16:1. Related reagents (**152**)–(**155**) give diastereomeric ratios not as high, but in each case the diastereomeric products are easily separated by chromatography; the predominant sense of preference is the same in each case. Because the anionic oxy-Cope then proceeds with total stereospecificity, the Cope product from (**150**) contains six contiguous asymmetric centers fixed in a single relative configuration. This convergent sequence, joining a chiral ketone with a chiral vinylorganometallic reagent, followed by oxy-Cope rearrangement, not only regenerates a carbonyl group but creates six or more asymmetric centers with high specificity and control.[148] An example of its application is shown in equation (102): addition of the cerium reagent (**156**) to (**148**) gives alcohol (**157**) in a 12:1 diastereomeric ratio, and oxy-Cope rearrangement then provides the *as*-indacene subunit of ikarugamycin with its six asymmetric centers.[149]

When one of the initial reagents is optically active and the other is used in excess, then the diastereomeric preference results in kinetic resolution. An example[150] is the reaction of racemic (**149**; sixfold excess) with (–)-isopiperitenone (**158**), which gives (+)-(**159**) and (–)-(**160**) in a ratio of 4.8:1. After separation each of these undergoes anionic oxy-Cope rearrangement to the optically active cyclodecadienones (**161**) and (**162**). These incisive studies demonstrate that the oxy-Cope rearrangement can be used to rapidly assemble complex polycyclic skeletons with remarkable control over the creation of multiple chiral centers.

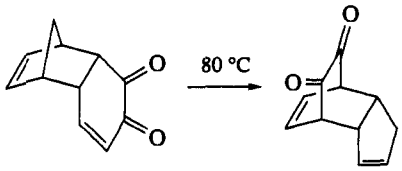


Scheme 17 Double diastereoselection with chiral vinyl organometallics

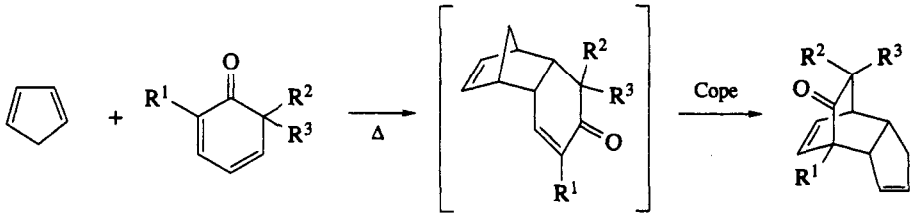
7.1.6.5 Tricyclic Skeletons

We close this section with a brief look at tricyclic skeletons formed by joining the vinyl group of a vinylbicycloalkane to the bicyclic ring system with additional carbons. Such skeletons are easily accessible through Diels–Alder reaction of cyclopentadienes with cyclic dienes or trienes. Cope rearrangements of dicyclopentadiene derivatives have the special property of regenerating the original ring system with shuffled carbons, as illustrated by rearrangement of (**12**) in Scheme 2. This reaction type was discovered by Woodward and Katz with the alcohols (**56**) and (**57**; Scheme 6), and a number of related examples are now known.[151]

When the vinyl group is situated in a ring larger than five, nondegenerate rearrangements of possibly more synthetic utility take place. The adduct (**163a**) of cyclopentadiene and *o*-benzoquinone, for example, rearranges to (**164a**) in refluxing benzene;[152] Cope rearrangement occurs so readily that frequently Diels–Alder adducts of cyclopentadienes are not isolated, as seen in equation (103) for the reaction with cyclohexadienones.[153]

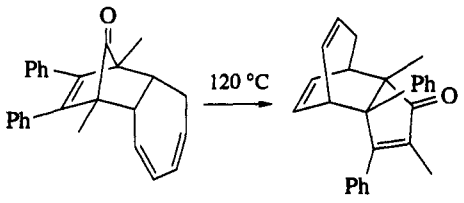


(**163a**) (**164a**)

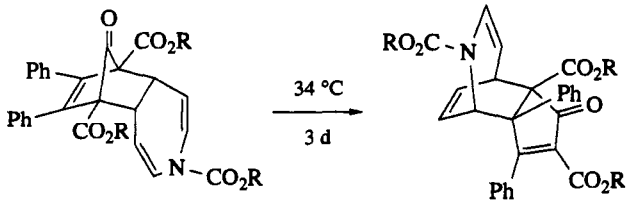


(103)

The facility of Cope rearrangement depends on the nature and length of the bridge connecting the vinyl group to the ring. Systems with bridges of three and four saturated carbons do not rearrange,[154] but unsaturated three-atom bridges still rearrange easily, as shown in equations (104)[155] and (105).[156]



(104)



(105)

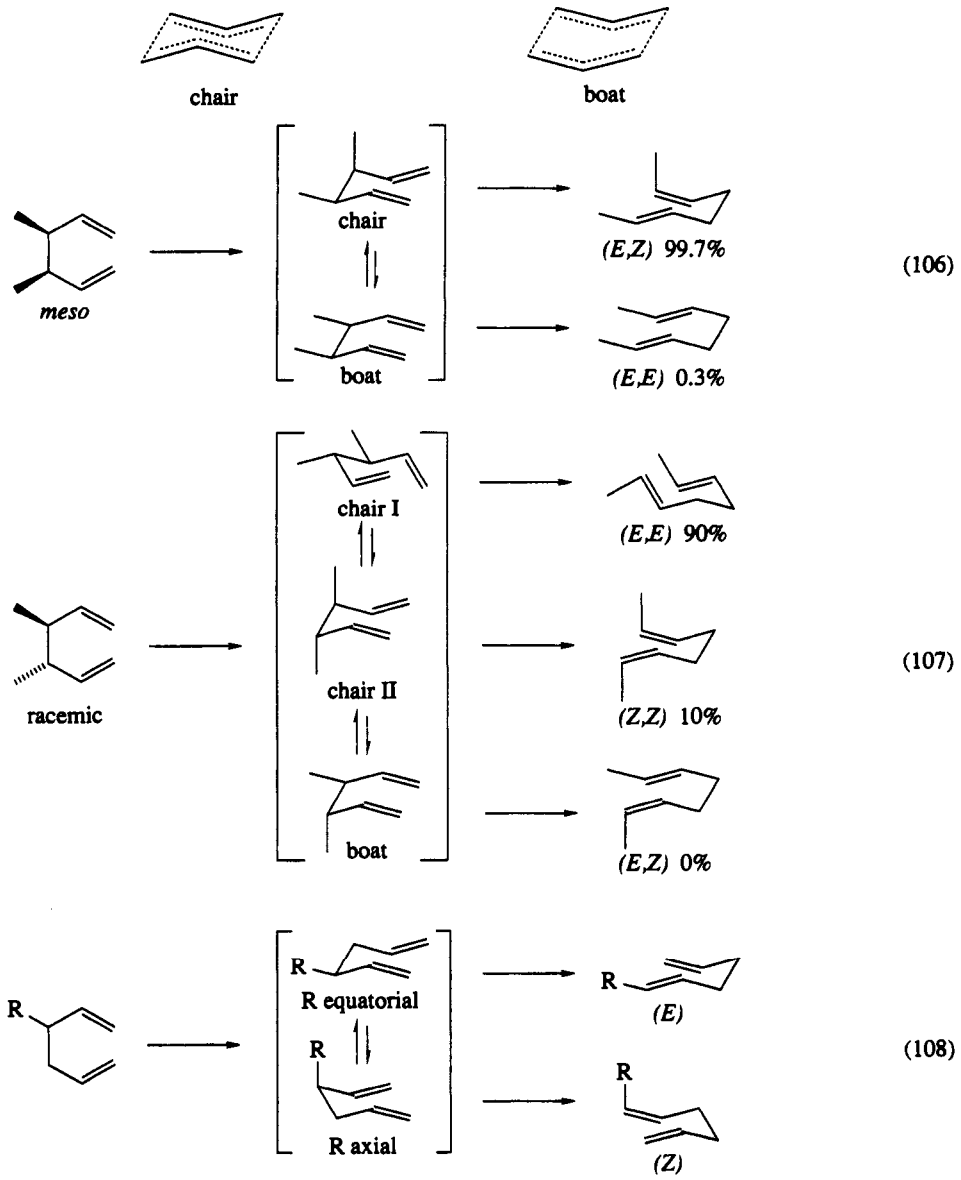
7.1.7 STEREOSPECIFICITY

The preceding discussion has demonstrated how the specificity inherent in the cyclic transition state may be used to fix structural elements in Cope products, establishing double bonds and other functional groups in definite relationships in a variety of acyclic and cyclic skeletons. This final section treats the remarkable consequences of cyclic transition states in stereochemical control, including alkene configuration and both relative and absolute configuration at stereogenic centers.[2]

7.1.7.1 Transition State Conformation

Restricting consideration to suprafacial–suprafacial geometries,[157] two limiting conformations are possible for the six-membered cyclic transition state, a four-center or 'chair' conformation with staggered allyl units which resembles chair cyclohexane, and a six-center or 'boat' conformation with

eclipsed allyl fragments which approximates boat cyclohexane (Scheme 18). The classic experiments of Doering and Roth[160] first showed the preference for chair conformations in Cope rearrangements of acyclic 1,5-dienes. *meso*-3,4-Dimethyl-1,5-hexadiene rearranged to the (*E*,*Z*)-isomer of 2,6-octadiene, with only 0.3% of the (*E*,*E*) isomer (equation 106), while the racemic starting material afforded 90% of the (*E*,*E*)-octadiene and 10% of the (*Z*,*Z*)-isomer (equation 107). These results revealed a difference of at least 5.7 kcal mol^{-1} in free energies of activation favoring chair conformations.



Scheme 18 Cope transition state conformations

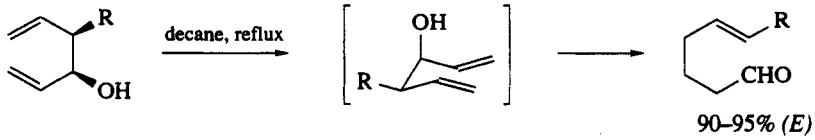
Several additional ingenious experiments devised to probe energy differences between chair and boat transition states have reached similar conclusions. In Scheme 1, equation (b), racemic 2,2′-bis(methylenecyclopentane), which must adopt a chair conformation for rearrangement, rearranges 18 000 times faster than its *meso* isomer, which must use a boat conformation.[20] Moreover, chair and boat transition states in equation (c), Scheme 1, would lead respectively to racemic and *meso* products; the observed product ratio of 130:1 gives an energy difference of 4.3 kcal mol^{-1} favoring the chair conformation.[21]

Although most Cope rearrangements thus prefer chair transition states, the boat conformation is clearly energetically accessible and may be required by special structural features. In Scheme 1, equation (d), for example, the lactol ring forces the substrate to rearrange through a boat transition state.[22] 1,2-Divinylcy-

clopropanes and most 1,2-divinylcyclobutanes employ boat transition states, as noted in Section 7.1.5 since the vinyl groups are held nearly eclipsed, but increasing ring size allows greater flexibility. In 1,2-divinylcyclopentanes both chair and boat conformations are observed (equation 64), and the 1,2-divinylcyclohexane–1,5-cyclodecadiene equilibrium uses only chair conformations (*cf.* **50**). Vinylbicycloalkene rearrangements are forced into inflexible boat transition state conformations, imposing a fixed (and predictable) stereochemical relationship of chiral centers in the products, as seen earlier in equations (12), (27), (90), (94) and (95).

7.1.7.2 Double Bond Configuration

A corollary of the preference for chair conformations is the accompanying preference for substituents at sp^3 carbons to occupy equatorial, rather than axial, positions. This is shown clearly in the rearrangement in equation (107), which proceeds primarily through chair I conformation, with both methyls equatorial, rather than chair II, with the methyls axial. The immediate and important consequence, as emphasized in equation (108), is that transition states with equatorial substituents lead to (*E*)-double bonds, while axial substituents afford (*Z*)-double bonds, and that accordingly double bonds produced by Cope rearrangement are nearly always (*E*). Examples of this predominant formation of (*E*)-alkenes have been seen in equations (17), (36), (74)–(76), (81)–(87), and Scheme 1, equation (a), and with compounds (**85**) and (**89**). When two substituents are attached to the same carbon in the substrate, the larger, of course, prefers the equatorial position, still affording usually the (*E*)-alkene [*cf.* Scheme 2, equation (d)]. The relationship between 'size' of substituent and (*E*)/(*Z*) product ratios can be put on a quantitative basis: using experimental values of $\Delta G°$ for equatorial/axial preference of substituents in cyclohexanes allows the prediction of (*E*)/(*Z*) ratios in Cope products.[161] In the rearrangement of (**75**) two substituents (methyl and ethynyl) are of similar size and the product is a 55:45 (*Z*):(*E*) mixture.[62] In oxy-Cope rearrangements the equatorial/axial preference of the oxygen substituent often depends on solvent or charge; the rearrangement in equation (109)[162] affords (*E*)/(*Z*) mixtures when catalyzed by bases but nearly pure (*E*)-isomer when carried out in a nonpolar solvent.[162]



90–95% (*E*) (109)

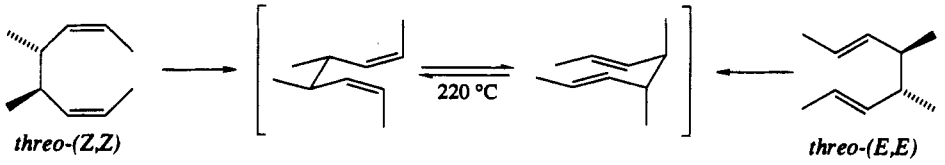
7.1.7.3 *Erythro–Threo* Ratios

When both vinyl groups contain β-substituents, two chiral centers are produced by Cope rearrangement. The asymmetry of two unsymmetrical double bonds is translated into a specific and predictable *erythro/threo* ratio by the cyclic transition state, as illustrated in equation (110). This *erythro/threo* specificity is nicely demonstrated in the experiments of Gajewski *et al.* (equation 111),[163] in which *threo*-(*Z,Z*)-4,5-dimethyloctadiene is cleanly equilibrated at 220 °C with the (*E,E*)-isomer. Another instructive study is that of Evans and Nelson,[13] who subjected all four racemates of alcohol (**163b**) to anionic oxy-Cope rearrangement; two are shown in equations (112) and (113). The *cis*- and *trans*-butenyl side chains lead to different stereoisomer mixtures, that in equation (112) giving a 96:4 ratio favoring one product, while in equation (113) the other predominates by 99:1. The specificity of these rearrangements was used to advantage in a stereospecific synthesis of (±)-juvabione. Another example of control of *erythro/threo* stereochemistry is seen in equation (16).

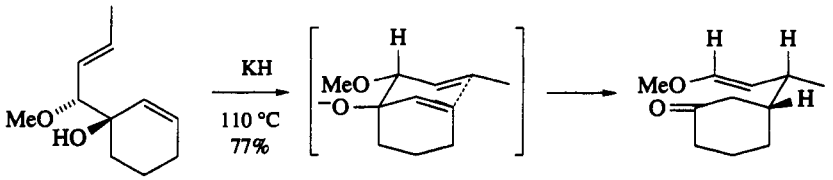
(110)

7.1.7.4 Transfer of Chirality

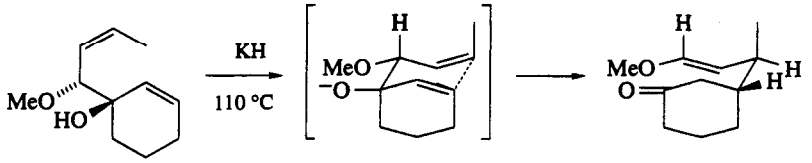
A final consequence of the chair transition state is its ability to effect a 'self-immolative' asymmetric synthesis, *i.e.* the transfer of chirality from a stereogenic center in the substrate to a new center in the



threo-(Z,Z) *threo-(E,E)* (111)



trans-(**163b**) (112)



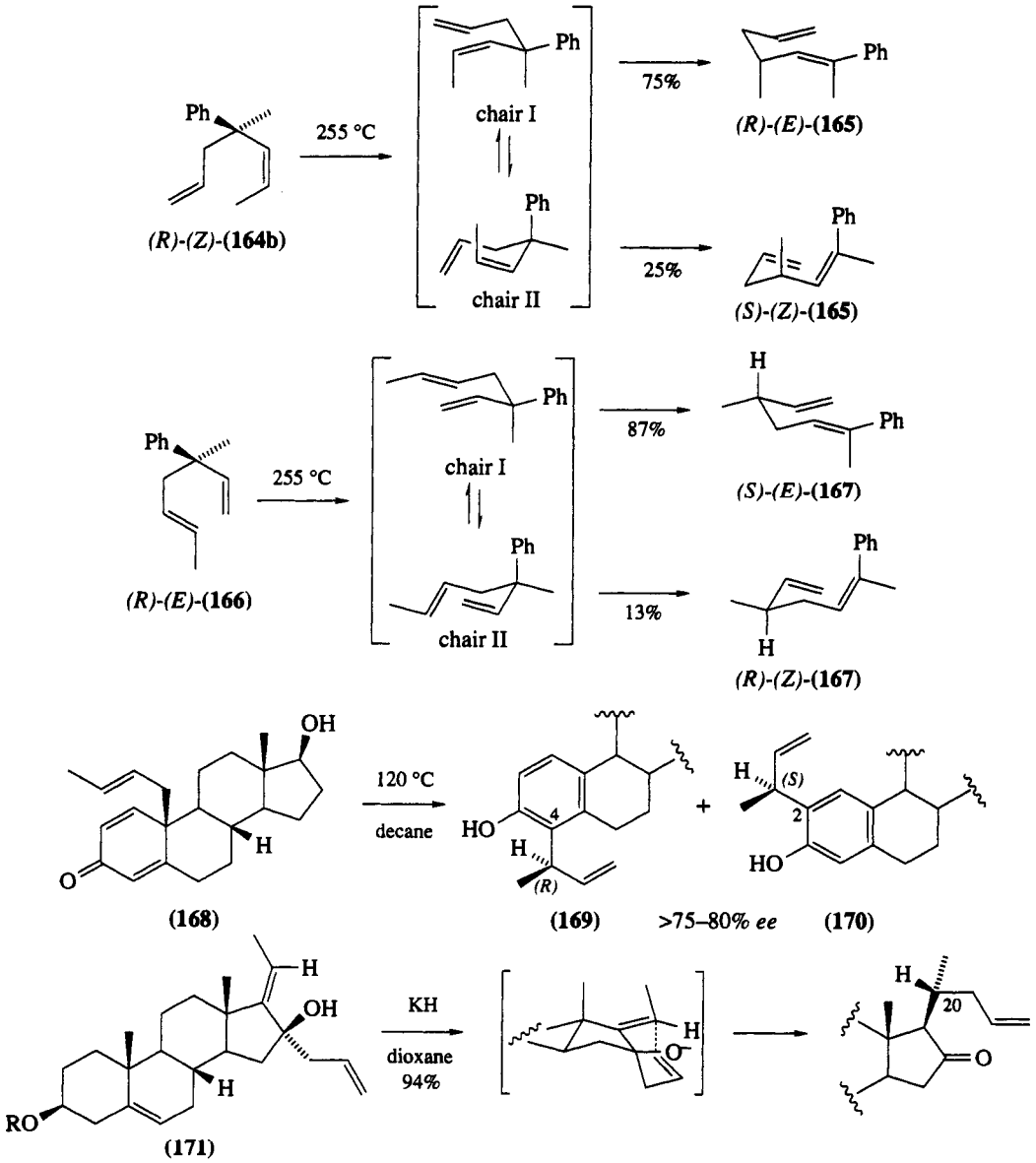
cis-(**163b**) (113)

product. This was first demonstrated by Hill and Gilman[24] in the investigation outlined in Scheme 19. Cope rearrangement of optically active (**164b**) led to two isomers of (**165**), resulting from the two chair transition states shown. The diastereomeric products had opposite configurations at both the double bond and asymmetric center, but most importantly, the degree of 'asymmetric transmission' was greater than 97%. Similar results were obtained with substrate (**166**), which gave the (*S*)-(*E*)- and (*R*)-(*Z*)-isomers of (**167**) in an 87:13 ratio, both formed with greater than 97% transfer of chirality. These results place an upper limit of 2–3% contribution from boat or any antara–antara transition states.[20] Another instructive example[164] is the Cope rearrangement of steroidal dienone (**168**); the chair transition state requires that an (*R*)-configuration be generated as the butenyl group migrates to C-4, but an (*S*)-configuration during migration to C-2.

The ability of the Cope rearrangement (as well as the Claisen and other sigmatropic rearrangements) to generate a new stereogenic center in a predictable configuration and with almost total stereospecificity is unique in organic synthesis in not requiring external chiral reagents, catalysts, or solvents; all the stereochemical information in the substrate is transferred to the product through a cyclic transition state which can usually be analyzed by the simple rules of cyclohexane conformational analysis. An elegant application is Koreeda's use of the anionic oxy-Cope rearrangement of (**171**) to create C-20 of the steroidal side chain in the correct (*R*)-configuration.[165] It is reassuring that the degree and direction of asymmetric induction in oxy-Cope and Pd-catalyzed Cope rearrangements[77] are essentially identical with those in simple thermal rearrangements.

7.1.8 CONCLUSIONS

Developments since 1940, when Cope first reported this striking rearrangement, have transformed it from a laboratory curiosity into a powerful synthetic method. Today's chemist can quickly assemble oxy-Cope substrates by Grignard additions and rearrange them at room temperature with base or metal catalysis. A wide range of ring sizes can be expanded or contracted by Cope rearrangements, and it has become one of the methods of choice for the preparation of medium rings. Equilibria can be controlled by choice of substituents and double bonds can be created in predictable configurations. The transfer of stereochemical information in a cyclic transition state allows stereogenic centers to be assembled in high optical purity. Finally, the emphasis in recent years on rearrangements of bridged bicyclic substrates has demonstrated that complex polycyclic molecules with six or more asymmetric centers can be constructed quickly and stereospecifically by rational design centered on Cope rearrangements.



Scheme 19 Transfer of chirality in Cope rearrangements

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7.2
Claisen Rearrangements

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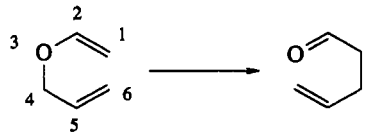
7.2.1 INTRODUCTION

This article surveys variants of the Claisen rearrangement that are of general use in stereoselective organic synthesis. Recent results concerning the influence of steric and electronic parameters on transition state geometries are highlighted. The impact of the Claisen methodology in modern synthetic strategy and its application for the preparation of highly functionalized derivatives is exemplified.

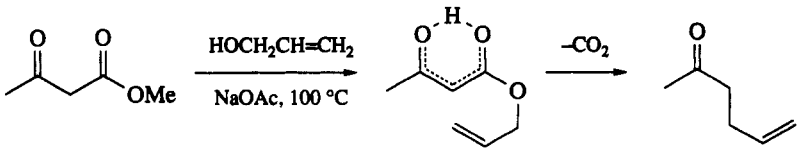
Since its discovery in 1912,[1] the Claisen rearrangement of allyl vinyl ethers (**1** → **2**; equation 1) has become one of the most powerful tools for stereoselective carbon–carbon bond formation.[2] Much of its current popularity is due to the subsequent development of a series of new variants of this 3,3-sigmatropic rearrangement. In 1940, Carroll reported the base-catalyzed rearrangement of β-keto esters and allylic alcohols to alkenic ketones (**3** → **4** → **5**; equation 2).[3] Twenty years later, Saucy and Marbet demonstrated the acid-catalyzed reaction of tertiary propargylic alcohols with isopropenyl methyl ether to

give β-ketoallenes in high yields (**6** → **7** → 8; equation 3).[4] An application of this process for the preparation of geranylacetone led to a commercial synthesis of vitamin A.



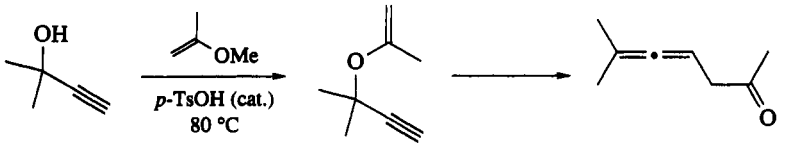
(1) (2)

Claisen (1)



(3) (4) (5)

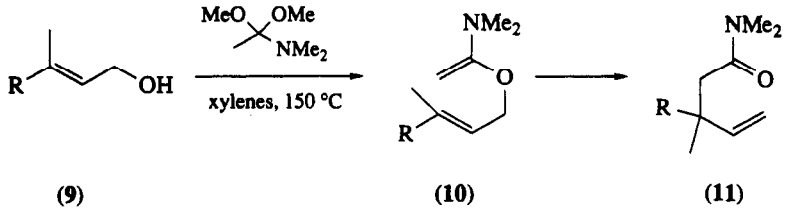
Carroll (2)



(6) (7) (8)

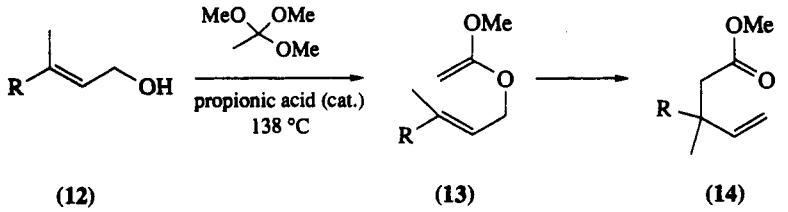
Saucy–Marbet (3)

Although the preparation of γ,δ-unsaturated carboxylic acids by the aliphatic Claisen rearrangement of magnesium enolates had been demonstrated as early as 1949,[5] a significant breakthrough was realized in 1964 by Eschenmoser and coworkers.[6] The exchange of amide acetals with allylic alcohols and subsequent *in situ* sigmatropic rearrangement greatly facilitated the stereoselective synthesis of γ,δ-unsaturated amides (**9** → **10** → 11; equation 4). The closely related acid-catalyzed exchange of orthoacetals with allylic alcohols, reported by Johnson and coworkers in 1970,[7] represents another important stage in the proliferation of the Claisen rearrangement in organic synthesis (**12** → **13** → **14**; equation 5). It is important to note that although both the Eschenmoser and the Johnson rearrangements are usually conducted at elevated temperatures, these conditions are required for the alcohol exchange reaction, and not for the actual rearrangement which can occur at significantly lower temperatures.[8]



(9) (10) (11)

Eschenmoser (4)

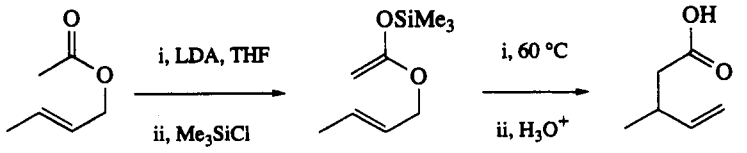


(12) (13) (14)

Johnson (5)

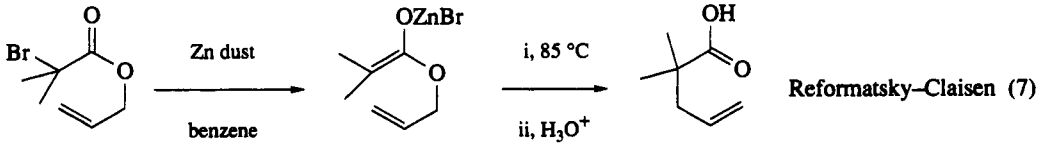
In 1972, a further brilliant improvement on the Claisen rearrangement was realized by Ireland and coworkers.[9] Ester enolization with lithium dialkylamide bases,[10] followed by silylation with TMS-Cl, generated reactive silyl ketene acetals at –78 °C or lower temperatures. Sigmatropic rearrangement to easily hydrolyzable γ,δ-unsaturated silyl esters occurred at ambient temperatures (**15** → **16** → **17**; equa-

tion 6). A particularly important aspect of this process is the simple control of enolate geometry that can be achieved by solvent selection.[11] The use of zinc enolates derived from α-halo esters in a Reformatsky–Claisen combination has also been briefly reported (**18** → **19** → **20**; equation 7).[12,13] However, the latter method has not been further developed, and in the past decade the Ireland silyl ester enolate sequence has proven to be perhaps the most general way to effect a stereocontrolled Claisen rearrangement.

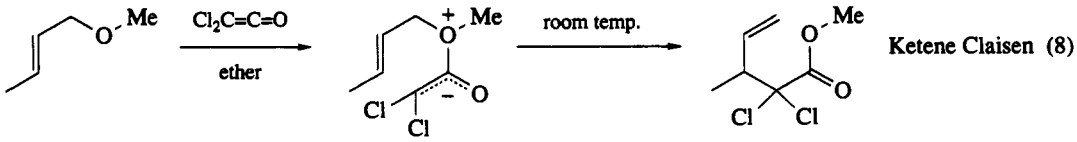


(15) **(16)** **(17)**

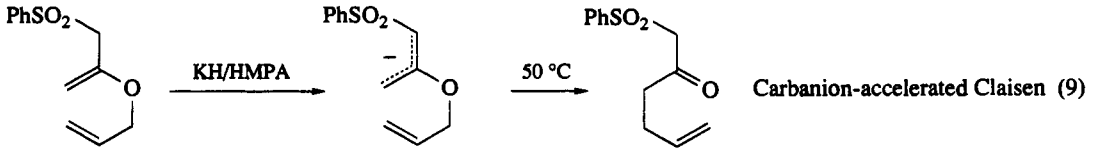
In 1978, Bellus and Malherbe reported a ketene version of the Claisen rearrangement. Treatment of allylic ethers with *in situ* prepared dichloroketene provided rearrangement products in good yield (**21** → **22** → **23**; equation 8).[14] This procedure works well also with allylic sulfides.[15,16] In 1982, finally, Denmark and Harmata demonstrated a first example of a carbanion-accelerated Claisen rearrangement (**24** → **25** → **26**; equation 9).[17] Related applications of the rate enhancement by formation of anionic species have been reported since,[18] and research in this area will undoubtedly provide further mechanistic insight into the 3,3-sigmatropic rearrangement and expand its synthetic scope even further.



(18) **(19)** **(20)**



(21) **(22)** **(23)**

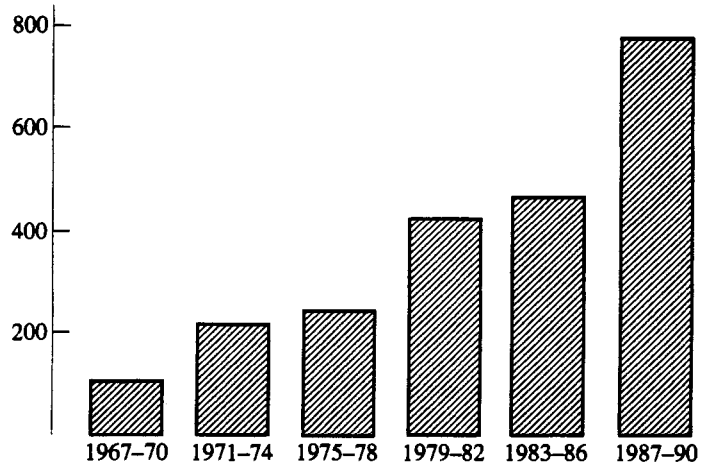


(24) **(25)** **(26)**

From 1964 to 1990, the discovery of highly versatile stereoselective variants supported a period of impressive growth in the number of synthetic efforts which employ a Claisen rearrangement for a key carbon–carbon bond forming process (Table 1). This increase in experimental applications was accompanied by a continuous interest in mechanistic analysis and theoretical understanding of the reaction.

In this review, the use of the Claisen rearrangement in stereoselective organic synthesis and mechanistic aspects of the reaction are highlighted. Due to the wealth of data, sections concerning the photo,[19] aza,[20] zwitterionic amino,[21] thia,[22] phospha[23] and metallo[24] as well as retro-Claisen[25] rearrangements had to be omitted. Polyhetero 3,3-sigmatropic shifts have also been excluded.[26] Consecutive processes involving Claisen rearrangements are covered in Chapter 7.3. The closely related 2,3-sigmatropic rearrangements are discussed in Chapter 4.6 of Volume 6 in this series. Literature examples were mostly taken from reports published between 1985 and 1990, in order to provide information complementary to previous[2] overviews.

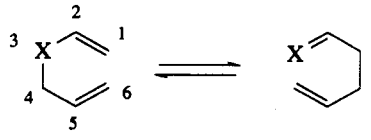
Table 1 Number of Publications with Reference to Claisen Rearrangements Between 1967 and 1990 (Source: Chemical Abstracts)



7.2.2 SYNTHETIC ASPECTS OF THE CLAISEN REARRANGEMENT

7.2.2.1 Definition

The Claisen rearrangement can formally be considered as the intramolecular S_N' addition of a carbonyl enol (X = O), thiocarbonyl enol (X = S) or enamine (X = N) to an allylic ether, sulfide or amine, respectively, forming a carbon–carbon σ-bond. The process involves concomitant π-bond migration and falls under the classification 3,3-sigmatropic shift.[27] It is usually referred to as concerted, although in fact a spectrum of mechanisms may be operative.[28] Other positions in (**27**) may be occupied by heteroatoms (hetero- and polyhetero-Claisen rearrangements) and the degree of unsaturation may be higher than depicted. In the aromatic Claisen rearrangement, carbons 1 and 2 are part of an aromatic system.



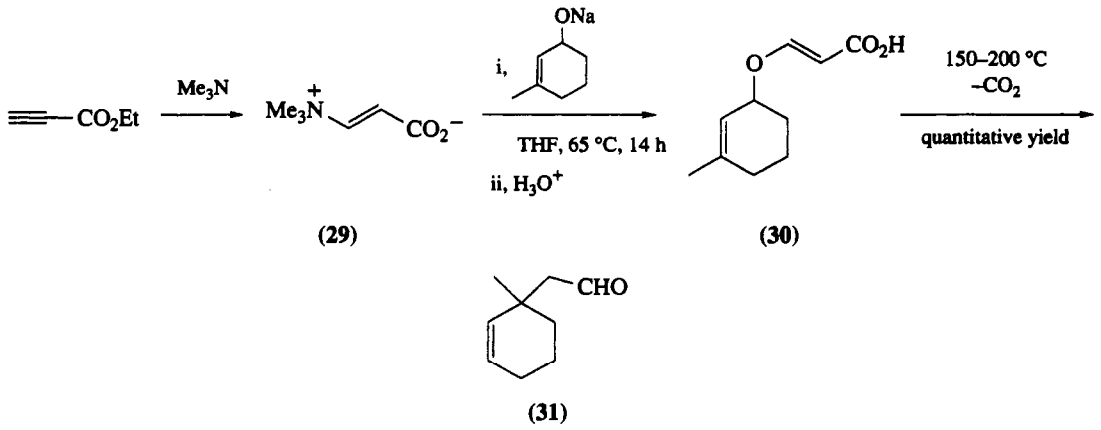
(**27**) (**28**)

X = O: Claisen rearrangement
X = S: thia-Claisen rearrangement
X = N: aza-Claisen rearrangement

7.2.2.2 Methods of Preparation of Allyl Vinyl Ethers

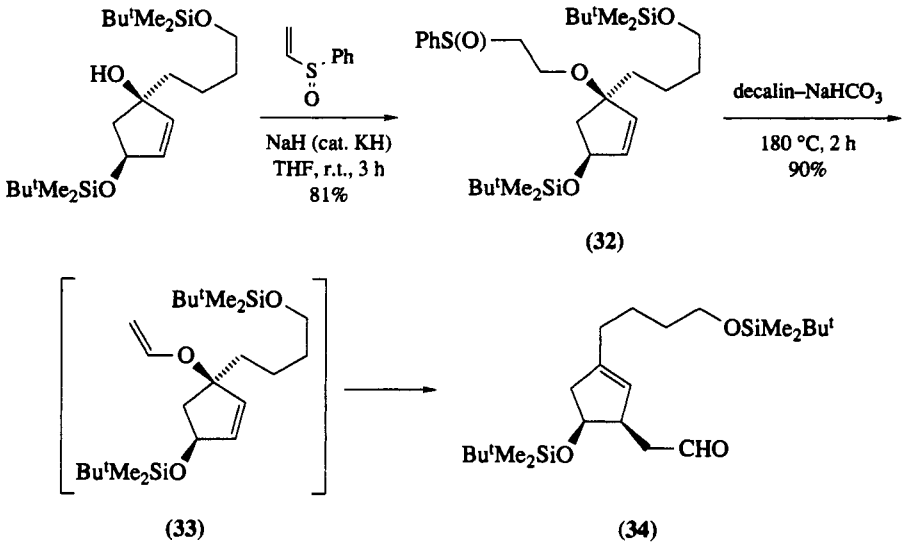
Allyl vinyl ethers are typically prepared by either mercury- or acid-catalyzed vinyl ether exchange with allylic alcohols or acid-catalyzed vinylation of allylic alcohols with acetals.[29] However, yields in these reactions are often low, and the use of mercury is not without concerns. Büchi and Vogel developed a mercury-free Claisen sequence, *via* reaction of sodium or lithium salts of primary and secondary allylic alcohols with the betaine (**29**) derived from ethyl propiolate and trimethylamine.[30] Heating of the product, (*E*)-3-(allyloxy)acrylic acid (**30**), leads to γ,δ-unsaturated aldehydes (**31**; Scheme 1). The scope of this reaction is limited to primary and secondary allylic alcohols. Tertiary allylic alcohols can be vinylated by a Michael-type addition to a vinyl sulfoxide, followed by elimination of PhSOH (Scheme 2).[31] This method is closely related to the earlier demonstrated intramolecular bromoetherification, followed by base-catalyzed elimination of HBr,[32] and the phenylselenenyl etherification/selenoxide elimination[33] reaction. Base-catalyzed intramolecular addition of allylic alcohols[34] or allyloxy radicals[35] to alkynes, or dehydration,[36] are alternative means for the construction of the vinyl ether functionality. Allyl vinyl ethers may also be generated from carbonyl precursors by Wittig-type alkenation reactions. Corey and Shulman made use of allyloxytrimethylphenylphosphonium ylides,[37] and Paquette and coworkers applied the Tebbe reagent for the preparation of allyl vinyl ether (**36**) from lactone (**35**) in the course

of a synthesis of (±)-precapnelladiene (Scheme 3).[38] Interestingly, this ring expansion occurs only when the methyl group on the six-membered ring can assume an equatorial position in the chair-like transition state. Epimerization at the carbonyl α-position occurs due to enolate formation under the strongly basic thermolysis conditions.



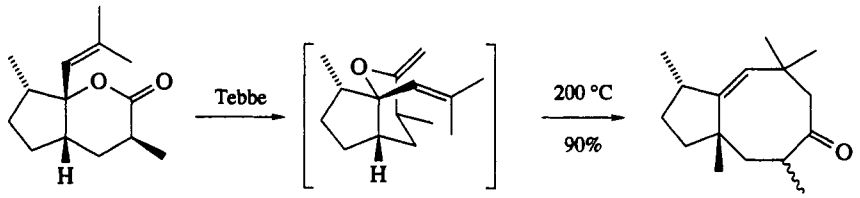
(29) (30) (31)

Scheme 1



(32) (33) (34)

Scheme 2



(35) (36) (37)

Scheme 3

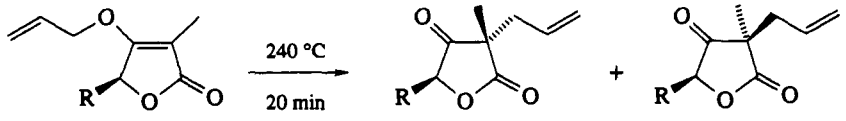
Whereas Eschenmoser and Johnson variants of the Claisen rearrangement utilize an excess of amide acetal and orthoester precursors, respectively, for generation of the vinyl ether functionality, the Carroll

and Ireland versions are especially useful because of the ease and economy in preparing the Claisen system, as will be seen in the following sections.

7.2.2.3 The Claisen Rearrangement of Allyl Vinyl Ethers

The uncatalyzed 'traditional' Claisen rearrangement of allyl vinyl ethers is still very much in use, especially for the preparation of quaternary centers of carbocyclic systems. The rearrangement is highly exothermic, but generally requires temperatures of 150–200 °C and is therefore limited to thermally stable compounds.

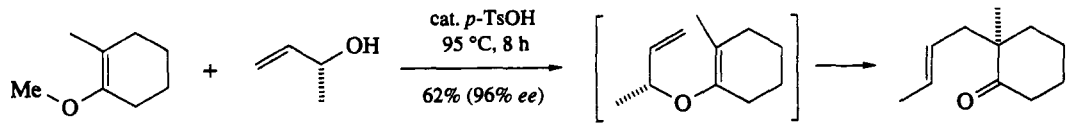
Recent representative examples of this procedure include an α-allylation of β-tetronic acids (Scheme 4),[39] the preparation of chiral 2,2-disubstituted cyclohexanones (**42**) in high enantiomeric excess *via* chirality transfer (Scheme 5),[40] and the rearrangement of intermediates for conformationally constrained peptide mimics (Scheme 6).[41] For their synthesis of neosporol, Ziegler and Nangia alkylated the potassium enolate (**46**) with mesylate (**47**) in HMPA.[42] The yield in the rearrangement of nitrile (**48**) was highly dependent upon the purity of the starting material. Trace impurities increased the amount of elimination product. In silylated glassware[43] and under high dilution conditions, a 16:1 mixture of diastereomeric ketones (**49**) and (**50**) was isolated (Scheme 7).



(**38**) (**39**) (**40**)

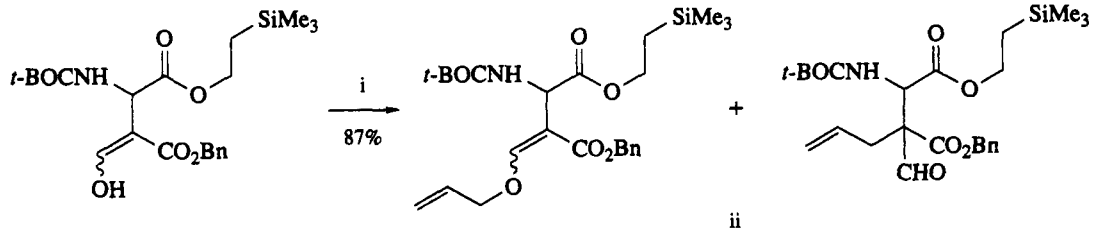
	Isolated yield (%)	
R = Me	56	14
R = Bn	56	18
R = Pr^i	58	7

Scheme 4



(**41**) (**42**)

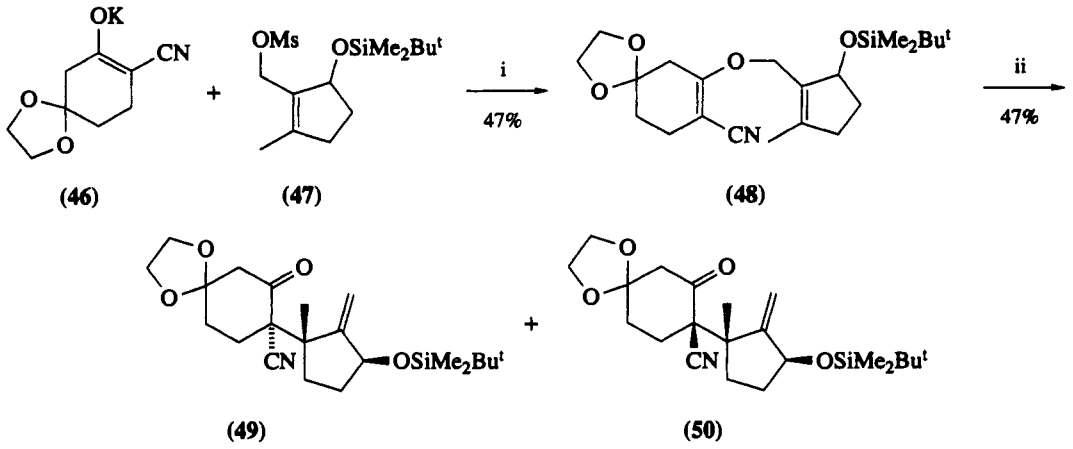
Scheme 5



(**43**) (**44**) (**45**)

i, allyl iodide (1.2 equiv.), Pr^i_2NEt (1.3 equiv.), acetone, 16 h; (**44**):(**45**) = 9:1; ii, decalin, reflux, 1 h

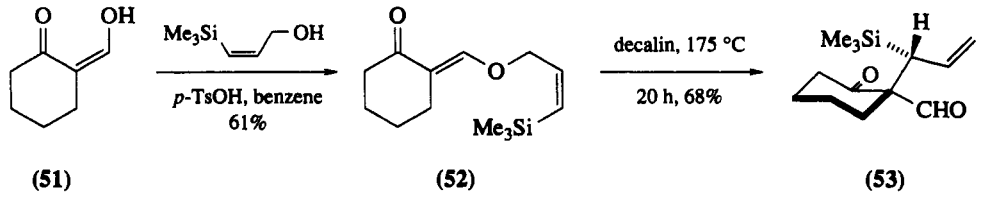
Scheme 6



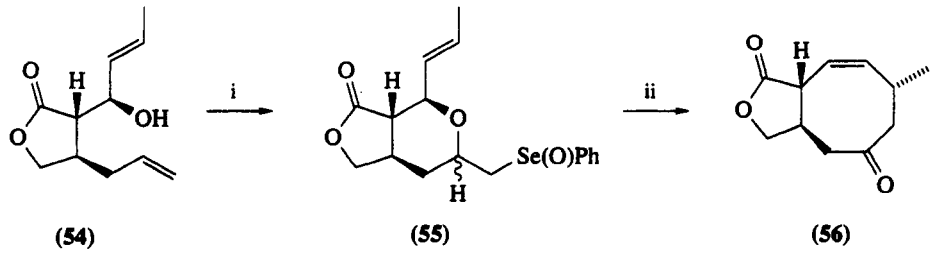
i, THF/HMPA, 0 °C, 18-crown-6, 2 h; ii, nonane, 151 °C, 4 h

Scheme 7

In a series of elegant studies, Paquette and coworkers demonstrated the potential of the Claisen rearrangement for the stereocontrolled total synthesis of natural products.[44] Dehydrative coupling[45] of (*Z*)-3-(trimethylsilyl)-2-propen-1-ol with cyclohexanone (**51**) under Kuwajima's conditions,[46] followed by rearrangement of enol ether (**52**) in decalin, led in excellent stereoselectivity (>99:1) to aldehyde (**53**; Scheme 8).[47] Concise construction of the eight-membered core of acetoxycrenulidine was achieved by intramolecular phenylseleno etherification of lactone (**54**), introduction of the exocyclic vinyl ether double bond by selenoxide elimination and subsequent Claisen rearrangement (Scheme 9, 66% from **54**).[48]



Scheme 8

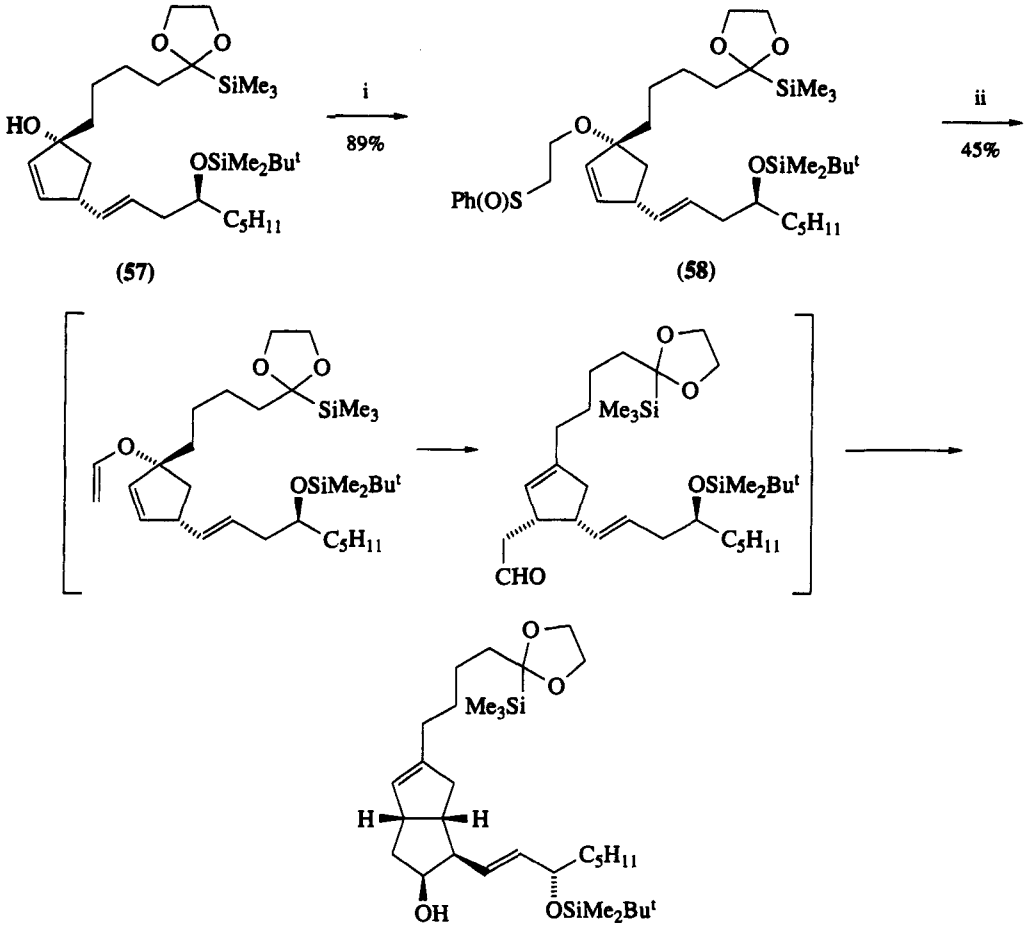


i, *N*-(phenylseleno)phthalimide, CH_2Cl_2; $NaIO_4$, $NaHCO_3$, MeOH, H_2O; ii, Et_2NH, mesitylene, Δ

Scheme 9

Mandai, Saito and coworkers recently described a new synthesis of isocarbacyclin, which features a crucial one-pot, three-step transformation: tandem tertiary allyl vinyl ether formation, Claisen rearrangement, and ene cyclization led from alcohol (**57**) directly to bicyclo[3.3.0]octane (**59**; Scheme 10).[49]

Clearly, due to improvements in the preparation of the allyl vinyl ether moiety, there is a trend even in the classical Claisen rearrangement to tackle more complex structural challenges successfully.



i, phenyl vinyl sulfoxide, NaH (1 equiv.)/KH (cat.), THF, r.t., 4 h; ii, $NaHCO_3$ (excess), decalin–α-pinane (2:1), 200 °C, 24 h

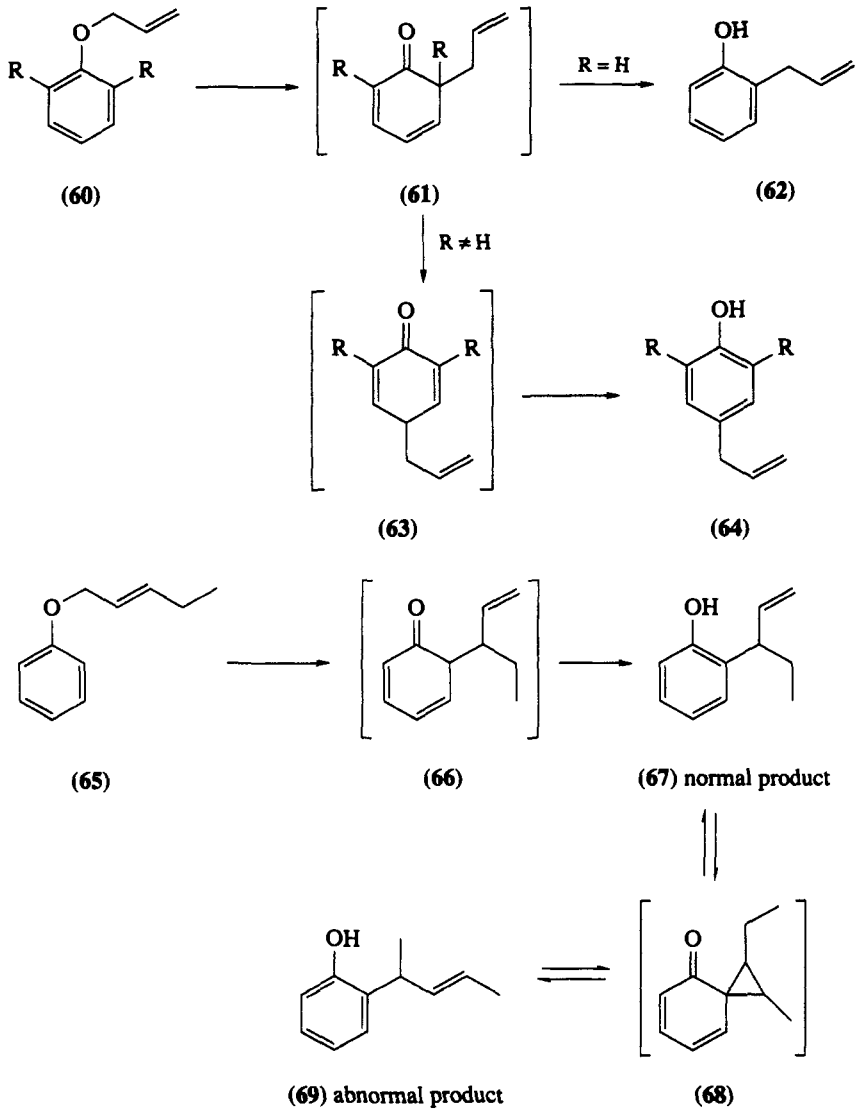
Scheme 10

7.2.2.4 The Aromatic Claisen Rearrangement

3,3-Sigmatropic rearrangement of an allyl aryl ether gives an *ortho*-dienone, which usually enolizes rapidly to the *ortho*-allylphenol (*ortho*-Claisen rearrangement, **60** → **62**, equation 10). If the *ortho* position is substituted, a second 3,3-sigmatropic shift followed by enolization yields a *para*-allylphenol (*para*-Claisen rearrangement, **60** → **64**, equation 10). In general, the *ortho*-Claisen product predominates, but sometimes some *para* product is obtained even if one or both *ortho* positions are unsubstituted.[50] No reaction occurs when all *ortho* and *para* positions are substituted. The rearrangement requires temperatures in the range of 150 to 225 °C and is usually regarded as concerted.[51] In the 'abnormal' Claisen rearrangement,[52] a subsequent homodienyl 1,5-sigmatropic H-shift leads to the formation of isomeric allyl phenols (**67**) and (**69**) (equation 11).[53] Recent applications of the aromatic Claisen rearrangement involve syntheses of flavenes,[54] dideoxydaunomycinone[55] and dihydrocoumarins.[56]

7.2.2.5 The Carroll Rearrangement

Among the most favorable features of the Carroll variant[3] of the Claisen rearrangement are the relative ease of preparation of the parent system by condensation of allylic alcohols with acetoacetic ester[57] or diketene and the defined configuration of the intermediately generated double bond. The Carroll rearrange-

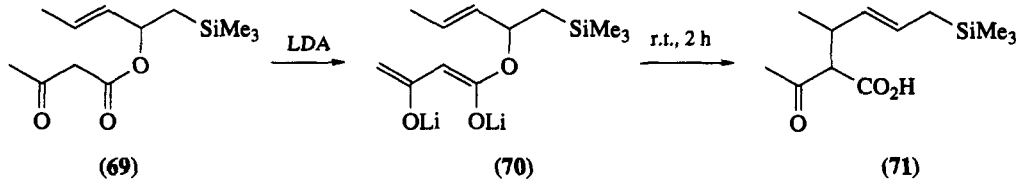


(10)

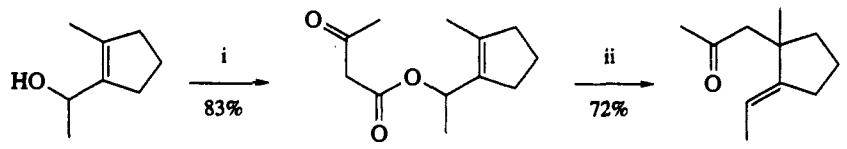
(11)

ment has been utilized on a commercial scale for the synthesis of geranyl acetone as well as β-ionone.[58,59]

An improved version of the Carroll reaction, the ester enolate Carroll rearrangement, was reported in 1984 by Wilson and Price.[60] Dianions of allylic acetoacetates, generated by treatment with 2 equiv. of LDA at –78 °C in THF, were rearranged at room temperature or 65 °C to yield β-keto acids in 40–80% yield (equation 12). In the course of a synthesis of the sesquiterpene isocomene, Snider and Beal used this method for the rearrangement of acetoacetate (**73**), prepared in 83% yield from reaction of cyclopentene (**72**) with diketene and a catalytic amount of DMAP (Scheme 11).[61] The (*E*)-isomer of ketone (**74**) is obtained stereospecifically, since there is a severe steric interaction between the methyl groups in the Carroll rearrangement transition state leading to the (*Z*)-isomer.



(12)

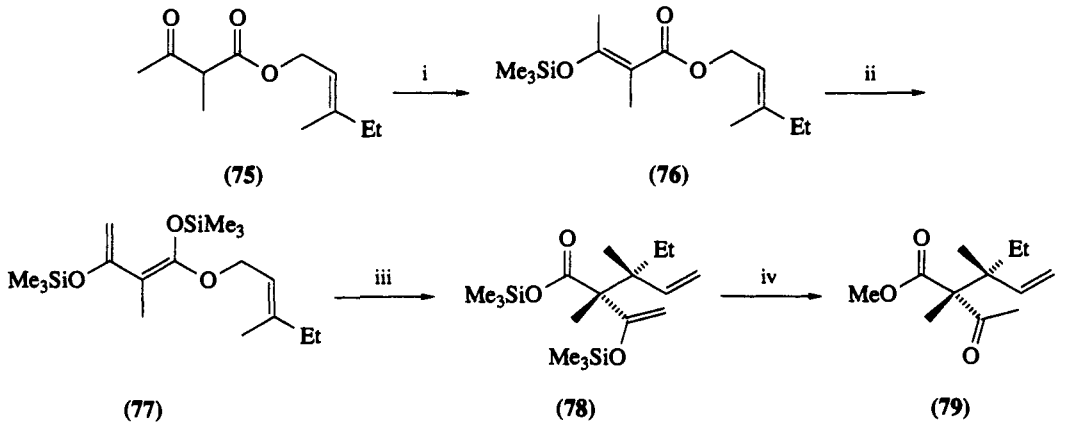


(72) (73) (74)

i, diketene, DMAP, ether, –25 °C to r.t.; ii, 2 equiv. LDA, THF, reflux and then CCl_4, reflux

Scheme 11

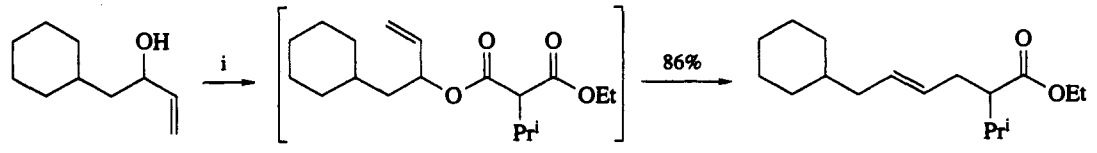
Another modification of the Carroll rearrangement was used by Gilbert and Kelly for the diastereoselective formation of contiguous quaternary centers.[62] Transformation of an allylic β-keto ester into a silylketene acetal is followed by a 3,3-sigmatropic rearrangement which generates the desired carbon–carbon bond in good yield and with excellent stereocontrol (Scheme 12). Ester (**79**) was thus isolated as a single isomer in 73% yield.



i, HMDS, imidazole, reflux; ii, LiTMP, TMEDA, THF, –50 °C; Me_3SiCl, Et_3N, HMPA, –78 °C, 4 h; iii, r.t., 3 h, then 40 °C, 12 h; iv, 1% HCl, MeOH, 0 °C, 15 min; CH_2N_2

Scheme 12

A Ciba-Geigy group used the Carroll reaction for the synthesis of hydroxyethylene dipeptide isosteres.[63] Alcohol (**80**) was converted with diethyl isopropylmalonate to the mixed malonic ester derivative (**81**) by $Ti(OEt)_4$ catalysis. Subsequent sigmatropic rearrangement of (**81**) was also effectively catalyzed by $Ti(OEt)_4$, thereby allowing a one-step conversion of the allylic alcohol (**80**) to ester (**82**) (Scheme 13).



(80) (81) (82)

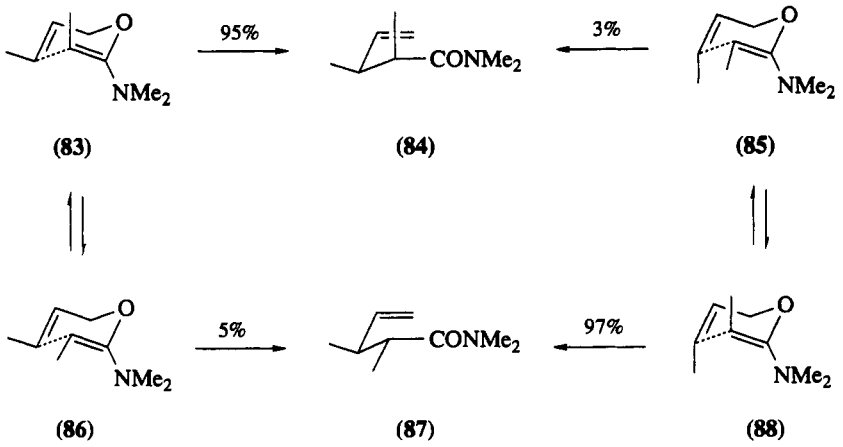
i, diethyl isopropylmalonate, $Ti(OEt)_4$, 160–190 °C

Scheme 13

7.2.2.6 The Eschenmoser Amide Acetal Rearrangement

The 3,3-sigmatropic shift of ketene *N,O*-acetals, first developed by Eschenmoser,[6,64] preceded studies of the ynamine-Claisen rearrangement,[65] where the reactive intermediate is formed at ambient tempera-

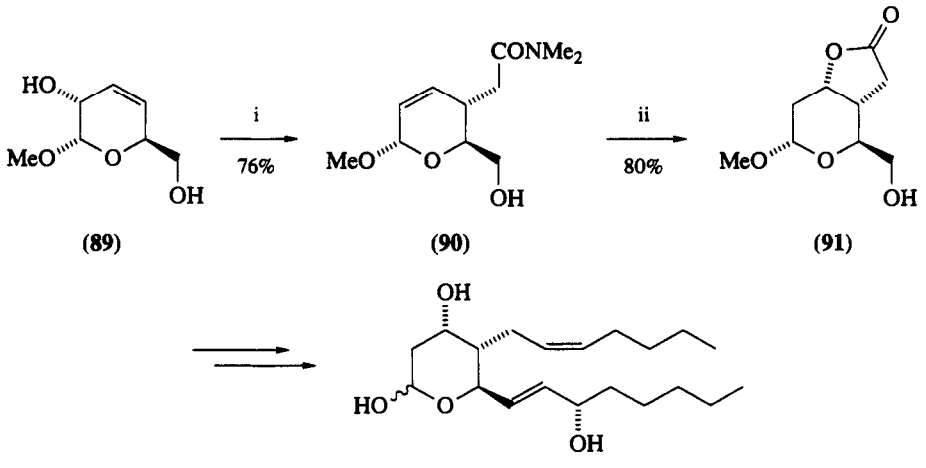
ture by treatment of the ynamine with an allylic alcohol. Sucrow and Richter have studied the stereochemistry of the rearrangement of the dimethyl acetal of *N,N*-dimethylpropionamide with (*E*)- and (*Z*)-crotyl alcohol.[66] Based on the assumption of a chair-like transition state,[67] the stereochemistry of the products can be explained by an axial orientation of the C(1)-methyl group of the ketene *N,O*-acetal (**83** and **88**; equation 13). (*Z*)-Ketene *N,O*-acetals (**83**) and (**88**) are predominant under thermodynamic reaction conditions. Using the ynamine method, Bartlett and Hahne succeeded in preparing the less stable kinetic diethylamide analogs of (*E*)-ketene *N,O*-acetals (**85**) and (**86**) at 140 °C, where rearrangement is competitive with isomerization.[68]



(13)

In a stereocontrolled route to thromboxane B_2, Corey and coworkers used the Eschenmoser rearrangement for the preparation of lactone (**91**; Scheme 14).[69] The product of the 3,3-sigmatropic shift, amide (**90**), is directly iodolactonized, thus avoiding often troublesome amide hydrolysis conditions. Another application involving a carbohydrate derivative was demonstrated by Fraser-Reid and coworkers (Scheme 15).[70] Reductive elimination of benzylidene (**92**), followed by *in situ* alkylation, Wittig reaction, DIBAL-H reduction and rearrangement, led to amide (**94**), which was transformed into the corresponding pyranoside diquinane by double radical cyclization.

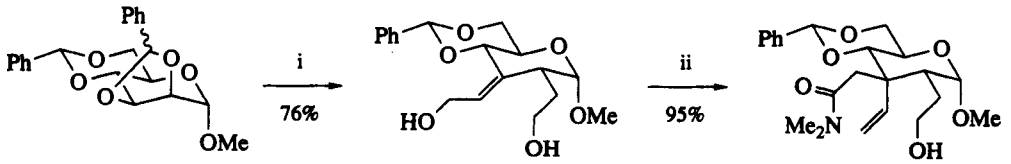
N-Silylketene *N,O*-acetals can also be generated from allyl *N*-phenylimidates by deprotonation and subsequent *N*-silylation.[71] Predominant (*Z*)-configuration of the vinyl ether double bond in (**96**) leads, under the assumption of a chair transition state, with allylimidates (**95a–d**) preferentially to *anti*-products



Thromboxane B_2

i, *N,N*-dimethylacetamide dimethyl acetal, diglyme, 25 to 160 °C; ii, I_2, THF/H_2O, 0 °C, then Bu_3SnH, $NaBH_4$, benzene

Scheme 14

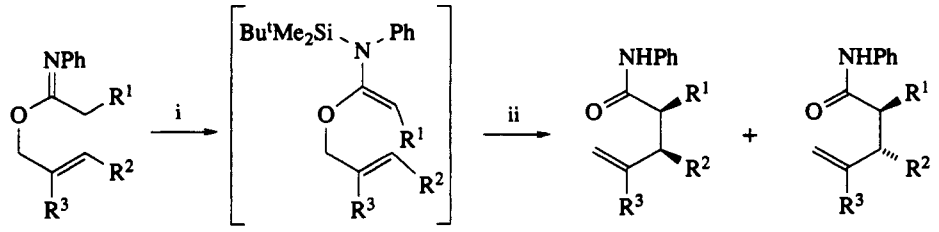


(92) (93) (94)

i, BuLi; $BrCH_2CO_2Et$; Ph_3PCHCO_2Et, THF; DIBAL-H, toluene; ii, *N,N*-dimethylacetamide dimethyl acetal, toluene, reflux, 4 Å MS; MeOH, H_2O, Et_3N

Scheme 15

(**97a–d**) (Scheme 16, Table 2). The sigmatropic rearrangement of (*E*)-configured allylic ester occurs smoothly at room temperature.[72] The striking drop in stereoselectivity observed for (**95e**) can be attributed to the partial formation of the (*E*)-configured enolate, probably due to energetically favorable chelate formation opposing energetically unfavorable $A^{1,3}$-strain[73] during the enolization process.



(95) (96) (97) (98)

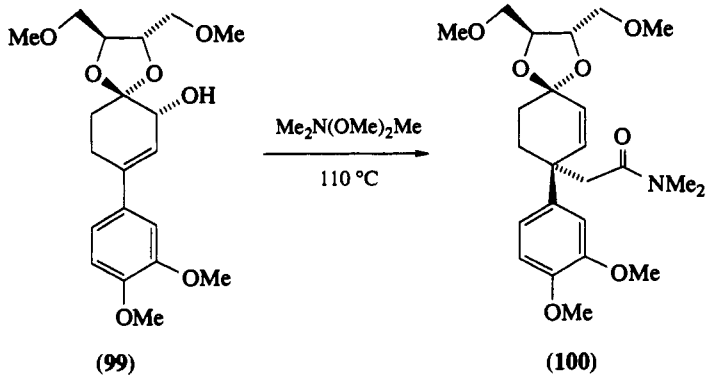
i, LDEA, THF, 1 h, –78 °C; Bu^tMe_2SiCl, HMPA, 1 h, –20 °C; ii, 24 h, r.t.; NH_4Cl, H_2O

Scheme 16

Table 2 Claisen Rearrangements of Allylimidates (**95**)[71]

Entry	R^1	R^2	R^3	*Yield (%)*	*Ratio* (**97**) : (**98**)
1	Me	Me	H	67	90.7 : 9.3
2	Me	*n*-Pr	H	66	90.9 : 9.1
3	Me	Me	Me	59	98.1 : 1.9
4	Me	Me	$SiMe_3$	64	99.2 : 0.8
5	OMe	Me	H	54	46.6 : 53.4

Complete chirality transfer in the formation of the quatemary center in acetal (**100**) was observed by Fujioka and coworkers in the synthesis of (*R*)-(+)-3′-methoxy-4′-*O*-methyljoubertiamine (Scheme 17).[74]

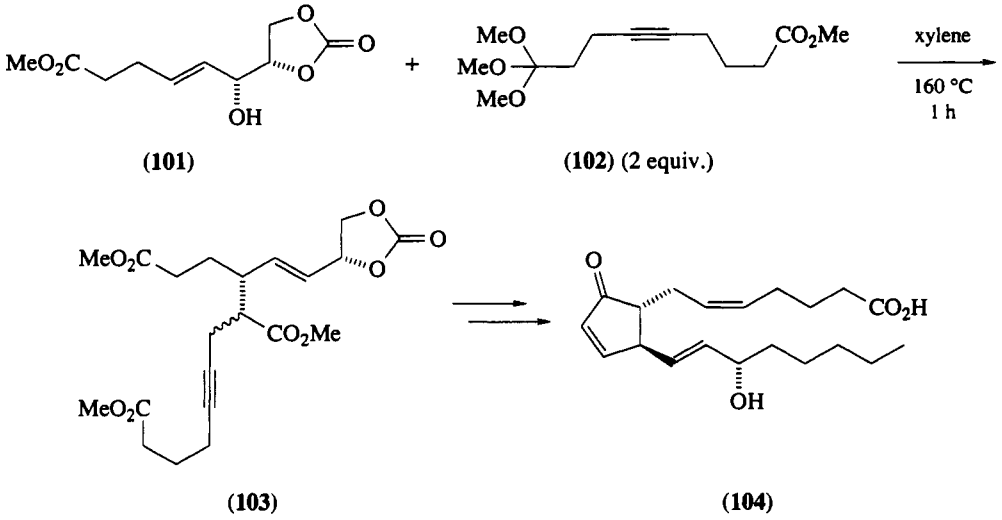


(99) (100)

Scheme 17

7.2.2.7 The Johnson Ortho Ester Rearrangement

Contrary to the Carroll and the Eschenmoser rearrangements, Johnson rearrangement[7] of propionic acid derivatives fails to give stereochemically defined ketene acetals.[75,76] This variant has therefore most successfully been applied to orthoacetates or ortho esters with fugitive groups in the α-position that are eliminated after the rearrangement step.[77] The stereoselectivity of the 3,3-sigmatropic shift itself, however, is excellent (generally >98%[7]). In an elegant synthesis of (+)-15(*S*)-prostaglandin A_2, Stork and Raucher used the Johnson rearrangement for a crucial transfer of chirality from alcohol (**101**) to ester (**103**) (Scheme 18a).[78] Due to expected formation of a mixture of (*Z*)- and (E)-ketene acetals, approximately a 1:1 mixture of epimers is formed (which in this particular synthesis is irrelevant because the center is equilibrated at the end).



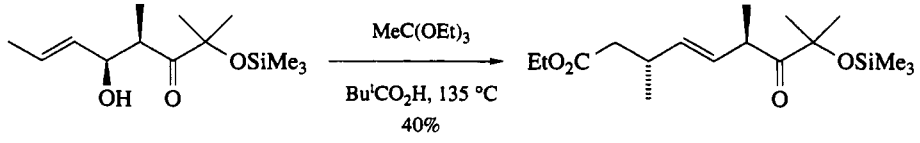
(**101**) (**102**) (2 equiv.)

(**103**) (**104**)

Scheme 18a

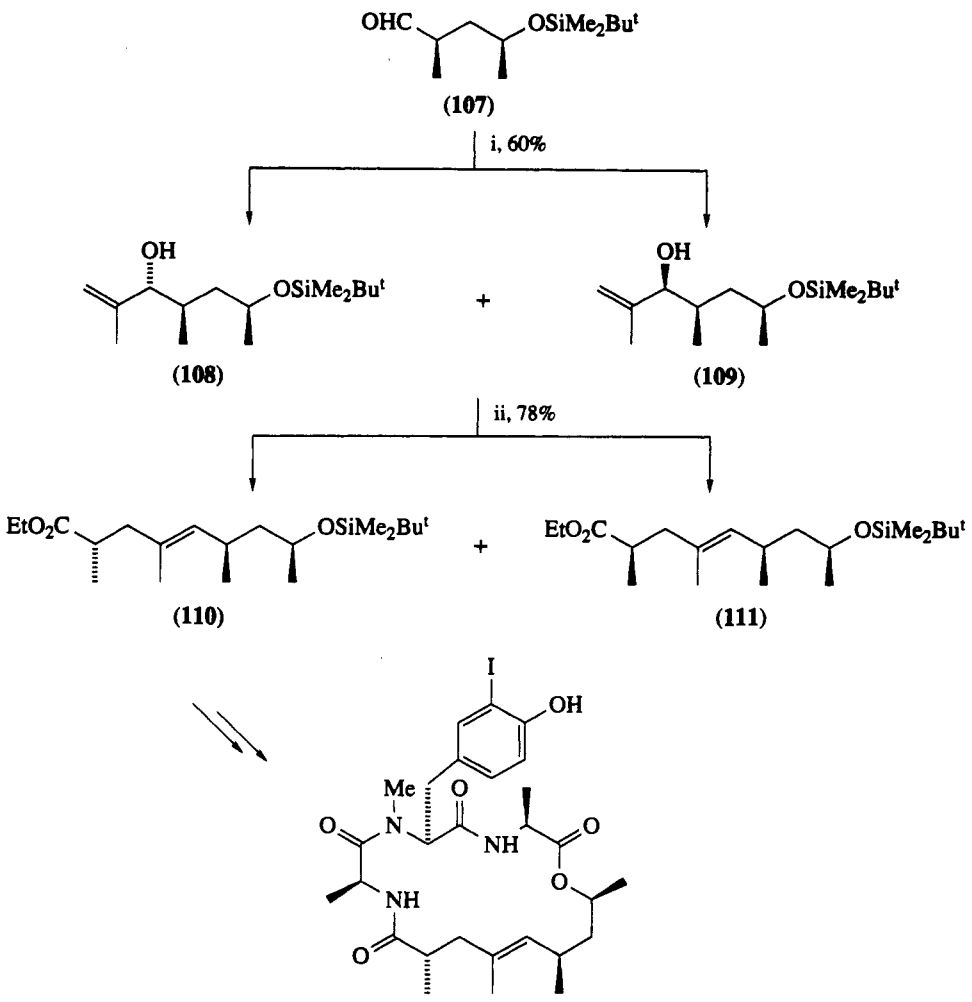
In an attempt to develop a synthetic strategy for 1,4- and 1,5-stereoselection by sequential aldol addition to α,β-unsaturated aldehydes followed by Claisen rearrangement, Heathcock and coworkers examined the Johnson–Faulkner rearrangement of aldol (**105**; Equation 14).[79] Although keto ester (**106**) was obtained in 40% yield, the major products seemed to derive from β-elimination.[80] In a somewhat related system, rearrangement of allylic alcohols (**108**) and (**109**), obtained by addition of isopropenylmagnesium bromide to aldehyde (**107**), yielded the same 1.5:1 mixture of ethyl esters (**110**) and (**111**) (Scheme 18b).[81] The desired isomer (**110**) was purified by HPLC and used in the total synthesis of the cyclodepsipeptide geodiamolide A. Suzuki, Kametani and coworkers applied the ortho ester rearrangement in their enantioselective synthesis of (–)-chokol A.[82] Allyl alcohol (**112**) was converted into the separable methyl esters (**113**) (51% yield) and (**114**) (19% yield), along with 5% recovered starting material (Scheme 19).

In the context of the synthesis of a precursor of 1α,25-dihydroxyvitamin D_3, Posner and Kinter treated allylic alcohol (**115**) with ethyl orthoacetate in a sealed tube.[83,84] The resultant γ,δ-unsaturated ester (**116**), formed in 85% yield, was sulfinated, oxidized and pyrolyzed to form the desired dienoate ester (**117**) in 35–40% overall yield (Scheme 20). This sequence was considerably improved by the use of sulfinylacetate (**118**). Johnson rearrangement and subsequent *in situ* sulfoxide pyrolytic 1,2-elimination gave ester (**117**) in a gratifying 89% yield as a 4:1 mixture of (*E*)/(*Z*) geometrical isomers.[85]



(14)

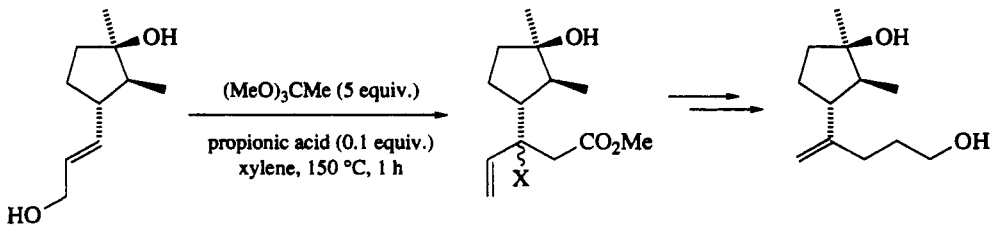
(**105**) (**106**)



Geodiamolide A

i, $H_2C{=}C(Me)MgBr$, THF, reflux; ii, $MeCH_2C(OEt)_3$, $EtCO_2H$, 110 °C

Scheme 18b

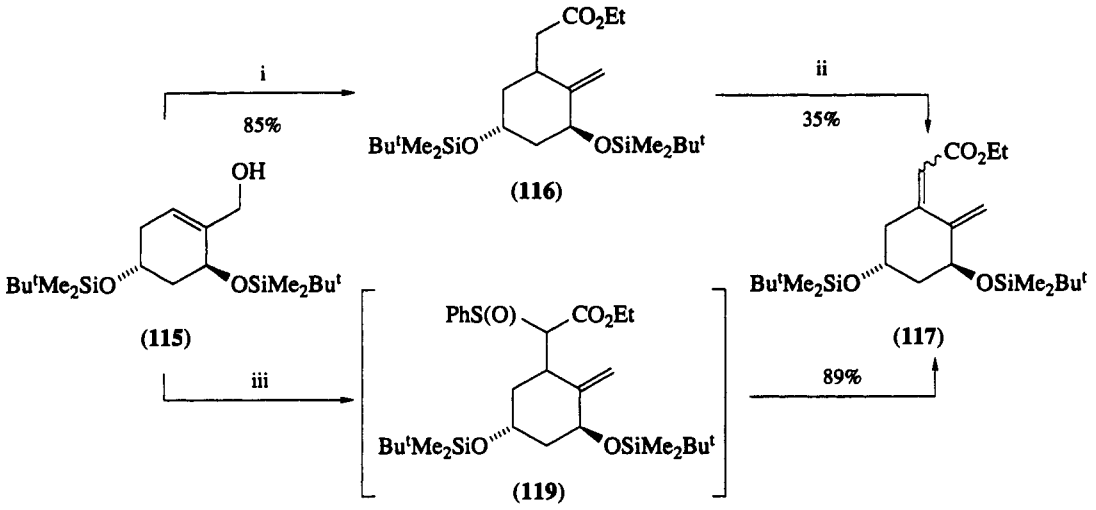


(112) (113) X = β-H (114) X = α-H (–)-Chokol A

Scheme 19

7.2.2.8 The Ireland Silyl Ester Enolate Rearrangement

Since its introduction in 1972,[9] the Ireland silyl ester enolate variant of the Claisen rearrangement has become increasingly popular in organic synthesis. Areas of successful applications include the polyether



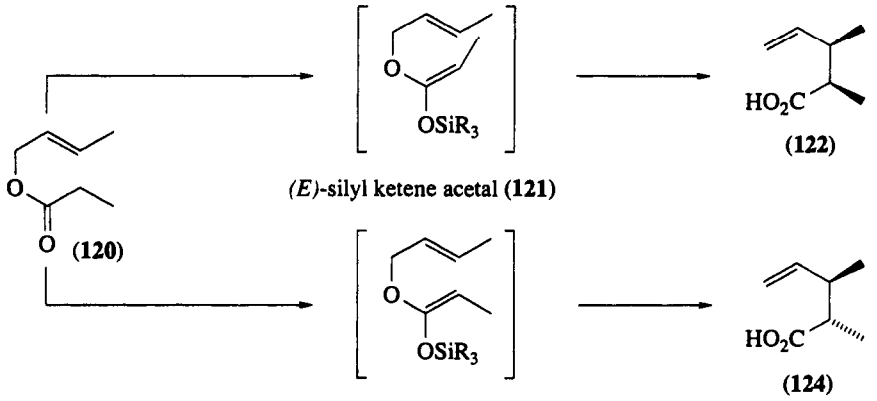
i, $MeC(OEt)_3$, CH_2Cl_2, acid (cat.), 150 °C, 2 h; ii, LDA, PhSSPh; MCPBA, 150 °C, 2 h; iii, $PhS(O)CH_2C(OEt)_3$ (**118**), trimethylbenzoic acid (cat.), CH_2Cl_2, 100 °C, 12 h

Scheme 20

antibiotics,[86] terpenes,[87] steroids,[88] iridoids,[89] tetronates,[90] amino acids,[91,92] *C*-glycosides,[93] carbocycles,[94] alkyl fluorides,[95] stannanes[96] and silanes.[97,98]

Several factors contribute to the versatility of the ester enolate Claisen rearrangement. Among these are the ability to use a stoichiometric combination of the alcohol and the acid components, the relatively low temperature[9c,99] of the pericyclic process that allows for the assembly of complex, highly functionalized structures, and the transformation of a carbon–oxygen into a carbon–carbon bond that lends itself easily to the assembly of contiguous quaternary centers.[100,101]

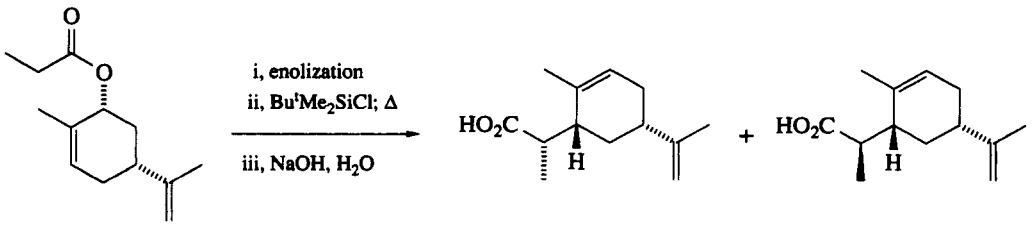
Another particularly important aspect of the Ireland rearrangement is that, through an efficient control of ketene acetal geometry, a highly reliable and predictable transfer of stereochemistry from starting material to product can be realized (Scheme 21).[9] Deprotonation of crotyl ester (**120**) with LDA[102] in THF leads, *via* the selective formation of the kinetically favored (*Z*)-ester enolate,[103,104] upon silylation to the (*E*)-silylketene acetal (**121**).[105] After rearrangement at 65 °C and mild hydrolysis of the silyl ester, an 87:13 ratio of γ,δ-unsaturated acids (**122**) and (**124**) is isolated in 79% yield. These two products can be obtained in a 19:81 ratio by using 23% HMPA/THF as a solvent system for the generation of the thermodynamically favored[106] (*Z*)-silylketene acetal (**123**) *via* the corresponding (*E*)-lithium enolate.[107]



Conditions	*Yield (%)*	*Ratio (122):(124)*
LDA, THF; Me_3SiCl; Δ; $NaOH/H_2O$	79	87:13
LDA, THF/23% HMPA; Me_3SiCl; Δ; $NaOH/H_2O$	73	19:81

Scheme 21

The stereoselectivity of the formation of the (*E*)-lithium enolate and thus of the entire rearrangement can be significantly increased by a change in the reaction solvent from 23% HMPA/THF to 45% DMPU/THF (Scheme 22).[108,109]

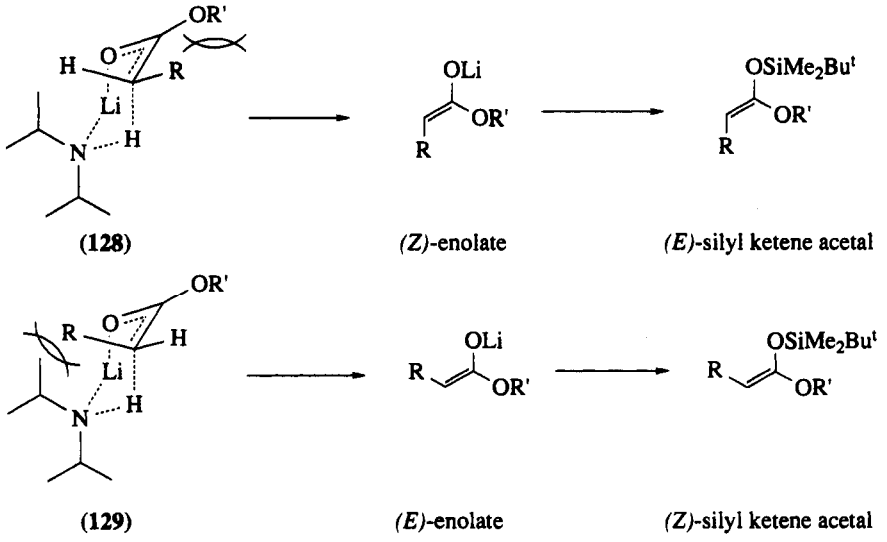


(125) (126) (127)

Enolization conditions	*(126):(127)*	*Yield (%)*
LDA, 45% DMPU/THF	98:2	60
LDA, 23% HMPA/THF	90:10	70
LDA, THF	25:75	56

Scheme 22

The preferred formation of the kinetically favored (*Z*)-silylketene acetal with amide bases in THF can be rationalized by a cyclic transition state model (**128**) that enables a close interaction between Li^+ cation, carbonyl oxygen and base (Scheme 23). The presence of additives such as HMPA or DMPU results in a greater degree of solvation of the lithium cation and a weakened Li^+–carbonyl oxygen interaction. Accordingly, the association between base and ester is diminished and the 1,3-diaxial strain in transition state (**129**) is reduced, whereas transition state (**128**) is still destabilized by $A^{1,3}$-strain.[110] In the presence of a slight excess of ester in the enolization mixture, a kinetic resolution process accounts for an additional increase in the ratio of the (*E*)- *vs.* the (*Z*)-lithium enolate (Table 3).[108]



(**128**) (*Z*)-enolate (*E*)-silyl ketene acetal

(**129**) (*E*)-enolate (*Z*)-silyl ketene acetal

Scheme 23

It is important to note, however, that an observed erosion of diastereoselectivity in the Ireland silyl ester enolate rearrangement can be attributed either to the geometric integrity of the silylketene acetals or the selectivity of the chair-like *vs.* boat-like transition states, and interpretation and improvement of experimental stereoselectivities must take into account both of these factors.

As the ester enolate Claisen rearrangement allows for a stoichiometric combination of alcohol and acid components, it has been used for the formation of strategically important C—C bonds by esterification or lactonization and subsequent rearrangement, such as is elegantly demonstrated in the synthesis of the antibiotic chlorothricolide (Scheme 24).[111] Radical decomposition[112] of the selenoester of (**132**) leads to

Table 3 Effect of Ester to Base Ratio on Stereoselectivity in Silylketene Acetal (SKA) Formation of Ethyl Propionate with LDA[108]

Entry	*Solvent*	*Ester:base*	*(Z)-:(E)-SKA*	*Yield (%)*
1	THF	1.4:1	1:1	5
2	THF	1 + 0.2:1[a]	20:80	35
3	THF	1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30% DMPU	1.2:1	≥98:2	70
6	THF/30% DMPU	0.95:1	67:33	90
7	THF/30% DMPU	0.8:1	68:32	85
8	THF/30% DMPU	0.5:1	60:40	95
9	THF/30% DMPU	0.3:1	60:40	95
10	THF/45% DMPU	1.05:1	≥98:2	80
11	THF/45% DMPU	0.8:1	93:7	90
12	THF/45% DMPU	0.5:1	84:16	85
13	THF/23% HMPA	1.2:1	93:7	65
14	THF/23% HMPA	1:1	85:15	80
15	THF/23% HMPA	0.8:1	59:41	40
16	THF/23% HMPA	0.6:1	55:45	35
17	THF/23% HMPA	0.4:1	54:46	40

[a]0.2 equiv. of the ester were added *after* addition of DMPU.

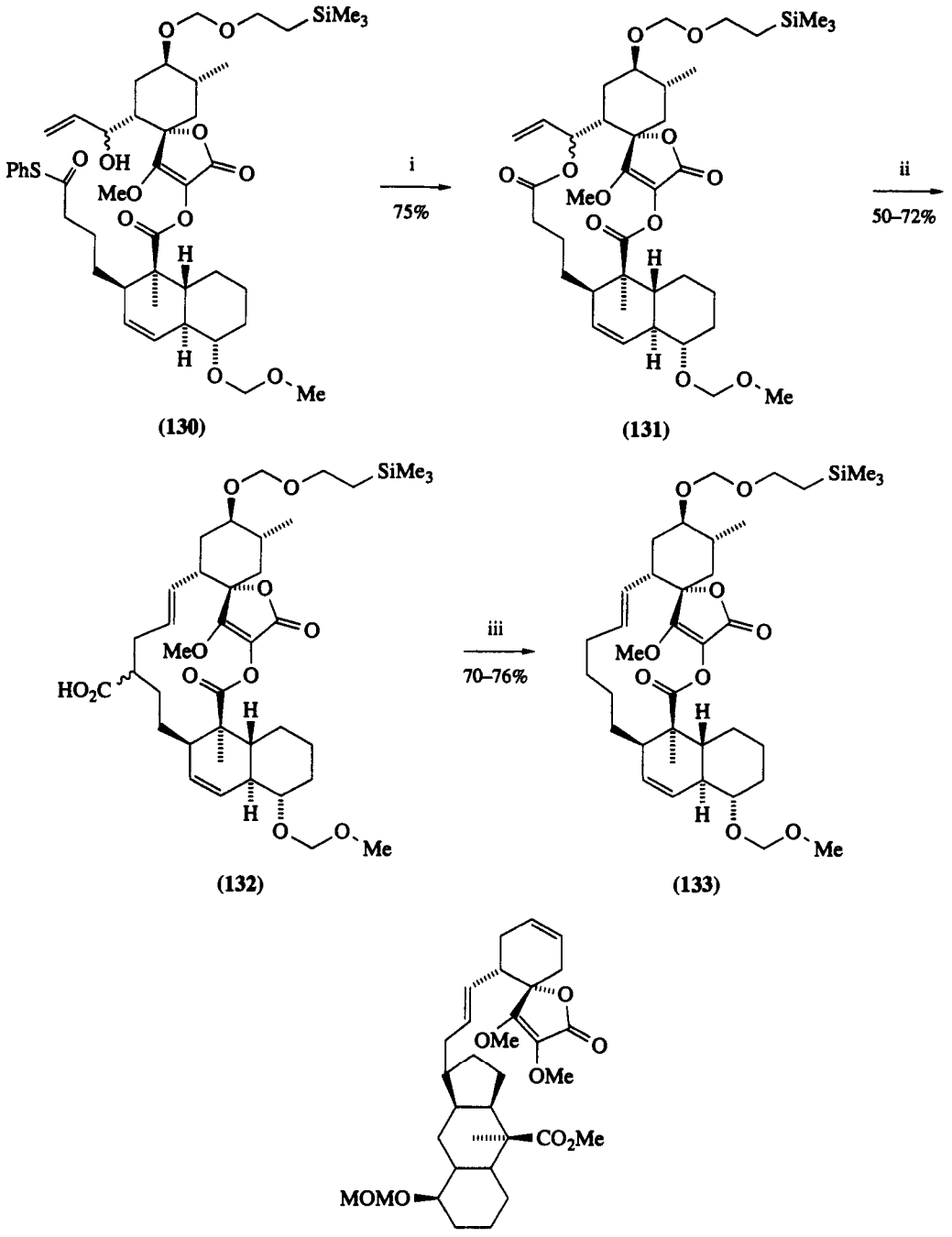
the decarbonylated product (**133**) in high yield. Interestingly, analogous reductive decarboxylation with open-chain precursors had led to cylopropanation or the formation of pentacycle (**134**) by radical cyclization.

In the total synthesis of the esterase inhibitor (±)-ebelactone A, Paterson and Hulme applied an aldol–Claisen strategy for a relay of 1,2-*syn* into 1,5-*syn* relative stereochemistry (Scheme 25).[79,113,114] The critical Ireland ester enolate rearrangement could be performed without protecting the C_9 ketone to give ester (**137**) in 74% overall yield.[115]

Danishefsky and coworkers have demonstrated the conversion of lactones to carbocycles by the 3,3-sigmatropic shift of silylketene acetals.[116,117] In the total synthesis of the *Fusarium* toxin equisetin, for example, keto lactone (**138**) was converted to its bissilyl derivative (**139**) by reaction with 2 equiv. of LDA and an excess of TMS-Cl.[118] *In situ* thermolysis of ketene acetal (**139**) led to a very smooth transformation into ester (**140**), which was carried on to equisetin (Scheme 26). This methodology was also applied by Schreiber and Smith in the preparation of the cyclohexyl moiety of the immunosuppressive agent FK-506.[119] Ireland–Claisen rearrangement of silylketene acetal (**142**), prepared by treatment with TBDMS-OTf and triethylamine at low temperature, provided, after hydrolysis of the silyl ester, the carboxylic acid (**143**) in 71% overall yield (Scheme 27). The strict translation of configuration *via* a boat-like transition state is typical for this permutation.

The Ireland ester enolate rearrangement of vinyl lactones can also be applied for the preparation of azacyclic systems. Silylketene acetal (**145**), again prepared by treatment of lactone (**144**) with a slight excess of TBDMS-OTf and triethylamine,[120] was easily converted to the substituted pipecolic acid (**146**) upon reflux in toluene (Scheme 28).[121] Claisen rearrangement mediated ring contraction of macrocyclic lactones was applied by Funk and coworkers for the preparation of the *in,out*-bicyclo[4.4.1]undecan-7-one core of the potent tumor promoter ingenol (Scheme 29).[122,123] The *in,out* bridged macrobicyclic lactone (**147**) does not suffer from the bending strain present in the smaller bicyclo[4.4.1]undecanone ring system and is therefore accessible without diversion to the *out,out* isomer. Addition of 4 equiv. of TIPS-OTf to a refluxing benzene solution of lactone (**147**) in the presence of 8 equiv. of triethylamine gave one major rearrangement product (**149**) in better than 15:1 selectivity and 77% yield. The stereochemical assignment of the two newly created stereogenic centers was verified by X-ray analysis of the bromolactone derivative.

Claisen ring contraction of lactones is amenable to the preparation of pyrrolidinecarboxylic acids, as demonstrated by Knight and coworkers in the enantiospecific total synthesis of (–)-α-kainic acid (Scheme 30).[124] Rearrangement of azalactone (**150**) proceeded smoothly only when the base (LDA) and the trapping agent (TBDMS-Cl) were premixed[125] at low temperature before addition of lactone (**150**). Silylketene acetal (**151**) underwent rearrangement at ambient temperature, and led, after hydrolysis of the silyl ester under mildly basic conditions, to the desired pyrrolidinedicarboxylic acid (**152**) in 55% overall yield. Previous studies have shown that such rearrangements proceed exclusively *via* a boat transition state when the lactone is 11-membered or smaller. An example of a tandem Brook[126]–Claisen rearrangement was recently reported by Kishi and coworkers in the total synthesis of ophiobolin C (Scheme

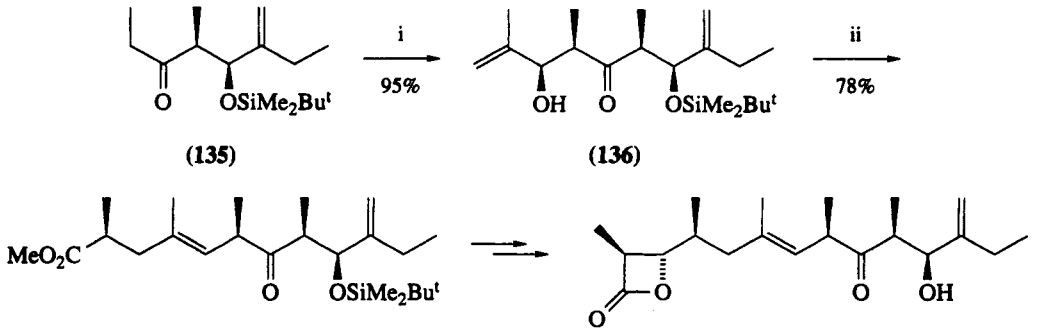


i, $Ag(O_2CCF_3)$, Na_2HPO_4, benzene, 82 °C; ii, KHMDS, THF, HMPA, –78 °C; HMPA, Me_3SiCl, Et_3N, THF; iii, Cl_2POOPh, Et_3N, THF, 0° C; PhSeH, Et_3N, THF, 0 °C; Bu_3SnH, AIBN, xylene, 130 °C

Scheme 24

31).[127] Silylketene acetal (**154**) was directly prepared from α-silyl ester (**153**) in xylene at 230 °C to give after acid hydrolysis the desired stereoisomer (**155**) in 72% overall yield with 6:1 stereoselectivity.[128,129]

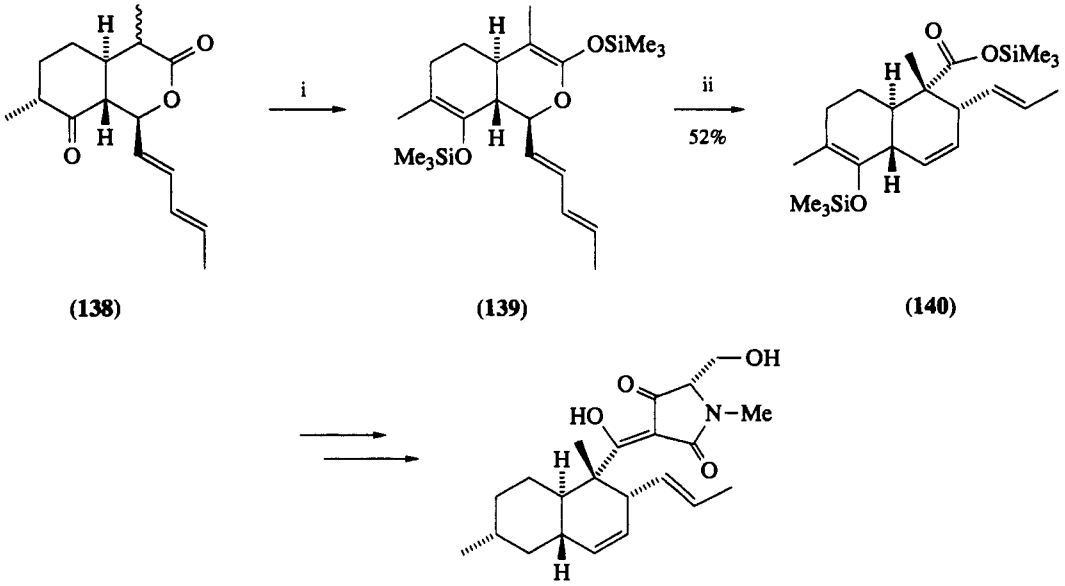
Silylketene acetals are also obtained by TMS-Cl accelerated conjugate addition of cuprates.[130] The latter method suffers presently from low diastereoselectivities,[131] though it offers the attractive possibility of one-pot formation of two carbon–carbon bonds and three contiguous chiral centers (equation 15).



(135) (136) (137) Ebelactone A

i, 9-BBNOTf, Et_3N, –78 °C, 3 h; $H_2C{=}C(Et)CHO$, –78 to 0 °C, 16 h; H_2O_2, MeOH–pH 7 buffer; ii, $(EtCO)_2O$, cat. DMAP, Et_3N, CH_2Cl_2, 0 to 20 °C, 2 h; Me_3SiCl, Et_3N, THF, LDA, –78 °C, 1 h; 20 °C, 1 h; 60 °C, 2 h; aq. 1% HCl; CH_2N_2, Et_2O, 0 °C

Scheme 25

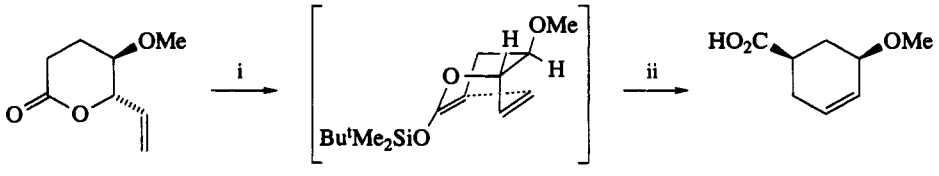


(138) (139) (140)

Equisetin

i, LDA, THF, Me_3SiCl, –78 °C, 30 min; ii, toluene, 105 °C, 10 h

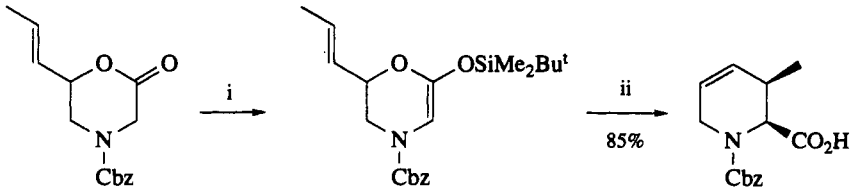
Scheme 26



(141) (142) (143)

i, Bu^tMe_2SiOTf, Et_3N, CH_2Cl_2, –78 to 0 °C; ii, toluene, 110 °C; THF, 1M HCl

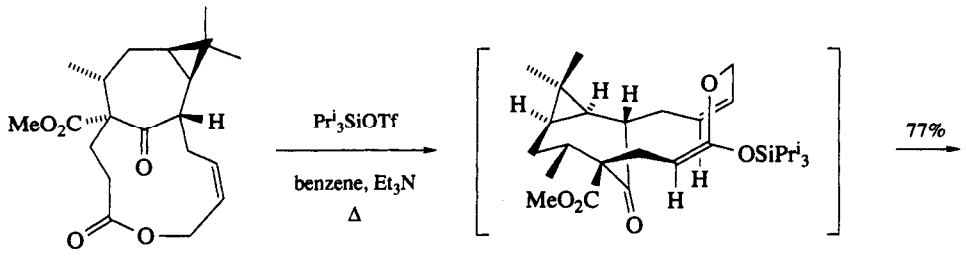
Scheme 27



(144) **(145)** **(146)**

i, Bu^tMe_2SiOTf, Et_3N, C_6D_6; ii, toluene, reflux, 2 h; NaOH, H_2O, THF

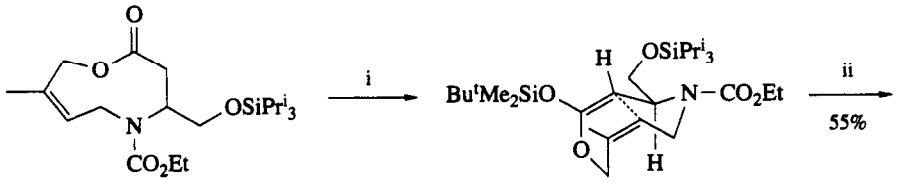
Scheme 28



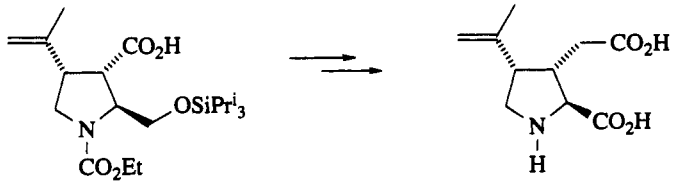
(147) **(148)**

(149) Ingenol

Scheme 29



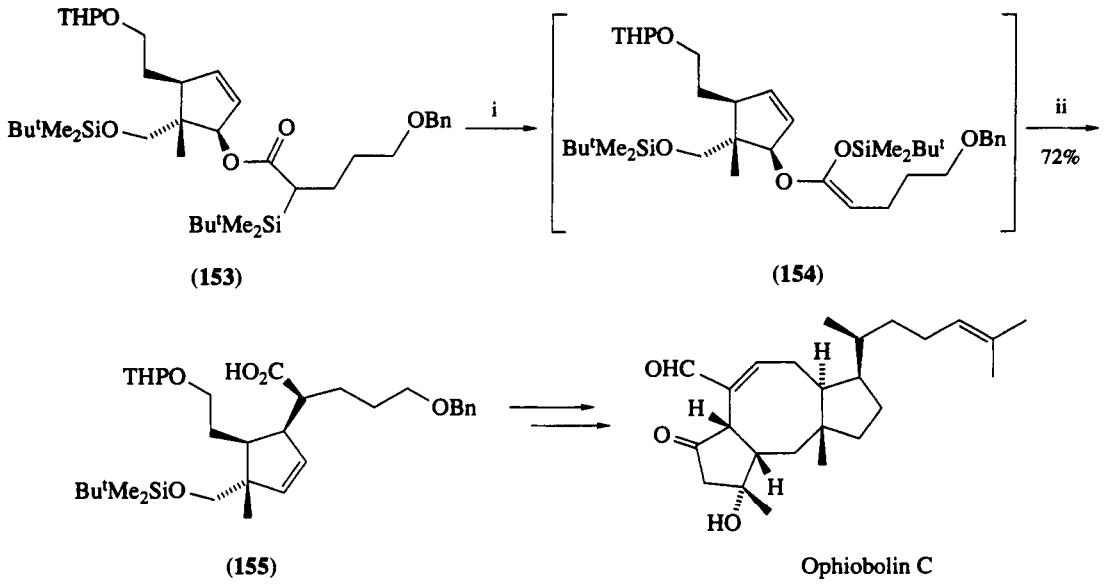
(150) **(151)**



(152) Kainic acid

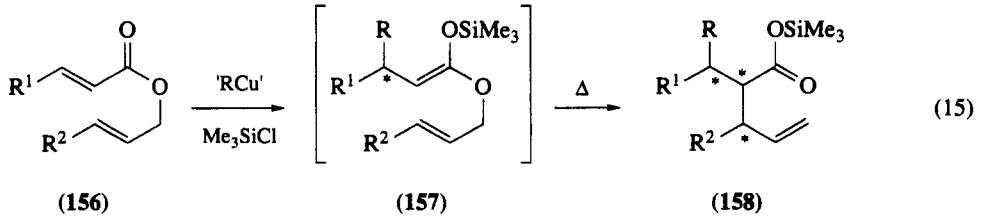
i, LDA (2 equiv.), Bu^tMe_2SiCl (2 equiv.), THF, −100 to 20 °C; ii, K_2CO_3, MeOH–H_2O, 20 °C, 2 h

Scheme 30



i, xylene, 230 °C; ii, 1 M HCl–MeOH–Et_2O (1:1:1), r.t.

Scheme 31



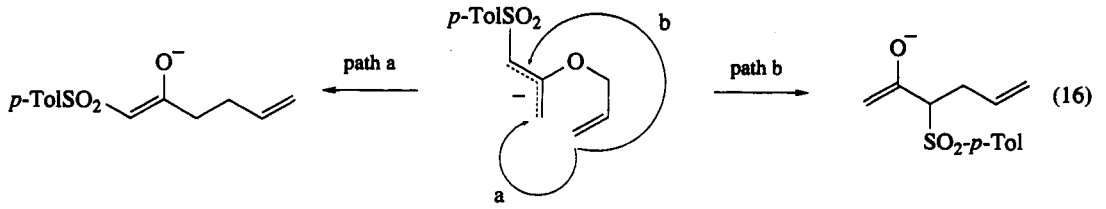
(15)

7.2.2.9 Charge-accelerated Claisen Rearrangements

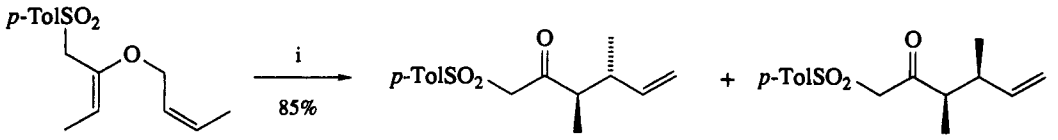
Although versions of the ester enolate rearrangement of magnesium,[5] sodium,[132] and lithium[9] enolates as well as the anionic oxy-Cope shift[133] gave early testimony of the potential of charge-accelerated rearrangements,[134] the first example of a carbanion-accelerated Claisen rearrangement was only reported in 1982 by Denmark and Harmata.[17] Since then, however, many other charge-accelerated Claisen rearrangements have been reported.[135,136] In contrast to ethoxycarbonyl-, cyano-, and cyanohydrin-stabilizing groups, which did not promote rearrangement, the arylsulfonylmethylene substituent was shown to be well suited for this role based on ease of incorporation and accelerating potential.[137] Because of the ambident nature of the allyl anion (**159**), two regioisomers (**160**) and (**161**) can be formed in the rearrangement (equation 16). However, only path a in equation (16) is observed, a fact which was explained by the large difference in relative stability between β-ketosulfone anion (**160**) and ketone enolate (**161**). The rearrangement itself is highly stereoselective, providing a 95:5 mixture of *anti*- to *syn*-β-ketosulfone (**163**):(**164**) in 85% yield upon deprotonation of vinyl ether (**162**) with KH in DMSO in the presence of LiCl and subsequent rearrangement at 50 °C (Scheme 32). Mechanistically, this implies a high barrier to alkyl anion stereomutation relative to rearrangement. A chair-like transition state (**165**) accounts for the observed stereochemistry.[137] The limitations on this method are for the most part related to incompatibilities with the presence of anionic intermediates.

A high degree of asymmetric induction has been realized in the carbanion-accelerated Claisen rearrangement of phosphorus-stabilized anions.[138] Treatment of 1,3,2-oxazaphosphorinane (**166**) with freshly prepared lithium dimsylate[139] led to a 95:5 ratio of α-methyl ketones (**167**) and (**168**) (Scheme 33). Li^+ coordination combined with steric interactions provide the necessary control elements for stabilization of the highly organized allyl anion conformation (**169**).

α-Allyloxy ketones have also displayed remarkable rate accelerations. Ponaras compared the relative rates of rearrangement of cyclohexenone (**170**) and its derivatives.[140] In refluxing THF, ketone (**170**) af-

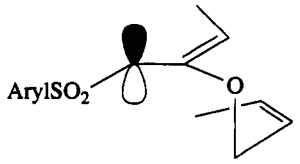


(160) (159) (161)



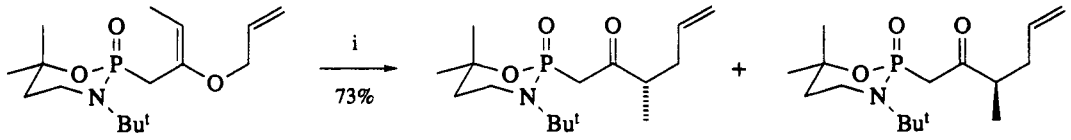
(162) (163) (164)

i, KH (2.6 equiv.), LiCl (15 equiv.), DMSO, 50 °C, 1.5 h



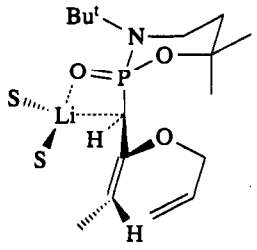
(165)

Scheme 32



(166) (167) (168)

i, Dimsyl Li, DMSO/THF (1:1), r.t., 15 min

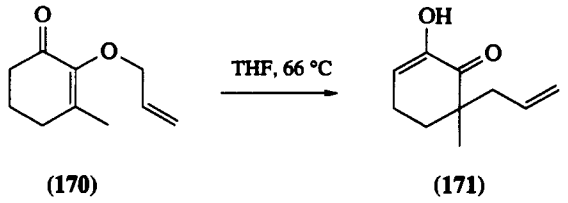


(169)

Scheme 33

fords diosphenol (**171**) with $t_{1/2}$ = 340 h, whereas acylhydrazone (**172**) and sodium salt (**173**) rearranged at $t_{1/2}$ = 22 h and $t_{1/2}$ = 1.5 h, respectively (Scheme 34).[141] This methodology can be applied for the formation of vicinal quaternary centers. In a related study, Koreeda and Luengo prepared copper enolate (**177**) by conjugate addition to 2-(allyloxy)-2-cyclohexenone (**176**).[18c] Warming of the reaction mixture to 0 °C resulted, within 15 min, in the smooth formation of the hydroxy ketone (**178**) in quantitative yield (Scheme 35). The silyl enol ether of (**177**), however, required a temperature as high as 63 °C to achieve a half-life of 1.6 h in its rearrangement. Koreeda and Luengo also measured rate acceleration as a function of the electron-donating ability of the MO group in enolate (**179**) (equation 17, Table 4).[18c] Rearrangement of the potassium enolate proceeded in toluene at –23 °C, whereas the sodium and lithium enolates

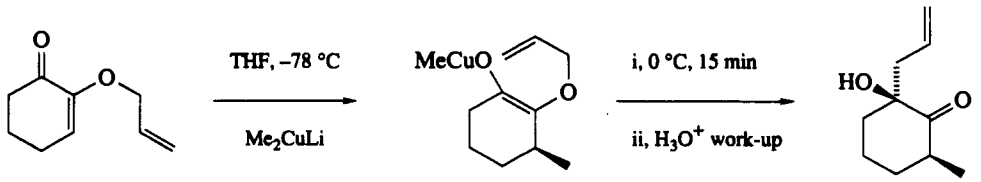
required temperatures of 0 °C and 96.5 °C, respectively. Interestingly, with THF as a solvent the conditions required for the rearrangement were significantly milder. The rate enhancement was explained by a vinylogous weakening effect of the oxyanion on the O(3)—C(4) oxygen–carbon bond, similar to the effect encountered in the anionic oxy-Cope rearrangement.[142] In an application of this methodology, tricyclic ketone (**181**) was enolized with potassium *t*-butoxide and rearranged in THF with a half-life of *ca.* 2 min at 50 °C to afford α-hydroxy ketone (**183**) in 94% yield (Scheme 36).[143]



(**170**) (**171**)

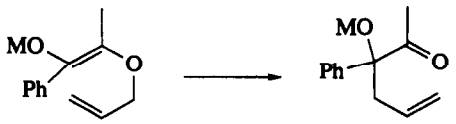
(**172**) R = N(H)CO_2Me
(**173**) R = N(Na)CO_2Me
(**174**) R = N(H)CO_2Me
(**175**) R = N(Na)CO_2Me

Scheme 34



(**176**) (**177**) (**178**)

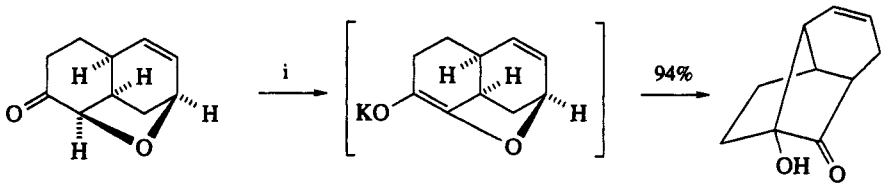
Scheme 35



(**179**) (**180**) (17)

Table 4 Results of Charge-accelerated Claisen Rearrangement of Enolates (**179**)[18c]

Entry	*Solvent*	*Compound* (**179**)	*Temperature* (°C)	$t_{1/2}$ (*h*)
1	Toluene	M = K	–23	3.3
2	Toluene	M = Na	0	2.6
3	Toluene	M = Li	96.5	1.1
4	Toluene	M = $SiMe_3$	71	0.5
5	THF	M = K	–42	6.2
6	THF	M = K	–23	⩽0.1
7	THF	M = Na	–23	2.4
8	THF	M = Li	67	1.3



(181) **(182)** **(183)**

i, $KOBu^t$ (10 equiv.), THF, 50 °C

Scheme 36

7.2.2.10 Catalysis of Claisen Rearrangements

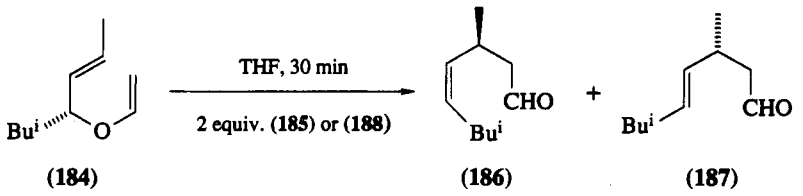
Catalysis of the Claisen rearrangement is as old as the rearrangement itself. In his original report,[1] Claisen mentioned the apparent rate-enhancing effect of ammonium chloride. Since then, modest to dramatic effects have been demonstrated for numerous Brønsted and Lewis acids, bases and transition metal complexes.[144] In an excellent comprehensive review, Lutz covered achievements in this field until 1984.[2f,145] In recent years, particular attention was given to increased stereocontrol, and aluminum catalysts emerged as especially useful reagents.[146,147,148] In many aspects, these systems can be considered as charge-accelerated 3,3-sigmatropic rearrangements.

An initial report by Oshima and coworkers stated that organoaluminum reagents promote the aliphatic Claisen rearrangement at room temperature under transfer of an alkyl or hydrogen residue to the aldehydic carbon.[149] Yamamoto and his group greatly expanded the scope of this process by the use of methylaluminum bisphenoxides. Rearrangement of optically active vinyl crotyl ether (**184**) with 2 equiv. of reagent (**185**) gave at –78 °C in 30 min an 84:16 ratio of the (*S*)-(*Z*)-aldehyde (**186**) and the (*R*)-(*E*)-aldehyde (**187**) in 74% yield with moderate transfer of the chirality (74–78% chiral transmission) (Scheme 37).[150] It is important to note that the thermal Claisen rearrangement of ethers such as (**184**) invariably results in highly (*E*)-selective product formation ($E/Z \approx 9:1$).[151] The alternative use of reagent (**188**) at –20 °C led to a 2:98 mixture of aldehydes (**186**) and (**187**) in 90% yield. The observed selectivities were explained by the two possible chair-like transition states (**189**) and (**190**) (equation 18). Conformation (**189**), highly unfavorable in the thermal Claisen rearrangement, would be favored over (**190**) in view of the severe 1,2-interaction between R and the exceptionally bulky organoaluminum reagent (**185**).[152] The origin of the exceedingly high (*E*)-selectivity with reagent (**188**) remained unclear. Yamamoto and coworkers subsequently applied this methodology to the highly regiospecific rearrangement of bisallyl vinyl ethers,[153] dienyl vinyl ethers, and the synthesis of the sex pheromone of the potato tuberworm moth.[154] Additionally, catalysis with chiral organoaluminum reagent (**192**) led to the successful asymmetric rearrangement of derivative (**191**; equation 19).[155,156] Acylsilane (**193**) was obtained in high optical purity (90% *ee*). This reaction sequence could also be applied to the corresponding trimethylgermyl derivatives.

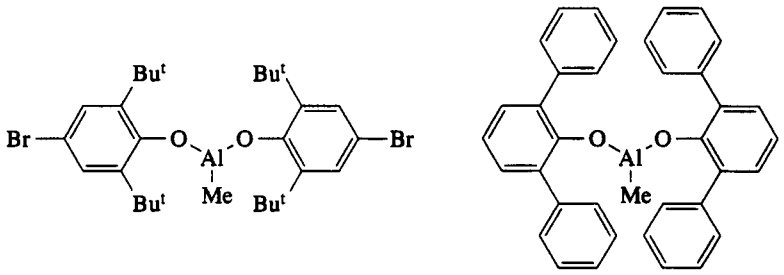
In a series of recent reports, Paquette and coworkers examined the scope and stereochemistry of the alkylaluminum-catalyzed Claisen ring expansion reaction.[157] Treatment of vinyl ether (**195**), obtained from lactone (**194**) and Tebbe reagent, with DIBAL-H induced acceleration of the Claisen process and *in situ* ketone reduction to cyclooctanol (**196**; Scheme 38).[158] After 5 h at 25 °C, a 7:3 ratio of the α-carbinol (**196a**) and the reduction product (**197**) was isolated in 42% yield. In contrast, the use of Bu^i_3Al led in high yield to a 5:1 mixture of carbinols (**196a**) and (**196b**), with no evidence for formation of (**197**). This process is completely (*Z*)-selective and provides the less strained *cis* double bond geometry. Due to steric constraints, rearrangement of endocyclic vinyl ether (**198**) has to proceed *via* boat-like transition state (**201**; Scheme 39). Tricycles (**199**) and (**200**) were isolated in 71% and 7% yields, respectively.[158]

7.2.2.11 Competitive Rearrangements

Typical side reactions that interfere in the aliphatic Claisen rearrangement are 2,3-sigmatropic shifts,[159] eliminations, and, especially in the Ireland variant, competitive Ferrier-type rearrangements,[160] ketene formation and *C*-silylation.[161] Usually, optimizing reaction parameters such as base, temperature, polarity of solvent and bulkiness of the silylating agents leads to a significant increase in the desired 3,3-sigmatropic pathway.[162,163]

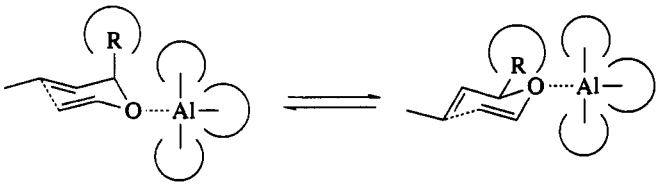


(184) (186) (187)



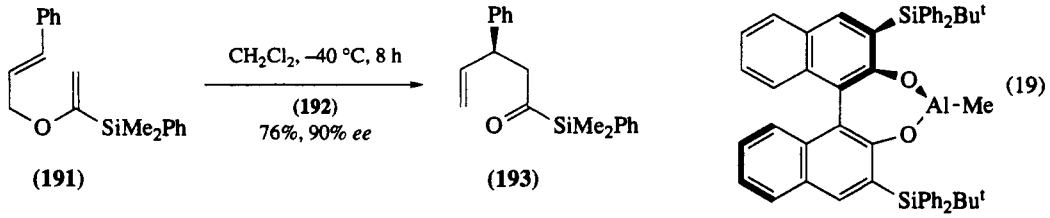
(185) (188)

Scheme 37



(18)

(189) (190)



(19)

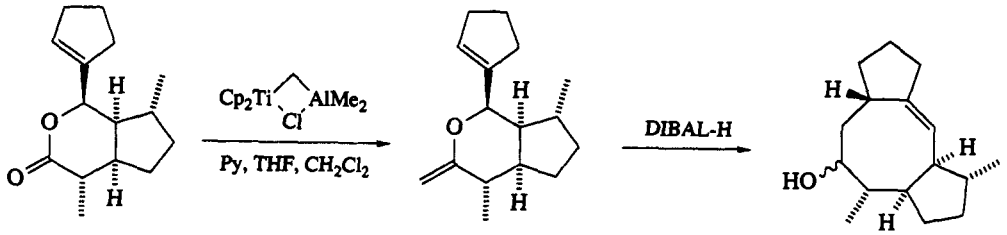
(191) (193) (192)

7.2.2.11.1 3,3 Claisen vs. *2,3 Wittig rearrangement*

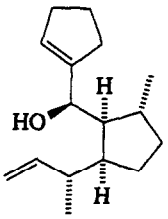
Generally, ester enolates of structure (**202**; R′ = M, R = Oalkyl) rearrange *via* a 3,3-shift,[164] whereas the corresponding amide enolates (**202**; R′ = M, R = N(alkyl)$_2$) and acid dianions (**202**; R′ = M, R = OM) prefer the 2,3-pathway (equation 20).[165] Both pathways have been observed with ketone enolates (**202**; R′ = M, R = alkyl). With substrate (**179**), Koreeda and Luengo observed only traces of Wittig rearrangement product (**205**), except for the lithium enolate, where (**205**) accounted for up to 20% of the reaction mixture (equation 21).[18c] Thomas and Dubini, however, reported predominant formation of 2,3 Wittig products (**207**) and (**209**) under base treatment of ketones (**206**) and (**208**) (equation 22).[166,167]

7.2.2.11.2 Regioselective rearrangement of divinylcarbinols

Several factors such as number and type of substituents contribute to the regioselectivity in the rearrangement of divinylcarbinols.[168,169] In a synthesis of the ring system of fastigilin-C, Tanis and coworkers succeeded in influencing the ratio of competitive Ireland–Claisen rearrangements through the cyclopentenyl or the furanyl double bond of substrate (**210**) by the nature of the alkyl groups on the silylating agent (Scheme 40).[170]

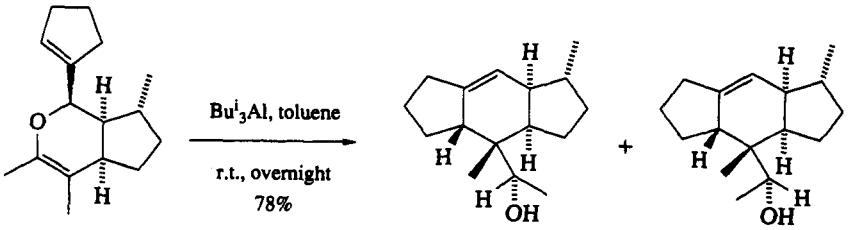


(194) (195) (196a) (α-OH) (196b) (β-OH)

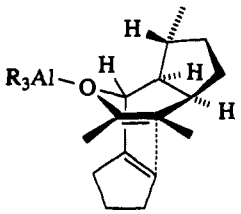


(197)

Scheme 38

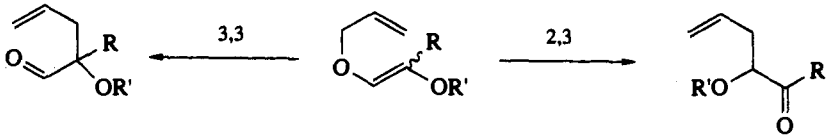


(198) (199) (200)

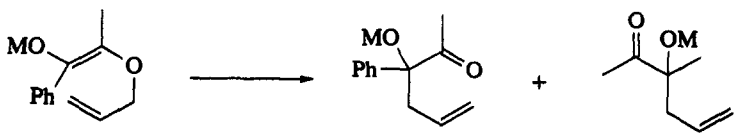


(201)

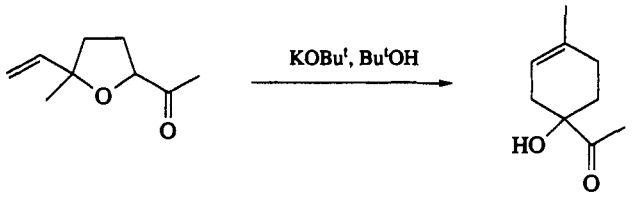
Scheme 39



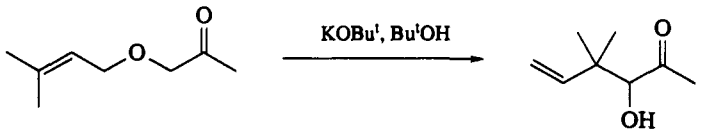
(203) (202) (204) (20)



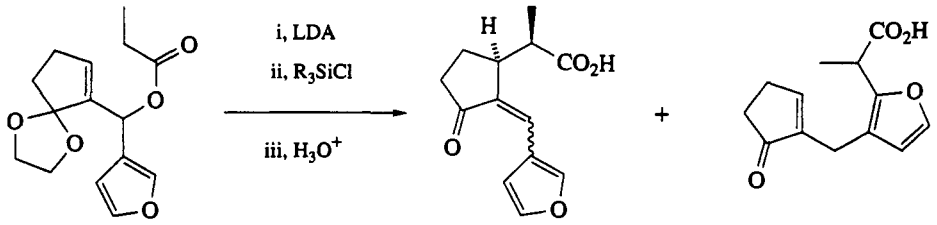
(179) M = Li, Na, K, $SiMe_3$ (180) (205) (21)



(206) (207) (22)



(208) (209)



(210) (211) (212)

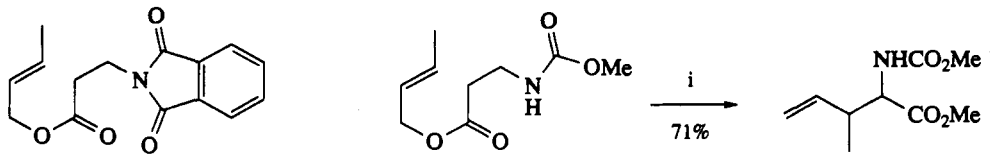
R_3SiCl	*Yield (%)*	*Ratio (211):(212)*
Bu^{t}Me$_2$SiCl	69	95:5
Me$_3$SiCl	79	75:25
Pr$^i_3$SiCl	73	20:80

Scheme 40

7.2.2.11.3 Elimination vs. *rearrangement*

Elimination of the allylic ether moiety effectively competes in certain cases with the 3,3-sigmatopic shift.[171] A change in the variant of the Claisen rearrangement often leads to significant reduction of undesired elimination processes.[172]

A related problem is elimination in ester enolates with leaving groups in the β-position. Knight and coworkers observed virtually no α-allyl-β-amino acid product in the Ireland silyl ester enolate rearrangement of phthalate (**213**; Scheme 41).[91d] Rearrangement of the *N*-methoxycarbonyl analog (**214**), however, provided methyl ester (**215**) in a 79:21 mixture of stereoisomers after treatment with etheral diazomethane.



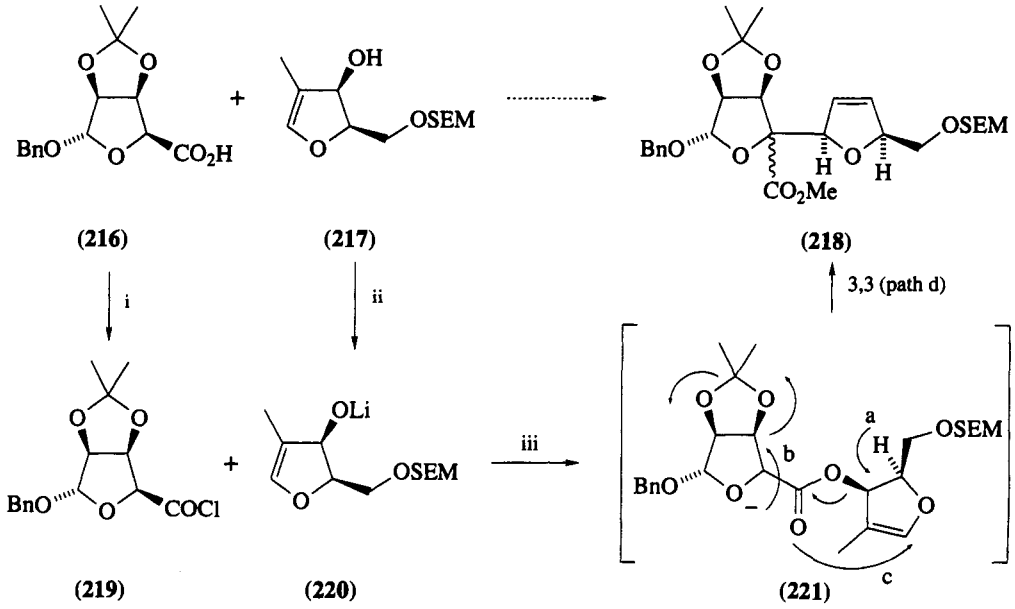
(213) (214) (215)

i, LDA, THF, –78 °C; Me_3SiCl; reflux, 4 h; hydrolysis; CH_2N_2

Scheme 41

Excellent experimental technique was required to effect formation of the monensin C/D ring system (**218**) *via* silyl ester enolate Claisen rearrangement of acid (**216**) and alcohol (**217**) (Scheme 42).[125a] Ester

(**221**) is extremely prone to fragmentation and furan formation (path a), β-elimination (path b) and Ferrier rearrangement (path c). Low temperature mixing of the furanoid acid chloride (**219**) and lithium alcoholate (**220**), followed by ester enolization in a solution of premixed LDA and TMS-Cl at –100 °C provided the corresponding silylketene acetal. Warming to ambient temperature, followed by methyl ester formation, then led to tricycle (**218**) in an excellent 80% yield (isolated as a 1.5:1 mixture of diastereomers).

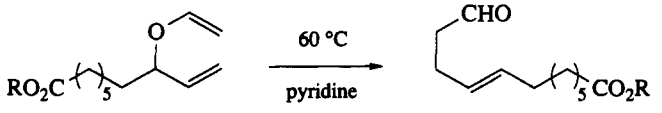


i, $(COCl)_2$, benzene, DMF (cat.); ii, Bu^nLi, DMAP, THF, –78 °C; iii, add (**219**) to (**220**), –78 °C; add mixture to LDA, THF, Me_3SiCl, Et_3N, 10% HMPA/THF, –100 °C; r.t.; H_3O^+; CH_2N_2, ether

Scheme 42

7.2.2.12 Solvent Effects

Due to a relative insignificance of Coulomb interactions, pericyclic processes generally show little correlation between solvent polarity and reaction rates.[173] The discovery of White and Wolfarth that polar solvents increase the rate of the *ortho*-Claisen rearrangement similarly to electron-donating substituents was therefore of profound consequence.[174,175] Aliphatic Claisen rearrangement of allyl vinyl ethers also demonstrated a profound rate acceleration in polar solvents.[176] These results were interpreted in terms of a tight ion pair or dipolar transition state.[177,178] Grieco and coworkers determined first-order rate constants for the Claisen rearrangement of carboxylate (**222**) and methyl ester (**223**) (equation 23, Table 5).[179] In particular, they demonstrated that rearrangement of allyl vinyl ether (**226**) in water/methanol (2.5:1) containing 1 equiv. of sodium hydroxide smoothly occurs at 80 °C, affording an 85% isolated yield of aldehyde (**227**; equation 24).[180] Only after extensive experimentation had this transformation previously been achieved in 60% yield by McMurry and coworkers at 220 °C in a base-washed silylated glass tube containing toluene and sublimed sodium *t*-pentoxide, the major problem being vinyl ether elimination and cyclopentadiene formation.[181]



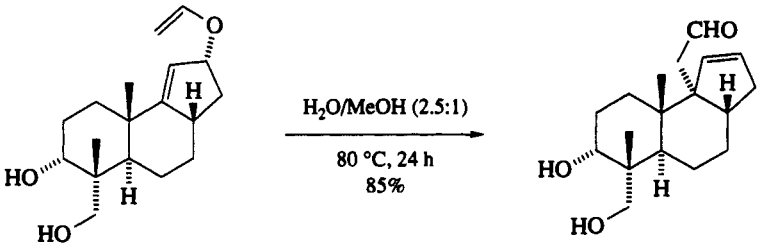
(**222**) R = Na
(**223**) R = Me

(**224**) R = Na
(**225**) R = Me

(23)

Table 5 Rate Constants for the Aliphatic Claisen Rearrangement of Sodium Carboxylate (**222**) and Methyl Ester (**223**)[179]

Entry	*Solvent*	$k \times 10^{-5}$ (s^{-1}) (**222**)	$k \times 10^{-5}$ (s^{-1}) (**223**)
1	H_2O	18	
2	75% H_2O/CF_3CH_2OH	6.9	
3	CF_3CH_2OH	2.6	4.7
4	75% H_2O/MeOH	11	
5	50% H_2O/MeOH	4.6	3.6
6	25% H_2O/MeOH	1.6	1.4
7	MeOH	0.79	0.72
8	75% H_2O/DMSO	3.0	
9	25% H_2O/DMSO	0.93	0.82
10	EtOH		0.51
11	Me_2CHOH		0.42
12	MeCN		0.25
13	Acetone		0.18
14	Benzene		0.17
15	Cyclohexane		0.084



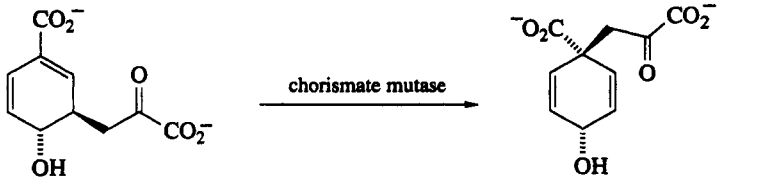
(24)

(**226**) (**227**)

7.2.3 ENZYMATIC CLAISEN REARRANGEMENTS

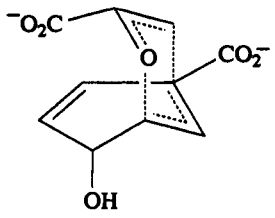
The 3,3-sigmatropic rearrangement of chorismate (**228**) to prephenate (**229**) in the shikimic acid pathway demonstrates the versatility of the Claisen rearrangement in a biochemical version (equation 25).[182] The enzyme chorismate mutase catalyzes this process by a factor of approximately 3×10^6.[183] The entropy and the enthalpy for the uncatalyzed reaction are 20.71 kcal mol^{-1} and −12.85 cal mol^{-1} K^{-1}, respectively;[184] and it was shown that both uncatalyzed and enzymatic rearrangements proceed through a chair-like transition state (**230**), stabilized in polar media.[176,185,186] Bartlett and coworkers prepared transition state analog (**231**), which in fact proved to be a potent inhibitor of *E. coli* chorismate mutase-prephenate dehydrogenase.[187] Knowles and coworkers proposed a mechanism for the enzyme reaction that involves a heterolytic cleavage of the ether bond of chorismate by attack of an enzymic nucleophile in the rate-limiting step,[188] and Berchtold and coworkers established the structural requirements for enzyme catalysis in this process.[189]

Discussions concerning this intriguing biological Claisen rearrangement have been further enriched by the development of synthetic protein catalysts based on monoclonal antibodies.[190,191] The conjugate of transition state model (**232**) with carrier proteins keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA) was used for production of antibodies specific for (**232**).[192] The rate of the antibody-catalyzed rearrangement of chorismate to prephenate was subsequently compared with that of the uncatalyzed thermal rearrangement, affording a value of k_{cat}/k_{un} of 1×10^4 at 10 °C and pH 7.0.[190]

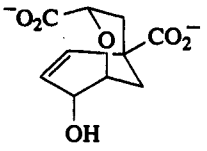


(25)

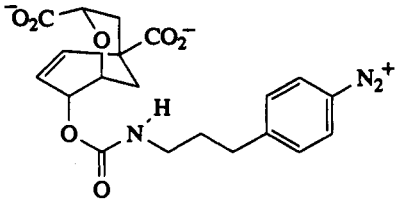
(**228**) (**229**)



(230)



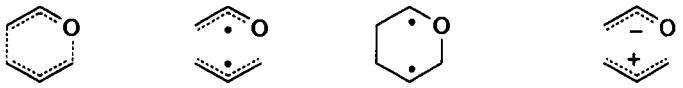
(231)



(232)

7.2.4 MECHANISTIC ASPECTS OF THE CLAISEN REARRANGEMENT

Claisen rearrangements are highly exothermic;[67,193,194] concerted but nonsynchronous[195] pericyclic reactions[196,197,198] with a characteristic negative entropy ($\Delta S^{\ddagger} = -10$ to -15 cal mol^{-1} K^{-1}) and negative volume of activation.[199] Secondary deuterium kinetic isotope studies by Gajewski and coworkers indicate an early transition state,[200,201,202] where bond breaking is more advanced than bond making.[99,203] There is, however, still some disagreement as to which of the limiting alternatives to the aromatic transition state (**233**)[204] — oxaallyl radical–allyl radical pair (**234**), 2-oxacyclohexane-1,4-diyl (**235**) or dipole (**236**) — more accurately represents or contributes to the transition state structure (Figure 1).[176,205,206,207] Stabilization of the transition state (TS‡) by resonance interactions is therefore clearly an important factor.[207]



(233) (234) (235) (236)

Figure 1

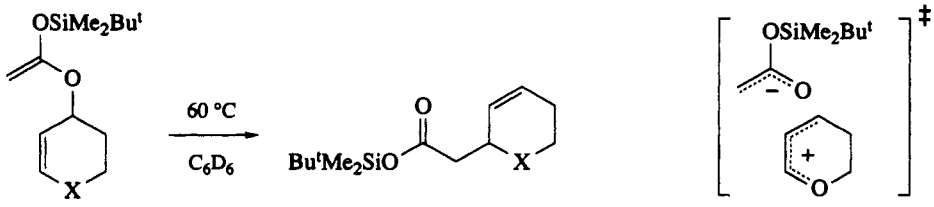
7.2.4.1 Kinetics

The influence of donor and acceptor substituents on the rates of the Claisen and other sigmatropic rearrangements has been widely investigated.[208,209,210,211] A theoretical model by Carpenter and Burrows, based on Hückel molecular orbital (HMO) calculations, assesses the conjugative electron-withdrawing and -donating abilities of substituents. It predicts accelerating effects of donor substituents at C-1 and both donor and acceptor substituents at positions 2 and 4 of the Claisen system. Acceptor substituents at positions 1 and 6 and donor groups at positions 5 and 6 are predicted to decelerate the reaction.[212] Carpenter and Burrows synthesized the five isomeric cyano-substituted derivatives of the basic Claisen system and found the predictions of the HMO model fulfilled. Rate accelerations were observed with the C-2 ($k_{rel} = 111$), C-4 ($k_{rel} = 270$) and C-5 ($k_{rel} = 15.6$) substituted allyl vinyl ethers, while C-1 ($k_{rel} = 0.90$) and C-6 substitution ($k_{rel} = 0.11$) led to deceleration.[213] However, the HMO model did not remain without criticism.[214,215] In allyl vinyl ethers with a trifluoromethyl substituent at C-2 on the Claisen system, a rate enhancement by a factor 73 over the parent system was found. At C-4, the trifluoromethyl group did not bring about a significant rate effect, in contrast to the energetic benefit of 3.5 kcal mol^{-1} with the cyano group at that position, suggesting that radical-stabilizing and not electron-withdrawing ability might be important in stabilizing the transition state.[216]

The accelerating effect of alkyl substituents on the Claisen rearrangement is well documented[9,217] but not as dramatic as the effect observed with electron-donating groups (R_2N—, EtO—, R_3SiO—) at C-2 of the allyl vinyl ether.[218] Accordingly, the ease of the Ireland Claisen reaction (the free energy of activation is reduced by roughly 9 kcal mol^{-1} relative to allyl vinyl ether itself)[9] is mainly due to the stabilization of the π-bond of the oxaallyl species by the 2-(trialkyl)silyloxy substituent.[219] This results in a TS‡ structure with much more advanced O(3)—C(4) bond breaking than in the parent, unsubstituted rearrangement system.[99,176,203,206,207]

A C(6) donor substituent exerts a similar enhancing effect on the rate of the Claisen rearrangement, though somehow less pronounced than the rate-accelerating effect of the 2-silyloxy substituent (approx. 1.4 kcal mol^{-1}). As Curran and coworkers reported,[178,211] this vinylogous anomeric effect[220] of the C(6) donor substituent is especially effective in glycal systems. The energy of the TS‡ is decreased by assist-

ance in the cleavage of the O(3)—C(4) bond, which results in an approximately tenfold acceleration of the rearrangement (Scheme 43). The combined accelerating effect of the 2- and 6-oxygen substituents most certainly leads to an increased dipolar character of the TS‡ for the silyl ester enolate Claisen rearrangement,[221] with bond breaking substantially more advanced than bond formation (*cf.* structure **239**).

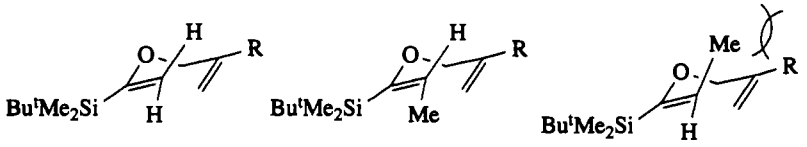


(237) **(238)** **(239)**

rates: X = O, 4.4 x 10^{-4} s^{-1}; X = CH_2, 4.9 x 10^{-5} s^{-1}

Scheme 43

Wilcox and Babston investigated the effect of alkyl substituents on the rate of the Ireland Claisen rearrangement of silylketene acetals (**240**)–(**242**) (R = H, Me, Et, Pr^i, neopentyl, CH_2SiMe_3; Figure 2).[222] Their data suggest the possibility of a '*syn*-diaxial' interaction in the order of 1.2 to 2.5 kcal mol^{-1} ($\Delta\Delta G_Z^{\ddagger}/E^{\ddagger}$) in the transition state of the (*E*)-isomer (**242**), depending on the nature of the substituent R. Generally, steric bulk at C-5 was found to be rate accelerating, electron donation at this position, however, rate decelerating.



(240) **(241)** **(242)**

Figure 2

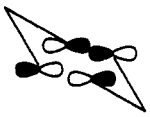
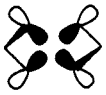
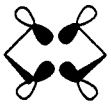
7.2.4.2 Transition State Structures

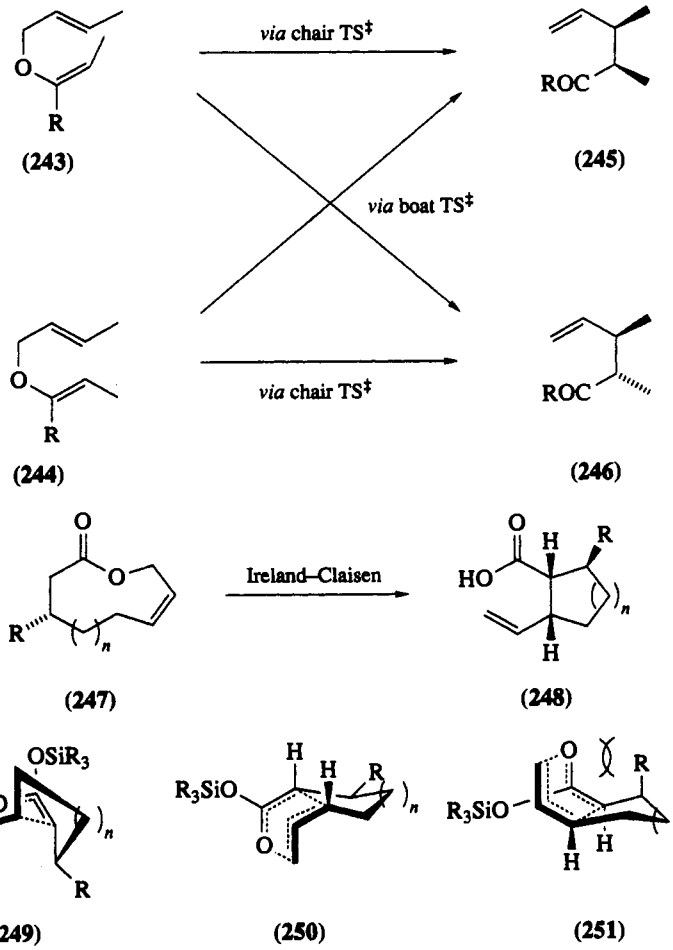
According to the Woodward–Hoffmann rules,[223] five concerted transition states are possible for the Claisen as well as the closely related Cope rearrangements: chair, boat, twist, cross and plane (Table 6).[224] Only the chair and boat TS‡ have to be considered, as twist, cross and plane are antarafacial–antarafacial processes and require highly elevated temperatures.[199,225,226] For the correct prediction of product stereochemistry it is nevertheless crucial to know the preference for chair- or boat-like transition state in the actual 3,3-sigmatropic shift.

In acyclic systems, Claisen rearrangements show a well-established preference for chair-like transition states. With crotyl propenyl ether, the chair selectivity amounts to 97–98% at 142 °C, which corresponds to an approx. 3 kcal mol^{-1} difference between the free energy of activation ($\Delta\Delta G^{\ddagger}$) of chair and boat TS‡ (equation 26).[67,227] The preference for a chair-like geometry in the TS‡ is even more pronounced in the Cope rearrangement: 99.7% of the 3,4-dimethylhexa-1,5-diene rearranges at 225 °C *via* a chair-like TS‡, corresponding to a $\Delta\Delta G^{\ddagger}_{chair-boat}$ of –5.7 kcal mol^{-1}.[9a,228] The latter result closely parallels the difference in energy of the chair and boat conformations of cyclohexane (5–6 kcal mol^{-1}).[229]

In cyclic systems, however, conformational constraints can override the inherent preference for chair-like transition states in Cope[230] as well as Claisen[231] rearrangements and lead to a partial involvement if not a dominance of boat-like TS‡ structures. In the Ireland rearrangement of lactones of type (**247**), for example, chair-like transition state (**249**) is accessible only when the diaxial bridging methylene chain becomes sufficient in length ($n = 7$, Scheme 44).[232] The preference of boat-like transition state (**250**) over (**251**) is due to a serious $A^{1,3}$-type interaction between the endocyclic oxygen atom and pseudoaxial substituent R in (**251**).

Table 6 Transition State Models for 3,3-Sigmatropic Rearrangements[199]

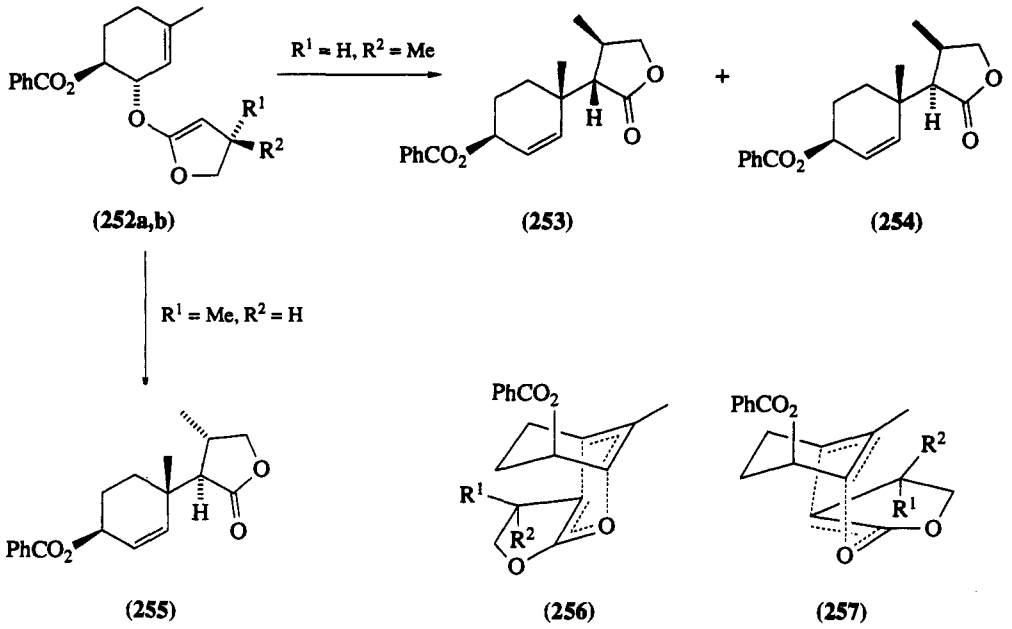
Notation	*Geometry*	*Symmetry*	*Type*
3*s*,3*s*		C_{2h}	Chair
3*s*,3*s*		C_{2v}	Boat
3*a*,3*a*		D_2	Twist
3*a*,3*a*		D_{2h}	Cross
3*a*,3*a*		C_{2h}	Plane



(26)

Scheme 44

In their syntheses in the vitamin D field, Lythgoe and coworkers demonstrated an impressive example of remote stereoselection in the Claisen rearrangement *via* differential transition state stabilization (Scheme 45).[233] Whereas (**252a**; R^1 = H, R^2 = Me) leads to a 70:30 mixture of diastereoisomers (**253**) and (**254**), respectively, with the chair-like transition state (**256**) providing the major isomer, its epimer (**252b**; R^1 = Me, R^2 = H) gives exclusively (**255**). Steric hindrance between the methyl group and the cyclohexane ring in (**256**) in this isomer overrides the chair–boat factor and leads to a clear preference for the boat-like transition state (**257**).



Scheme 45

The Ireland Claisen rearrangement of pyranoid glycals such as (**258**) generally occurs *via* a boat-like TS‡,[86a,86b,87c,90,93,234,235] presumably due to destabilizing steric interactions of the silyloxy substituent and the dihydropyran ring atoms in chair-like TS‡ (**260**) (Scheme 46).[9,37b,235] In furanoid glycal systems, the destabilizing interaction between the silyloxy substituent and the ring carbons in the chair-like TS‡ should be considerably diminished. However, there is still a strong preference for boat-like TS‡ geometries (Scheme 47). Additionally, the parent carbocyclic systems mostly demonstrate the usual chair selectivity in the 3,3-sigmatropic shift.[236,237] These striking results were explained by a stereoelectronic effect of the C(6) oxygen substituent on the relative stabilities of chair-like and boat-like TS‡ in the silyl ester enolate Claisen rearrangement.[238] A vinylogous anomeric effect of the C-6 oxygen leads to an increased relative stabilization of the more loosely organized[239] *endo*-type boat TS‡ in the order of 1 to 2 kcal mol^{-1}. This effect is especially pronounced in glycal systems and is apparently based on a more dipolar character of the boat-like TS‡ in these systems (**239**; Figure 3).[238] It was further demonstrated that the preferred transition state in the rearrangement of six- and five-membered carbocyclic systems such as (**266**) and (**267**) is highly dependent on steric factors, as the energy difference between chair- and boat-like TS‡ tends to be small.[238] With straight chain substrates, a significant contribution of the boat-like TS‡ to the rearrangement product mixture is only expected in bis-donor substituted allylic esters such as (**268**) (Figure 4).[238,240,241]

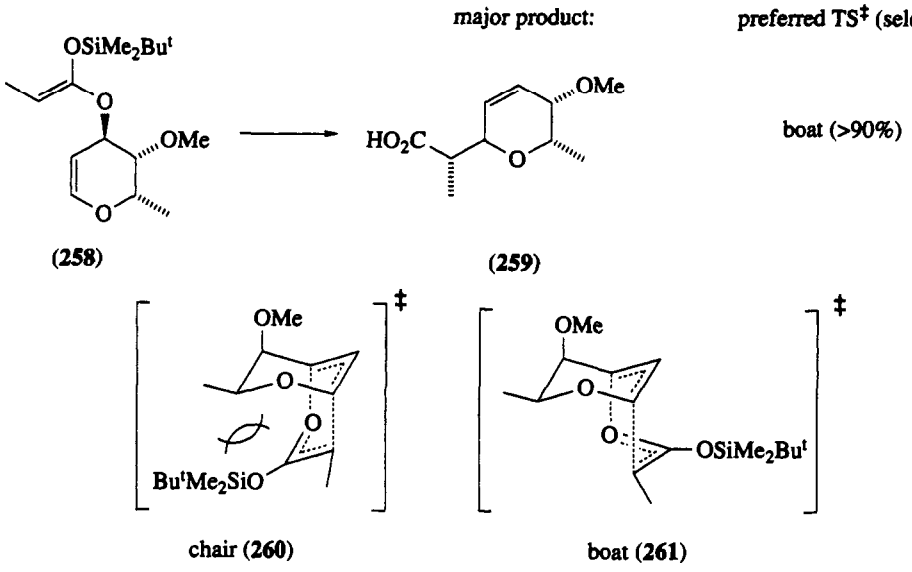
7.2.4.3 Elements of Stereocontrol

As pointed out earlier, the aliphatic Claisen rearrangement and its variants are powerful means to effect stereocontrolled C,C-bond formation. Highly ordered transition states effect a reliable transfer of stereochemistry from starting materials to products. Naturally, the geometry of the vinyl ether bond and the conformation of the transition state are crucial parameters in this process. The former issue is strongly dependent on the Claisen variant that is employed,[242] whereas the transition state geometry is controlled by both steric and electronic features of the Claisen system.[243] Additionally, the choice between

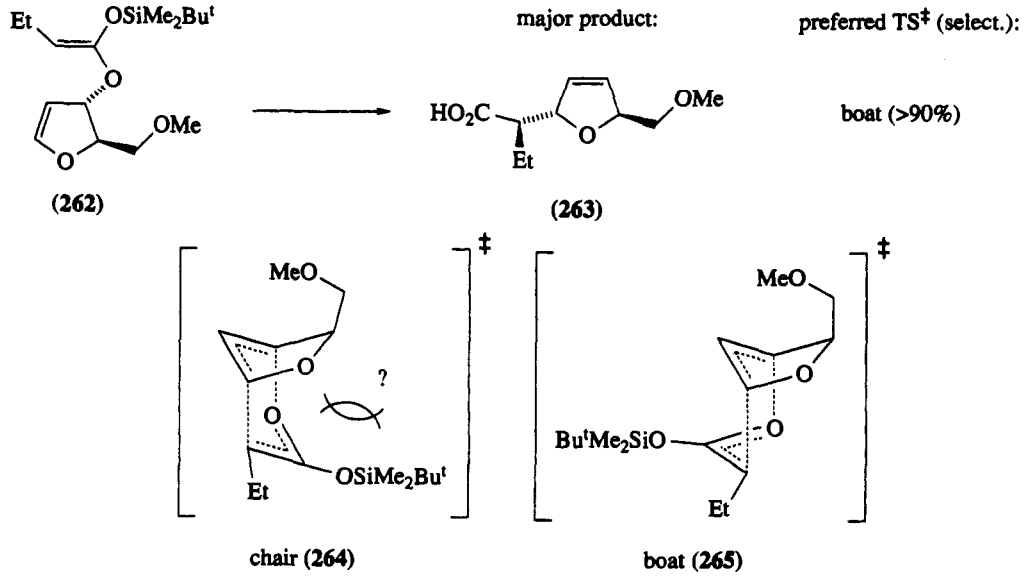
diastereomeric transition states is often strongly influenced by stereogenic groups within, adjacent to, or even considerably removed from the allyl vinyl ether moiety.

7.2.4.3.1 Intrinsic transfer of stereochemistry

Up to three chiral centers can directly be involved in the Claisen rearrangement (Equation 27). The configuration of the allylic chiral center at C-4 in (**269**) specifically relates to the configuration of the newly formed chiral centers in (**271**) and (**273**). Moreover, the ratio of diastereomeric transition states (**270**) and (**272**) greatly depends on the relative steric bulk of substituents R^4 and $R^{4'}$.[244] Thus, generally a highly selective course of the reaction *via* pathway A or pathway B can be predicted. It is important to note that the primary chiral center is destroyed in the rearrangement ('self-immolative' process[245]) and



Scheme 46



Scheme 47

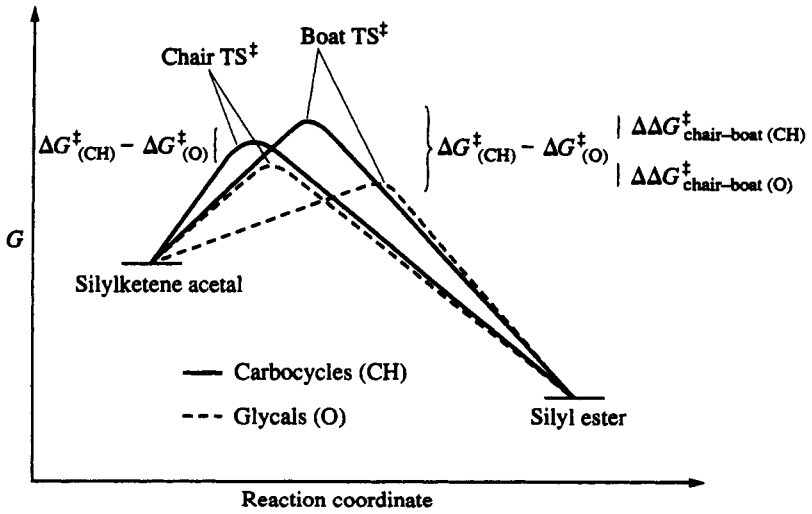
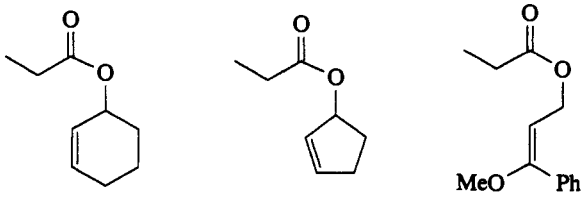


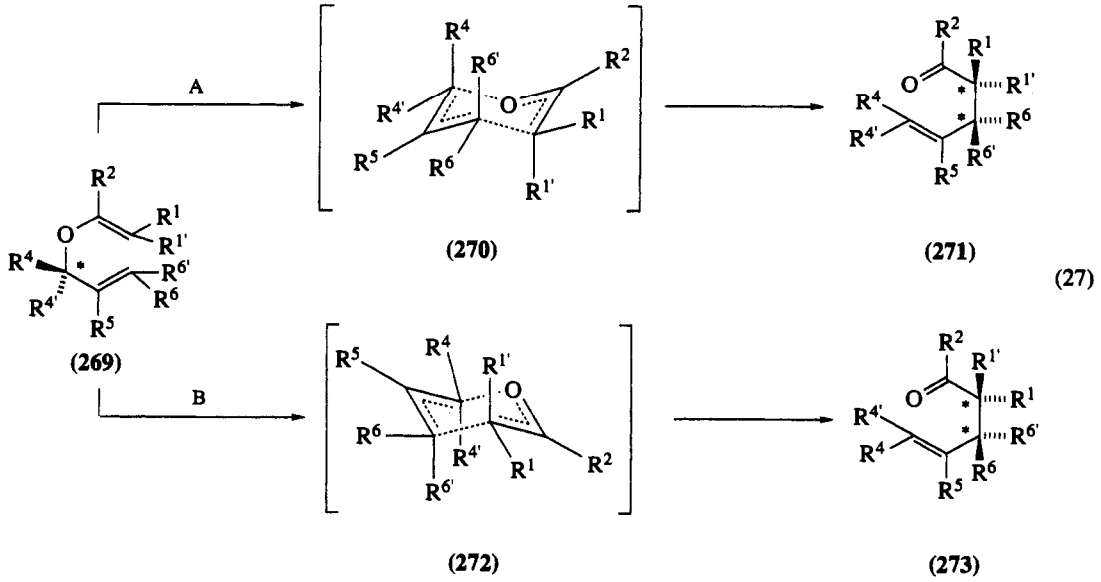
Figure 3 Qualitive effect of C-6–carbon and C-6–oxygen substituents on the transition state energy of the ester enolate Claisen rearrangement



(266) (267) (268)

Figure 4

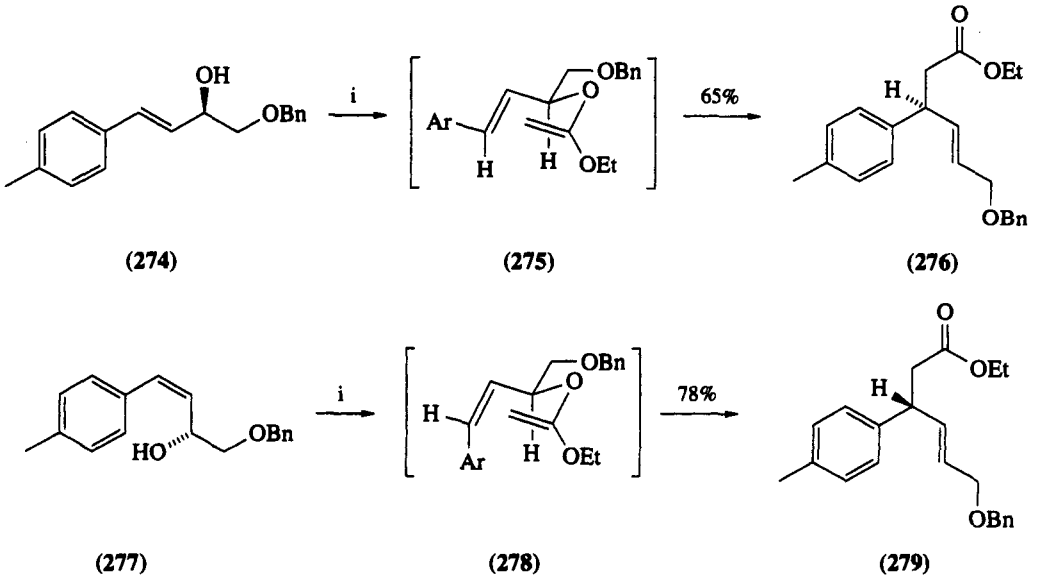
that a complementary set of products is obtained by a simple change in the geometry of the double bonds.



(269) (270) (271) (272) (273) (27)

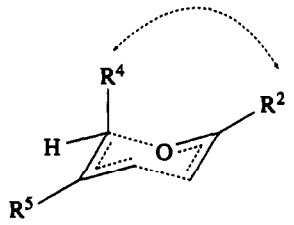
(i) Acyclic substrates

Johnson rearrangement of allylic alcohols (**274**) and (**277**) led to the enantiomeric γ,δ-unsaturated esters (**276**) and (**279**), respectively (Scheme 48).[246] Both transition states (**275**) and (**278**) favor a pseudo-equatorial position of the benzyloxymethylene substituent; the newly formed chiral center is obtained in very high optical purity through the chirality transfer process. As a consequence of this geometrical preference, secondary allylic alcohols invariably provide predominantly (*E*)-configured double bonds upon thermal Claisen rearrangement.[247,248] The (*E*)-selectivity usually increases with the steric bulk of the C-2 substituent, an effect which was rationalized by a pseudo-1,3-diaxial interaction in the transition state leading to the (*Z*)-alkene (**280**; Figure 5).[249]



i, $MeC(OEt)_3$ (12 equiv.), pivalic acid (7 mol%), reflux 22 h

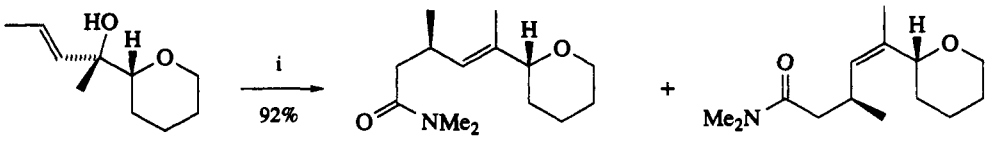
Scheme 48



(280)

Figure 5

As expected, with tertiary allylic alcohol derivatives, the selectivity for the formation of the corresponding trisubstituted alkenes is significantly reduced.[29d,250] Eschenmoser rearrangement of alcohol (**281**), for example, led in 92% yield to a 7.1:1 ratio of (*E*)- to (*Z*)-amides (**282**) and (**283**) (Scheme 49).[251,252]



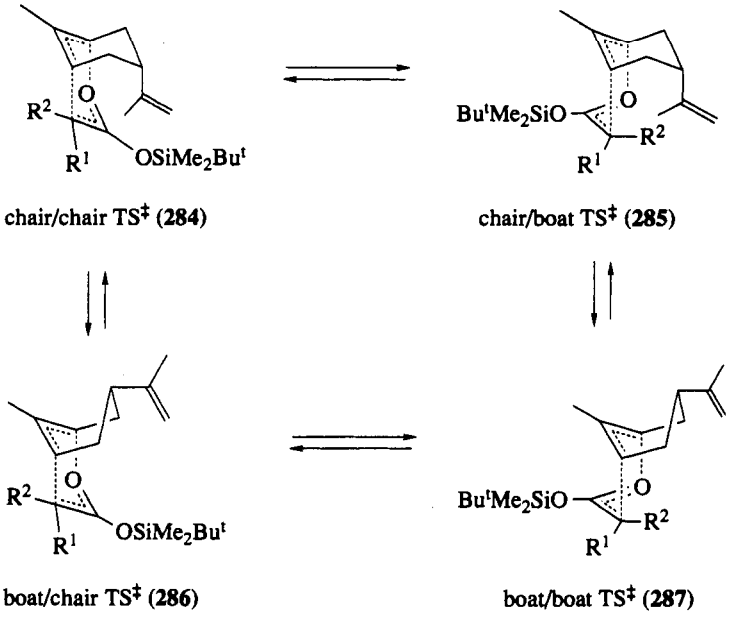
(281) **(282)** **(283)**

i, $MeC(NMe_2)(OMe)_2$, 120 °C

Scheme 49

(ii) Cyclic substrates

In substrates where the allyl vinyl ether moiety is part of a cyclic system, steric and electronic constraints can profoundly affect transition state selection.[253] Ireland rearrangement of propionate (**125**), for example, leads in THF *via* the (*E*)-silylketene acetal to a 25:75 ratio of carboxylic acids (**126**) and (**127**) in 56% yield (Scheme 22).[238] Enolization in THF/45% DMPU generates the corresponding (*Z*)-silylketene acetal, which upon rearrangement and hydrolysis provides acid (**126**) in 60% yield as the only NMR detectable isomer. In THF/23% HMPA a 90:10 ratio of isomers is detected, in accord with the enolization stereoselectivity.[254] Consideration of the possible transition states for the 3,3-shift of propionate (**125**) leads to the conclusion that both the chair/chair- and the chair/boat-like transition states (**284**) and (**285**) shown in Scheme 50 are strongly destabilized due to the severe interaction between the axially oriented isopropenyl substituent and the vinyl ether portion. However, an alternative set of transition states, where the cyclohexene ring adopts a boat conformation, avoids these destabilizing interactions (**286** and **287**). With both the (*E*)-silylketene acetal (R^1 = H, R^2 = Me) and the (*Z*)-silylketene acetal (R^1 = Me, R^2 = H) geometry, boat/chair transition state (**286**) seems to be preferred over boat/boat transition state (**287**).[238]



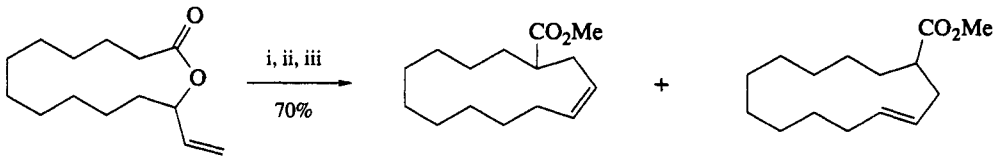
chair/chair TS‡ (**284**) chair/boat TS‡ (**285**)

boat/chair TS‡ (**286**) boat/boat TS‡ (**287**)

R^1, R^2 = H, Me

Scheme 50

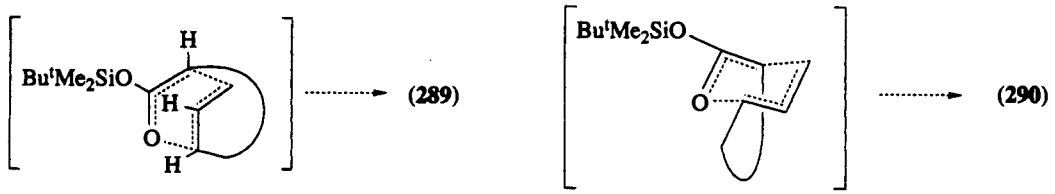
Ireland rearrangement of the unsaturated macrolide (**288**) in THF/HMPA (3:1), followed by desilylation in aqueous hydrogen fluoride in acetonitrile, led in 70% yield to a 72:28 mixture of acids (**289**) and (**290**) (Scheme 51).[255] The intermediate silylketene acetal was found to be a single isomer, therefore both transition states (**291**) and (**292**) seem to participate in product formation (Figure 6).



(**288**) (**289**) (**290**)

i, LDA (2 equiv.), THF/HMPA (3:1), –78 °C; Bu^tMe_2SiCl; ii, toluene, reflux, 8 h; iii, aqueous HF/pyridine; CH_2N_2, ether

Scheme 51



(291) (292)

Figure 6

7.2.4.3.2 Remote stereocontrol

Besides the intrinsic stereochemistry that can be introduced into the Claisen system by an asymmetric carbon in the 4 position, remote centers of asymmetry can also lead to significant diastereocontrol in the rearrangement.

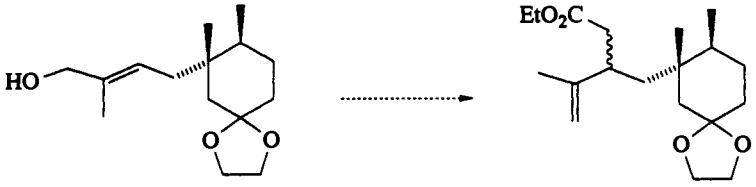
(i) Acyclic substrates

Ziegler and coworkers reported low diastereoselectivities in the Johnson rearrangement of an (*E*)-allyl alcohol positioned as a side chain of a trisubstituted cyclohexanone ketal derivative (equation 28).[256] Only a modest stereoselectivity was observed with the center of asymmetry in the vicinal position to the Claisen system, such as in the rearrangement of dioxolane derivative (**295**; Equation 29).[257,258] Ortho ester rearrangement of allylic alcohol (**297**), however, gave esters (**298**) and (**299**) in a ratio of 11.5:1 (Scheme 52).[259] Replacement of the bulky (t-butyldimethylsilyl)oxy group in (**297**) by a hydroxy group led to a drop in the observed diastereoselectivity of the rearrangement to 5.2:1. This indicates a possible destabilizing interaction of the ethoxy group and the ring substituent in transition state (**301**).

(ii) Cyclic substrates

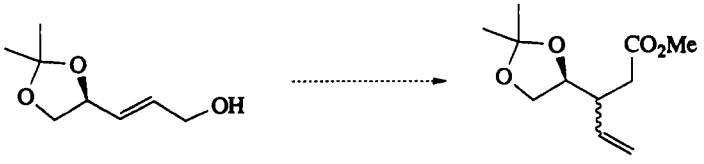
Generally, Claisen rearrangement of ring-bearing substrates with remote asymmetric centers has led to higher stereoselectivities than in the acyclic series.[260] Kurth and coworkers used amino acid derived chiral auxiliaries such as (**302**) for the preparation of enantiomerically pure carboxylic acids.[261] The excellent facial selectivity in these systems was hampered, however, by poor chair *vs.* boat selectivities.

In the acid-catalyzed ortho ester Claisen rearrangement of allylic alcohol (**303**) with trimethyl orthobutyrate, diastereomers (**304**), (**305**) and (**306**) were isolated in a ratio of 63:30:7 (Scheme 53).[262] The 3,3-sigmatropic rearrangement occurred with a high degree of stereofacial selectivity from the β-face of the allylic alcohol (α:β > 13:1 for H_a).[263] In contrast, Claisen rearrangement of the enol ether (**307**) at 135–140 °C (PhH, sealed tube) provided the desired β-dicarbonyl compound (**308**) as a single diastereomer at



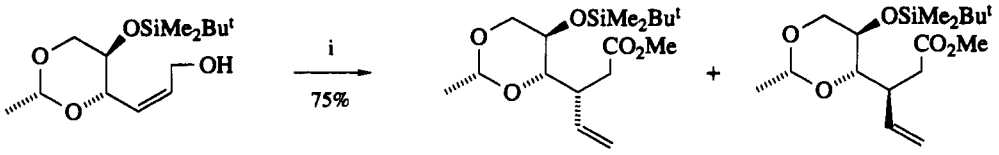
(28)

(293) (294)



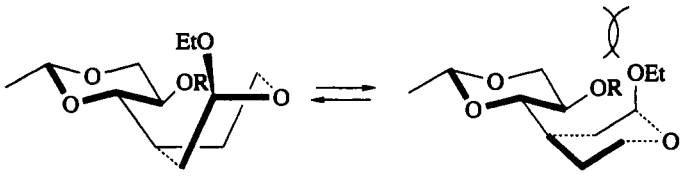
(29)

(295) (296)



(297) (298) (299)

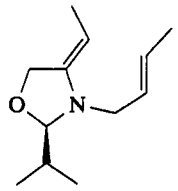
i, $MeC(OEt)_3$, propionic acid (cat.), 135 °C, 27 h



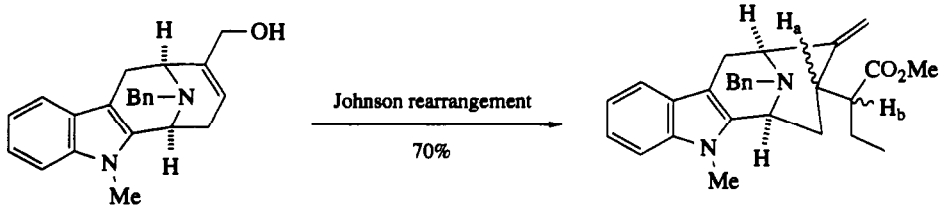
(300) (301)

Scheme 52

C-15 in 55% yield (Scheme 53). In this case, the thermal Claisen rearrangement occurred stereospecifically from the α-face of the bicycle, presumably *via* chair transition state (**309**) (Scheme 54). Therefore it was concluded that the ortho ester rearrangement occurred predominantly *via* boat transition state (**310**), providing the first example of a difference in transition state geometry observed in Claisen variants with the same substrate.

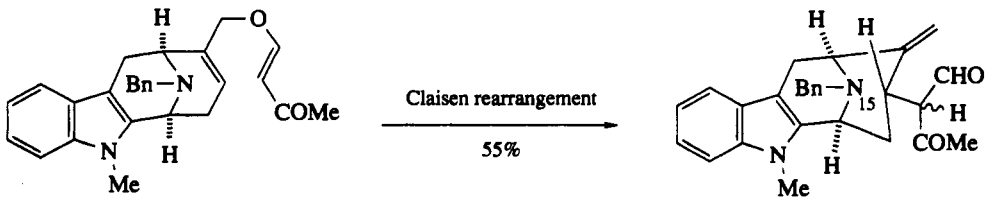


(302)



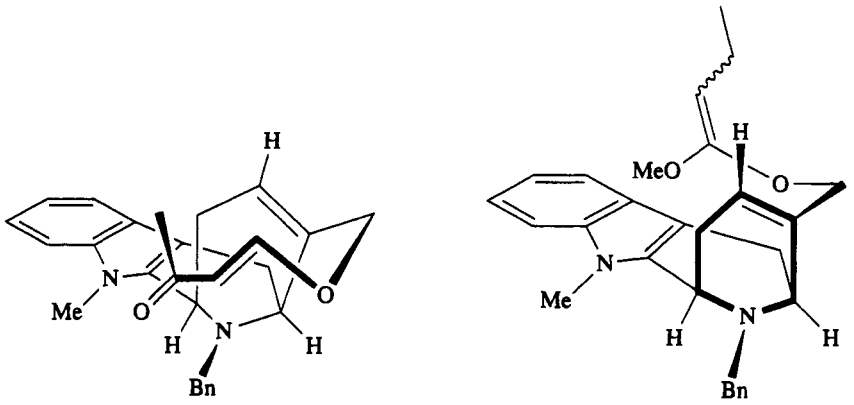
(303)

(304) α-H_a, β-H_b
(305) α-H_a, α-H_b
(306) β-H_a, β-H_b



(307) (308)

Scheme 53



(309) (310)

Scheme 54

7.2.5 CONCLUSIONS

During the 1970s and the 1980s the Claisen rearrangement of allyl vinyl ethers has clearly become an extremely valuable tool in stereocontrolled organic synthesis. However, it still offers mechanistic challenges and synthetic opportunities attractive to the entire chemical community. Certainly, future research in areas such as the influence of substituents and catalysts on transition state structures of the Claisen rearrangement will have a significant impact in the general understanding of chemical reactivity and selectivity.

7.2.6 REFERENCES

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7.3
Consecutive Rearrangements

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7.3.1 INTRODUCTION

Sigmatropic rearrangements involve the allylic migration of σ-bonds that are in conjugation with the π-framework of the double bond. Not only do sigmatropic rearrangements provide for the formation of sigma bonds, but the migration of the double bond can establish new, reactive functionality that initiates subsequent rearrangements.

Consecutive rearrangements can be classified in three general categories: tandem, sequential and iterative. Tandem rearrangements require the reacting components of the rearrangement to be attached to one another prior to the initial rearrangement. Sequential rearrangements require chemical modification of the first rearrangement product prior to the second rearrangement. Iterative rearrangements are similar to sequential rearrangements except that the process may be conducted many times, and are often used for the synthesis of substances with repeating units.

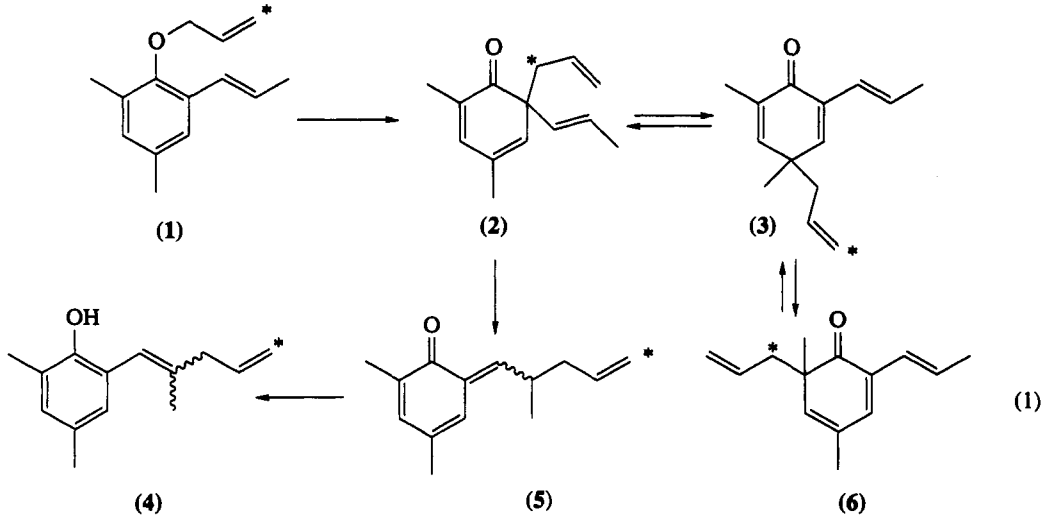
The concept of consecutive reactions need not be limited strictly to sigmatropic reactions. However, only those reactions that involve a minimum of two sigmatropic rearrangements will be considered.

7.3.2 TANDEM AND SEQUENTIAL REARRANGEMENTS

7.3.2.1 [3,3]–[3,3] Rearrangements

7.3.2.1.1 Claisen–Cope

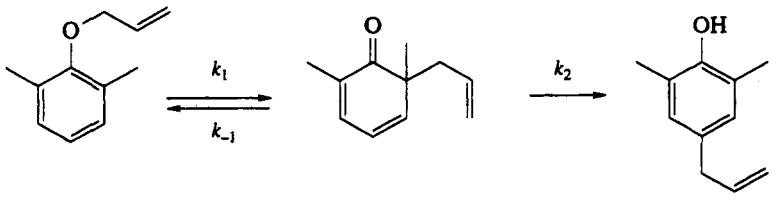
The first example of a tandem Claisen–Cope rearrangement was reported by Claisen in his final scientific paper.[1] Thermolysis of allyl aryl ether (**1**) provides phenol (**4**) in which the allyl residue has been incorporated into the propenyl side chain of (**1**; equation 1). The reaction proceeds through an initial Claisen rearrangement to afford transient 1,5-hexadiene (**2**) which undergoes a subsequent Cope rearrangement to provide unsaturated ketone (**5**). Rearomatization of (**5**) occurs, ostensibly catalyzed by the phenol, to afford irreversibly the observed product (**4**). Intermediate (**2**) may transfer the allyl group to both the *para* position (**3**) or to the methyl-bearing *ortho* position (**6**). Structure (**6**) may also be realized from allyl ether (**1**) by a direct Claisen rearrangement. The presence of 2- and 6-substituents prohibits premature tautomerization to an *o*-allylphenol.



(1) (2) (3) (4) (5) (6) (1)

This reaction has been independently reinvestigated by Lauer[2] and Schmid.[3] Rearrangement of (**1**), bearing a ^{14}C label at the distal carbon of the allylic moiety (starred), gives phenol (**4**) with 84% of the label at the terminal carbon of the side chain and 16% at the methylene group. This result demonstrates that the reaction proceeds principally through a double transposition of the allylic residue; the labeling pattern is maintained independent of the pathway to phenol (**4**).

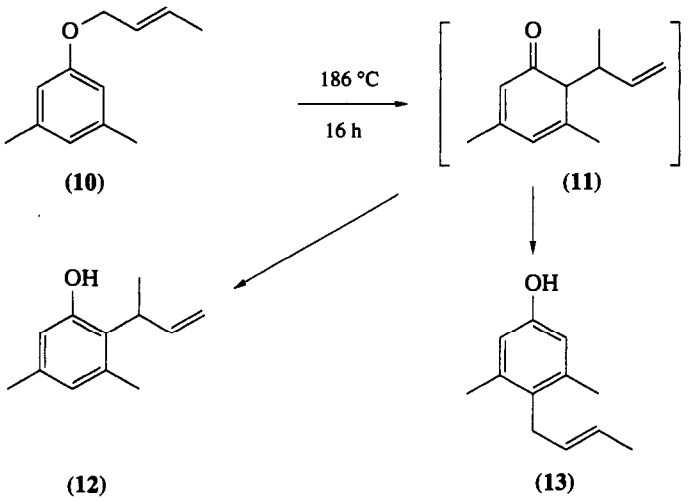
The dienone (**8**; equation 2), prepared independently by allylation of sodium 2,6-dimethylphenolate, has been shown to undergo irreversible rearrangement to the *p*-allylphenol (**9**) and aryl allyl ether (**7**) (k_2/k_{-1} = ~2.5; 75–100 °C).[4] The rate constant k_1 for the forward reaction is negligible. In the aromatic Claisen–Cope sequence, the Claisen rearrangement is the slower step because the aromaticity of the ring must be overcome.



(7) (8) (9) (2)

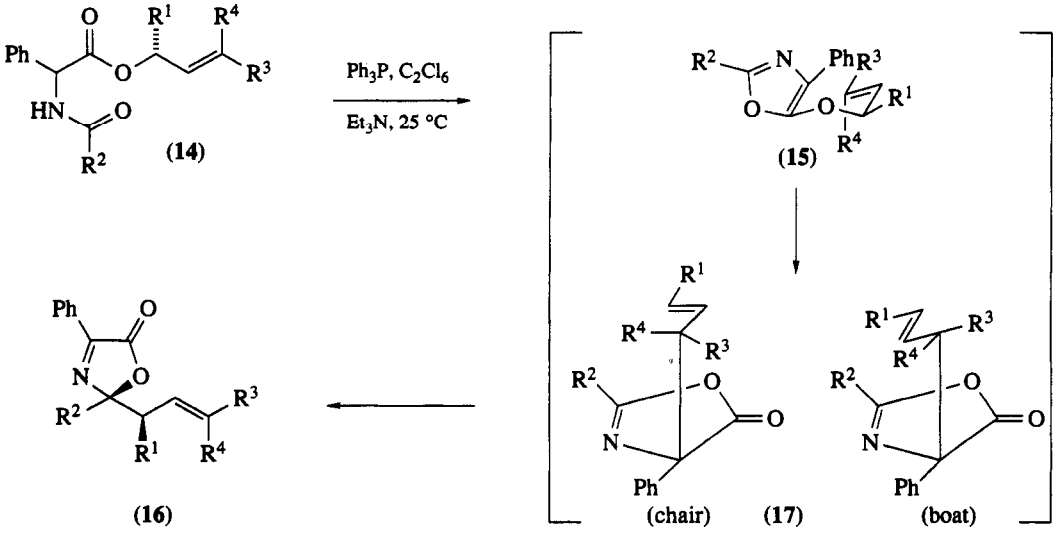
Although substituents at the 2- and 6-positions of the aromatic ring are generally employed to prohibit the formation of 2-substituted products, the tandem rearrangement has been observed in aryl vinyl ethers

that are devoid of substituents at these positions. The rearrangement of aryl crotyl ether (**10**; equation 3) proceeds through intermediate (**11**), which can partition between 2-substituted phenol (**12**) and the Claisen–Cope product (**13**). The product distribution is solvent dependent; the prototropic isomerization of (**11**) to the *ortho*-substituted product (**12**) is facilitated by polar solvents (solvent, **12**/**13**): neat, 1/1; decalin, 1/1; *N*,*N*-diethylaniline, 4/1; benzonitrile, 8/1; *N*,*N*-dimethylformamide, 60/1.[5]



(3)

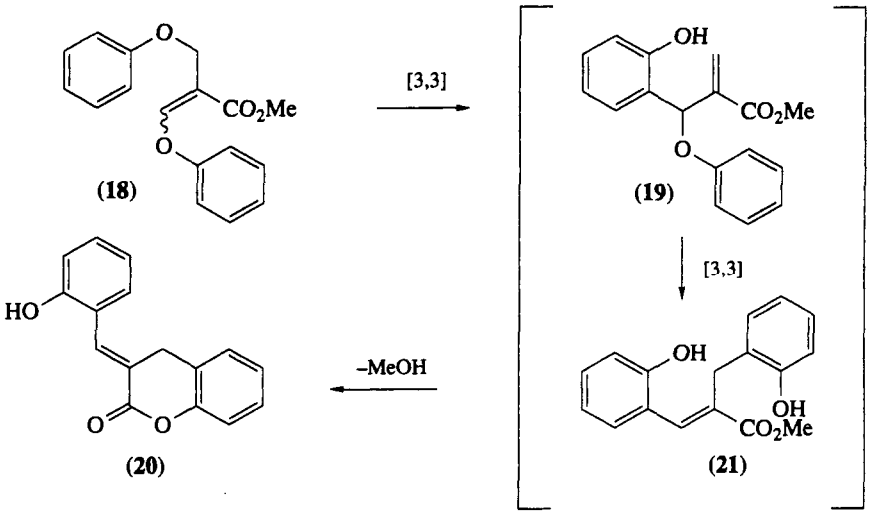
Steglich[6] has observed a tandem rearrangement in the transformation of aroyl phenylglycinates (**14**) to their respective oxazolinones (**16**; equation 4). The (*E*)-cinnamyl ester (**14a**) and the (*Z*)-cinnamyl ester (**14b**) provide the single (*E*)-alkene (**16a**). Both Claisen rearrangements (**15a** or **15b** giving **17a** or **17b**) are presumed to proceed through the more favorable chair-like transition state, while the aza-Cope rearrangement of the (*E*)-isomer (**17a**) (giving **16a**) occurs *via* the chair-like transition state and the (*E*)-isomer (**17b**) (giving **16b**) proceeds through the boat-like transition state.[7,8] In addition, the chiral (*E*)-ester (**14c**) (66% *ee*) undergoes tandem rearrangement with 100% chirality transfer *via* two chair-like transition states to afford oxazolinone (**16c**). The aza-Cope rearrangements are controlled by the allylic phenyl groups assuming an equatorial position in the transition state. Reductive removal of the heterocyclic ring of (**16c**) provides a route to chiral, nonracemic β,γ-unsaturated ketones.



(4)

a: R^1 = H, R^2 = *p*-ClC_6H_4, R^3 = Ph, R^4 = H; **b**: R^1 = H, R^2 = *p*-ClC_6H_4, R^3 = H, R^4 = Ph;
c: R^1 = Me, R^2 = R^3 = Ph, R^4 = H

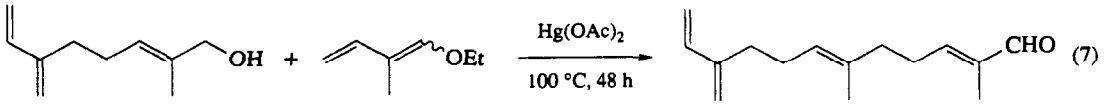
Tandem [3,3] rearrangements in the aromatic series may involve consecutive Claisen rearrangements. Thermolysis of ester (**18**; equation 5) is reported to give the benzopyran-2-one (**20**), whose structure is supported by an IR carbonyl frequency at 1690 cm^{-1} (extended conjugation through the phenolic hydroxy) and a ^1H NMR alkenic proton at δ7.67. The rearrangement of the initial Claisen product (**19**) to the (*E*)-cinnamate (**21**) is claimed to occur through transition state (**22**). Clearly, transition state (**22**) leads to (*Z*)-cinnamate (**23**; equation 6). Although stereochemical and mechanistic ambiguities remain, the tandem nature of the process is secure.[9]



(5)

(6)

The application of consecutive rearrangements to aliphatic systems has been exceptionally rewarding. A seminal contribution is provided by the work of Thomas, who has prepared β-sinesal (**26**; equation 7), a constituent of the essential oil of the Chinese orange, by the tandem Claisen–Cope rearrangement.[10]

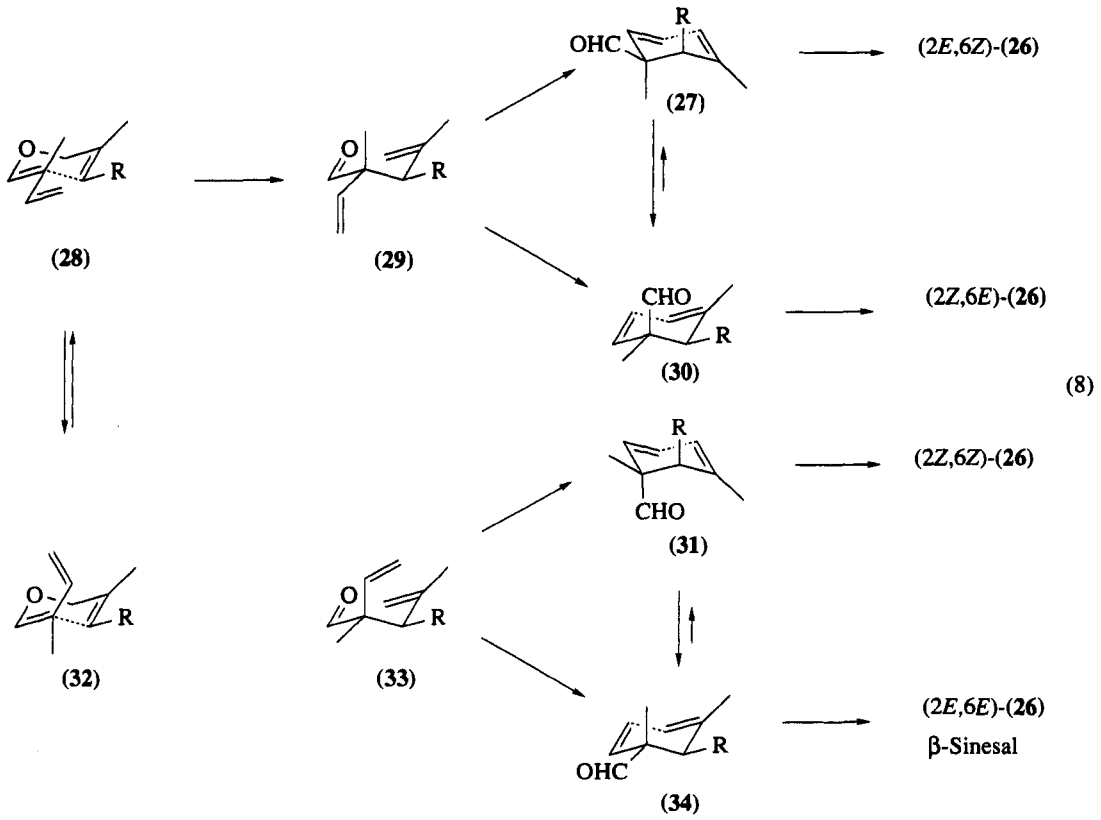


(7)

(**24**) (**25**) (**26**)

Mercury(II) acetate catalyzed exchange of allylic alcohol (**24**) with 1-ethoxy-2-methyl-1,3-butadiene (**25**) ostensibly forms the isomeric vinyl ethers (**28**) and (**32**) that do not interconvert rapidly under the reaction conditions (equation 8). Claisen rearrangement of the isomers affords the diastereomeric aldehydes (**29**) and (**33**). Although the chair-like transition state is generally preferred in Claisen rearrangements where the double bonds are not contained in rings, no stereochemical features are present in aldehydes (**29**) and (**33**) that will distinguish the chair-like from the boat-like transition state. Thus, diastereomer (**29**) is accessible from the (*E*)-vinyl ether *via* the chair-like transition state (**28**), or from the (*Z*)-vinyl ether *via* a boat-like transition state. Conversely, the (*E*)-vinyl ether rearranging through a boat-like transition state or the (*Z*)-vinyl ether rearranging through the chair-like transition state (**32**) gives diastereomer (**33**). The (6*E*)-double bond of β-sinesal must arise from Cope transition states (**30**) or (**34**) that bear the R substituent (R = $CH_2CH_2C(=CH_2)CH=CH_2$) in the equatorial position. Although no (2*Z*,6*E*)-isomer of β-sinesal (**26**) is detected as a product, the (2*Z*)-geometry has been observed in related rearrangements (*vide infra*) and presumably isomerizes to the more stable (2*E*)-geometry during the course of the reaction. The tandem Claisen–Cope rearrangement of equation (8) is the operational equiv-

alent of the γ-alkylation of the anion of (*E*)-2-methyl-2-butenal, of which (**25**) is the dienol ether, with an activated form of the alcohol (**24**).

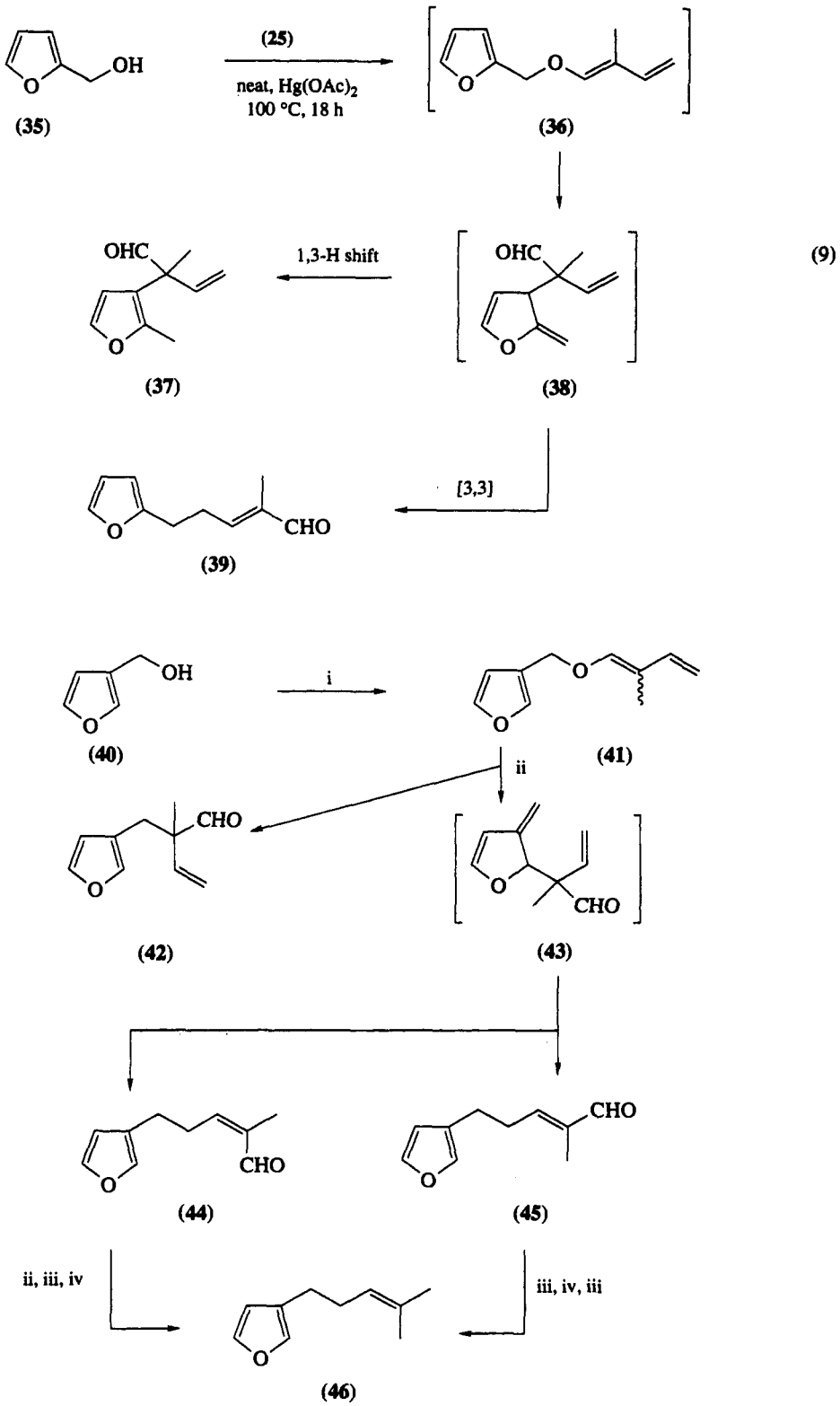


Because the Cope rearrangement is an equilibrium driven reaction, the application of the Claisen–Cope rearrangement to synthesis requires the target substrates to be more stable than their Cope precursors. Thus, in the instance of equation (8), the 1,5-hexadienes (**30**) and (**34**) bear a monosubstituted and a 1,1-disubstituted double bond, which are less stable than the trisubstituted double bonds of β-sinesal.

Thomas and Ozainne[11] have explored the tandem Claisen–Cope rearrangement on aromatic substrates. Treatment of 2-furfuryl alcohol with diene (**25**; equation 9) provides a 9:1 mixture of Claisen–Cope product (**39**) and furan (**37**), respectively. The minor component arises *via* the 'forbidden' [1,3] prototropic shift of the initial Claisen intermediate (**38**), thereby reestablishing the aromaticity of the furan ring.

When the reaction conditions that are successful with 2-furfuryl alcohol are applied to 3-furfuryl alcohol (**40**), only the product of alcohol exchange, diene (**41**), as a 1:1 mixture of isomers, is obtained (Scheme 1). Elevated temperature (350 °C) is required for the success of the rearrangement. Although the [1,3] prototropic rearrangement of intermediate (**43**) is not observed, the aldehyde (**42**) is produced as a minor component of the reaction mixture ostensibly arising *via* a homolytic scission–recombination of dienol ether (**41**). The products of [3,3] rearrangement are the unsaturated aldehydes (**45**) and (**44**), which are produced in an 85:15 ratio, respectively. Assuming that the chair-like transition state is operative, the (*E*)-isomer (**45**) is produced when the aldehyde group is equatorial (*cf.* transition state **50**), and the (*Z*)-isomer is formed when the aldehyde group is axial (*cf.* transition state **51**). The mixture of aldehydes is transformed in a two-step process into the natural product perillene (**46**).

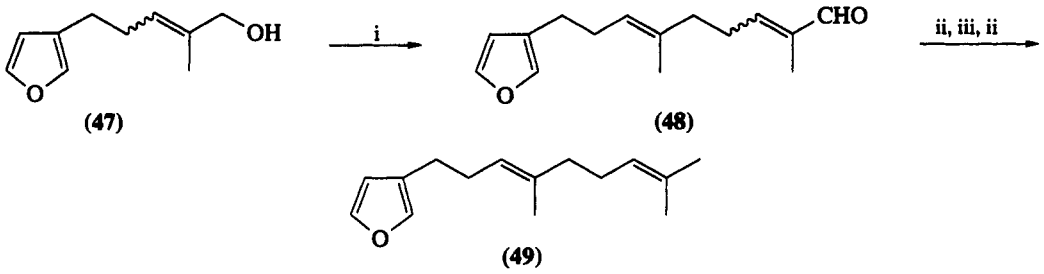
The 85:15 mixture of alcohols (**47**) that serves as an intermediate in the synthesis of perillene can undergo a second Claisen–Cope rearrangement under moderate temperature conditions to afford an 80:20 mixture of the (*E*)-unsaturated aldehydes (**48**), torreyal and its (*Z*)-stereoisomer, respectively. Reduction of the aldehyde group of the mixture provides dendrolasin (**49**; Scheme 2). Both alcohols of the alcohol mixture (**47**) can channel through 1,5-hexadienes (**52**) and (**53**) after the initial Claisen rearrangement. The exclusive formation of the (6*E*)-double bond geometry is the result of the β-(α-furfuryl)ethyl chain occupying the equatorial position in the ensuing Cope rearrangement of (**52**) and (**53**). The iterative nature of the process permits the continuing interpolation of '(*E*)-isoprene' units into the growing chain.



(9)

i, (25), $Hg(OAc)_2$, 100 °C, 15–24 h; ii, 350 °C; iii, $LiAlH_4$; iv, TsCl

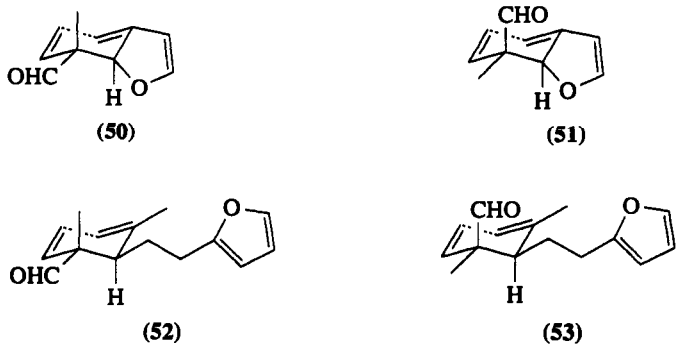
Scheme 1



(47) (48) (49)

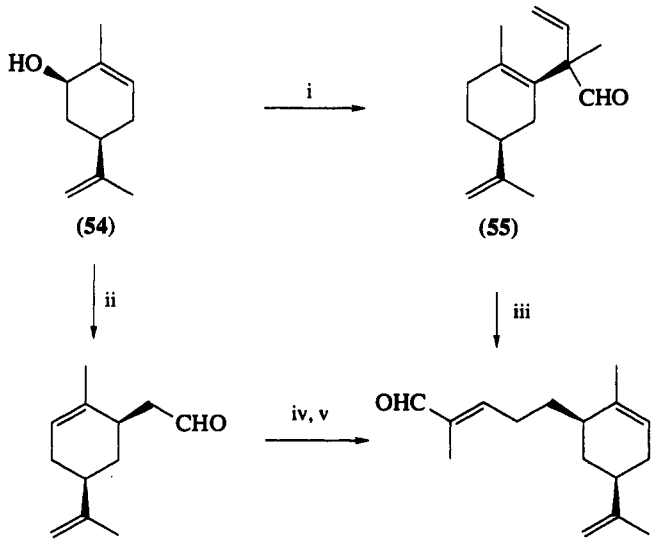
i, (25), $Hg(OAc)_2$, 100 °C, 18 h; ii, $LiAlH_4$; iii, TsCl

Scheme 2



(50) (51) (52) (53)

When the Claisen–Cope rearrangement is applied to (–)-*cis*-carveol (**54**; Scheme 3) at 100 °C, a dextrorotatory mixture of aldehydes (**55**) is isolated after the initial Claisen rearrangement, in addition to small amounts of the Claisen–Cope (*E*)-unsaturated aldehyde (**57**) ($[\alpha]_D = -5°$) and its (*Z*)-isomer. Thermolysis of (**55**) at 150 °C gives aldehyde (**57**) ($[\alpha]_D = -8.4°$) and at 400 °C the product displays no rotation. At elevated temperature the reaction presumably occurs *via* a diradical species as the rotation of *ent*-(**57**), prepared via (**56**) from (**54**), is $[\alpha]_D = +12°$.[12]

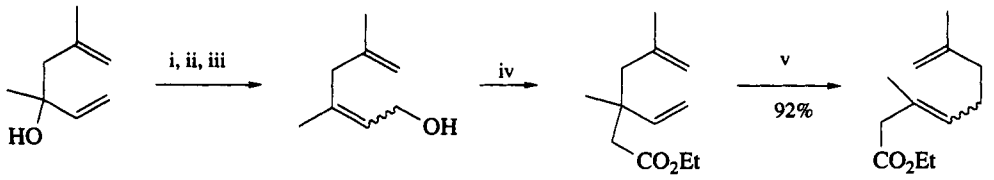


(54) (55) (56) (57)

i, (25), $Hg(OAc)_2$, 100 °C, 17 h; ii, $EtOCH{=}CH_2$, 120 °C, 24 h; iii, 400 °C; iv, $MeCH{=}CHN(Li)Bu^t$, Et_2O; v, H_3O^+

Scheme 3

The success of the Claisen–Cope rearrangement need not be limited to the production of aldehydes *via* enol ethers. Allylic alcohol (**58**) is successively transposed into a mixture of allylic isomers (**59**; Scheme 4), and is subjected to an orthoester Claisen rearrangement[13] at 150 °C to provide ester (**61**). The moderate temperature of the Claisen step permits the isolation of an intermediate (*cf.* Scheme 3) prior to the final Cope rearrangement (195 °C) to β,γ-unsaturated esters (**60**). The esters (**60**) are a 55:45 mixture of (*E*)- and (*Z*)-double bond isomers owing to the near equal steric bulk of the methyl and acetic acid residues in the transition state for the Cope rearrangement.[14]

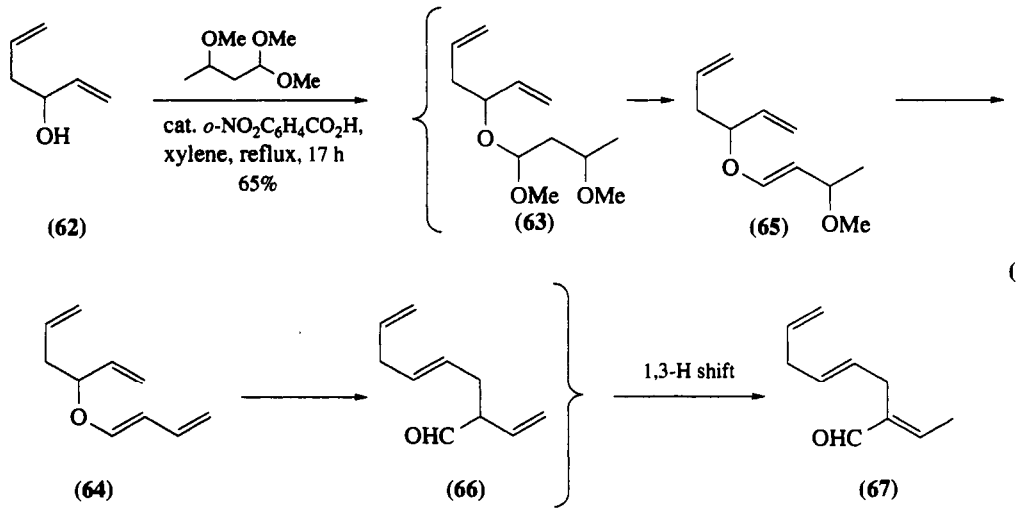


(**58**) (**59**) (**61**) (**60**)

i, PBr_3, Et_2O; ii, NaOAc/DMF; iii, KOH/MeOH;
iv, $MeC(OEt)_3$, cat. 2,6-dimethylphenol, 150 °C, 3 h; v, 195 °C, 5.5 h

Scheme 4

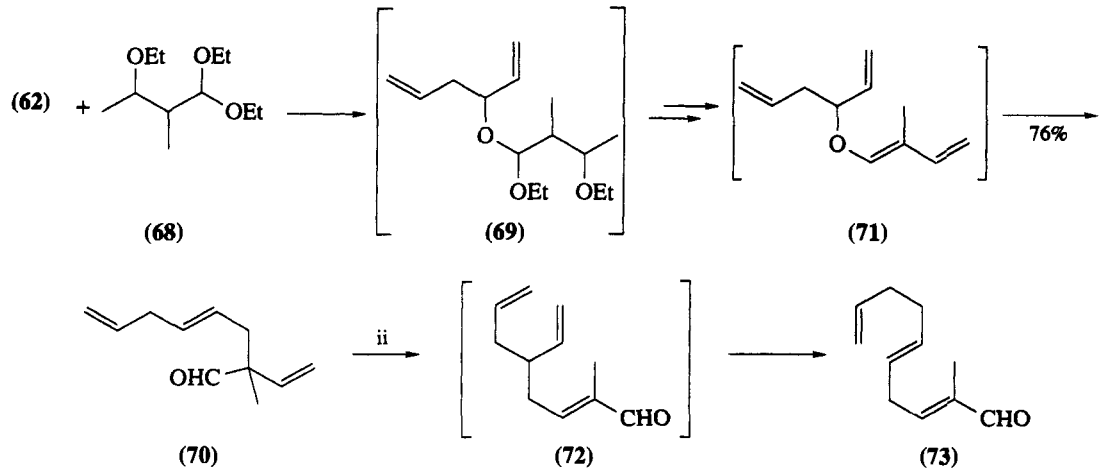
Cookson[15] has studied substrates that can, in principle, effect a tandem Claisen–Cope–Cope rearrangement. By employing 1,1,3-trimethoxybutane as a surrogate for 1-methoxy-1,3-butadiene (equation 10), allylic alcohol (**62**) undergoes acid-catalyzed exchange to provide the transient β,γ-unsaturated aldehyde (**66**) which, lacking a substituent at the α-position, suffers a facile conjugation of the double bond that preempts the tandem process. This phenomenon has been also observed by Thomas.[10]



(**62**) (**63**) (**65**) (**64**) (**66**) (**67**) (10)

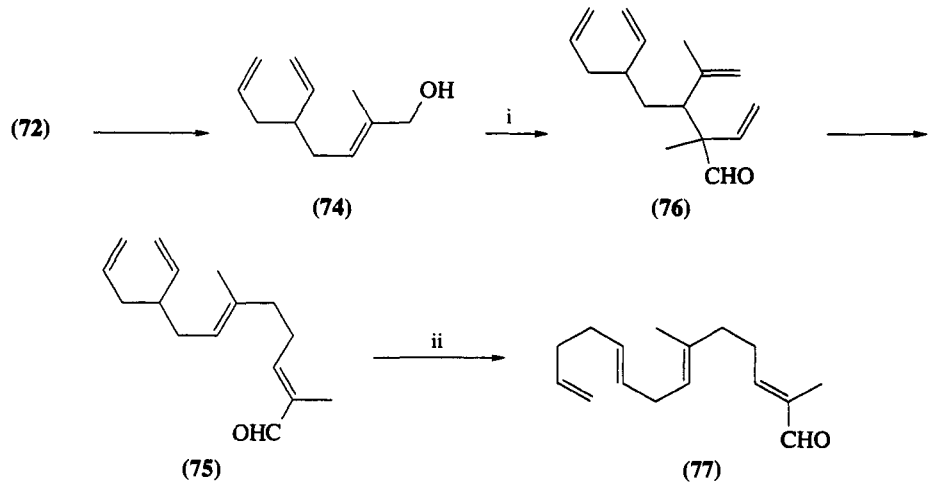
Alternatively, the acetal (**68**; Scheme 5), the analog of (**25**), provides aldehyde (**70**); in refluxing toluene the sequence stops after the Claisen rearrangement. When aldehyde (**70**) is heated at 190 °C, two successive Cope rearrangements occur; first, the α,β-unsaturated aldehyde (**72**) is formed, but not isolated, followed by rearrangement of the 1,5-hexadiene system of (**72**) to aldehyde (**73**). The initial Cope rearrangement, the product of which bears an aldehyde group on the 1,5-hexadiene framework, has a lower activation energy than the second rearrangement. When the reaction is run at 160 °C, aldehyde (**72**) can be isolated as an intermediate.

Reduction of aldehyde (**72**) to its alcohol (**74**; Scheme 6) followed by rearrangement with acetal (**68**) at 110 °C affords a 1:1 mixture (30% yield) of the initial Claisen rearrangement product (**76**) and the tandem Cope–Claisen product (**75**) that is formed from (**76**). These conditions illustrate the ease with which the Cope rearrangement can occur when a carbonyl function is present as a substituent. Once again, elevated temperature is required for the unsubstituted Cope transformation, (**75**) to (**77**). These operations provide another example of the iterative introduction of '(*E*)-isoprene' units into a growing chain.



i, cat. *o*-$NO_2C_6H_4CO_2H$, toluene, 110 °C, 48 h; ii, decalin, 190 °C, 3 h

Scheme 5

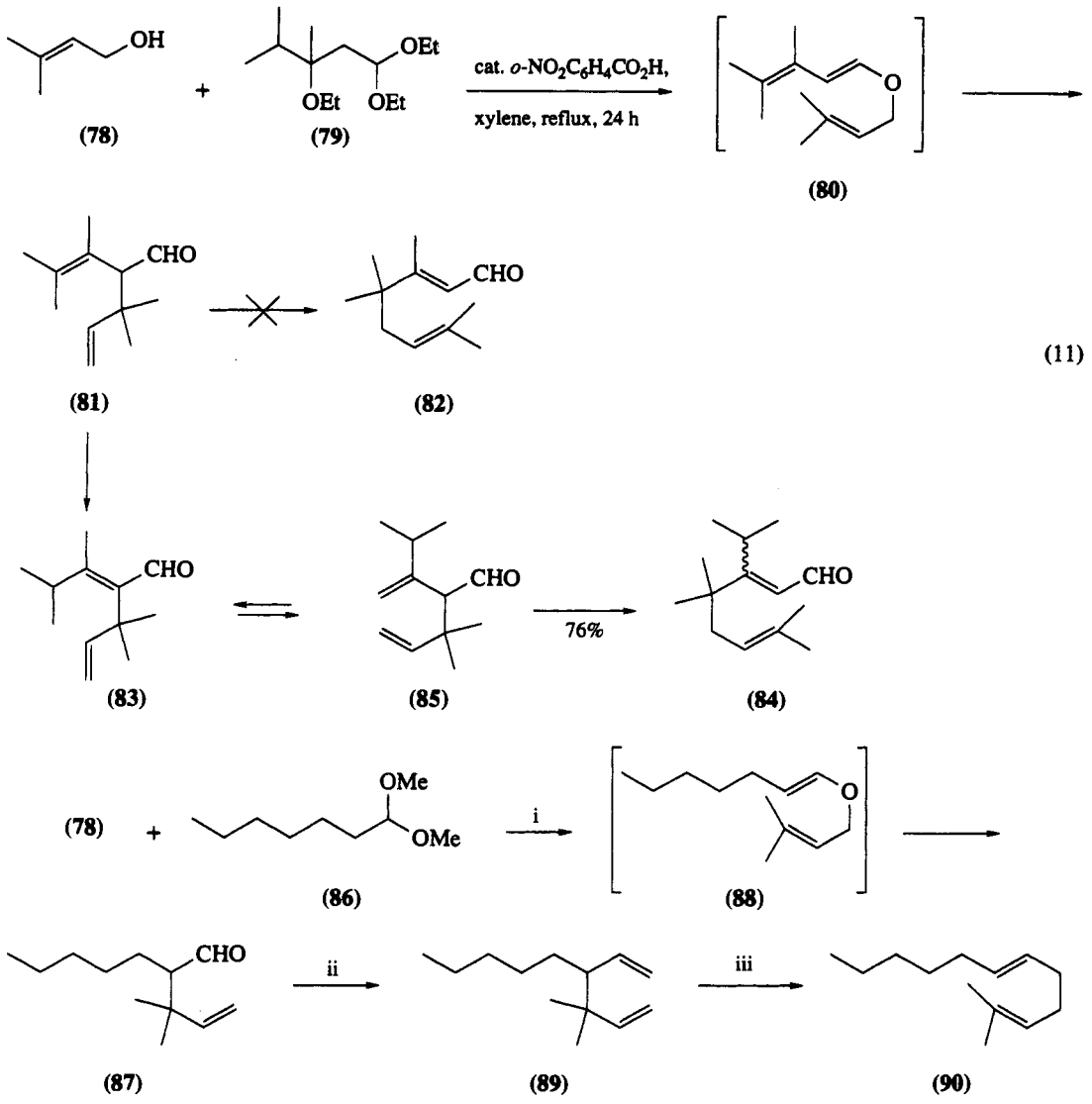


i, (**68**), cat. *o*-$NO_2C_6H_4CO_2H$, toluene, 110 °C, 48 h; ii, decalin, 190 °C, 24 h

Scheme 6

In the aborted Claisen–Cope rearrangement of equation (10), the presence of an additional substituent on the aldehyde α-carbon is required to prohibit enolization.[16] However, the absence of a substituent does not preclude a successful Claisen–Cope rearrangement if the conjugation step is reversible. Thus, exchange of β,β-dimethylallyl alcohol (**78**) with acetal (**79**) realizes aldehyde (**81**; equation 11) after the initial Claisen rearrangement; the Cope rearrangement product (**82**) is not observed. Alternatively, the β,γ-unsaturated aldehyde (**81**) undergoes reversible conjugation to (**83**) and deconjugation to the β,γ-unsaturated aldehyde (**85**), which rearranges irreversibly to a 70:30 mixture of (*E*)- and (*Z*)-aldehydes (**84**).

A Claisen–Cope rearrangement for the synthesis of 1,5-hexadienes is provided in Scheme 7.[17] The allyl vinyl ether (**88**), formed by acid-catalyzed exchange of alcohol (**78**) and 1,1-dimethoxyheptane (**86**), affords aldehyde (**87**). Conversion of the aldehyde to the diene (**89**) *via* a Wittig reaction and subsequent Cope rearrangement provides the more stable diene (**90**) that bears the (*E*)-double bond owing to the chain residing in an equatorial position in the transition state. This sequence requires an independent transformation before the second rearrangement and is, therefore, a sequential rearrangement. The process is formally a transmutation of the oxygen atom of the allyl vinyl ether (**88**) to the carbon in product diene (**90**).



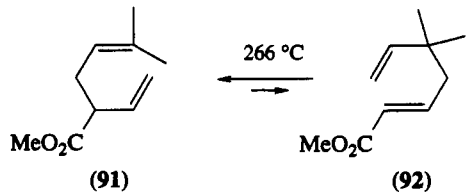
i, cat. o-$NO_2C_6H_4CO_2H$, mesitylene, 170 °C, 1 h; ii, Ph_3PCH_2, DMSO, 20 °C, 16 h; iii, DMSO, 190 °C

Scheme 7

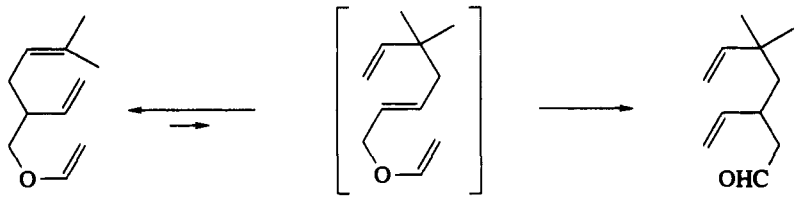
7.3.2.1.2 Cope–Claisen

One of the shortcomings of the tandem Claisen–Cope rearrangement is that the Cope rearrangement is equilibrium controlled. When the tandem reaction is practised in the reverse sense, any unfavorable Cope equilibria are driven to completion by an irreversible Claisen rearrangement. If the activation energy of the Claisen rearrangement is lower than that of the Cope rearrangement, which is generally the case, no intermediates will be isolated. Owing to the unfavorable Cope equilibrium of equation (12) (**91**/**92**, 4:1), ester (**92**) is an unsuitable precursor for the formation of allyl vinyl ether (**94**) and its eventual transformation to aldehyde (**95**). This difficulty is overcome by reduction of ester (**91**) to its alcohol and subsequent conversion of the resultant alcohol to vinyl ether (**93**). Thermolysis of (**93**; equation 13) provides the aldehyde (**95**) directly; allyl vinyl ether (**94**) is not observed.

The tandem Cope–Claisen rearrangement of triene (**96**; equation 14) creates a product with three new stereogenic centers. Only two of the four possible stereoisomers are formed, namely, aldehydes (**100**) and (**98**) in a 78:22 ratio. The factors that control the stereochemistry are the chair-like *versus* boat-like transition state of the Cope rearrangement (**96** giving **97**) and the formation of the carbon–carbon bond in

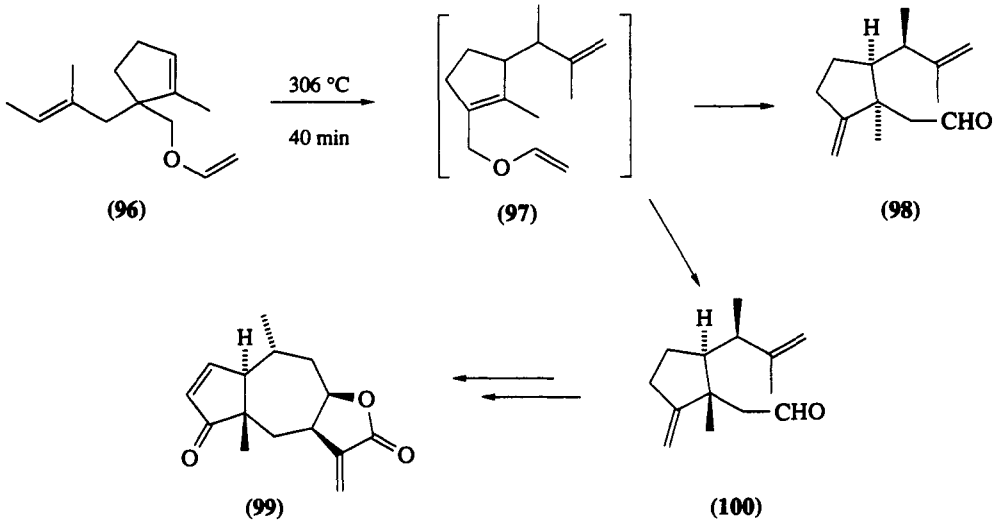


(91) (92) (12)



(93) (94) (95) (13)

the Claisen step *cis* or *trans* to the ring substituent of (**97**). The stereochemistry of the Cope rearrangement arises exclusively through the chair-like transition state, while the Claisen rearrangement proceeds preferentially *via* bond formation *trans* to the ring substituent. The major diastereomer (**100**) has been transformed into the pseudoguaianolide, aromatin.[18,19]

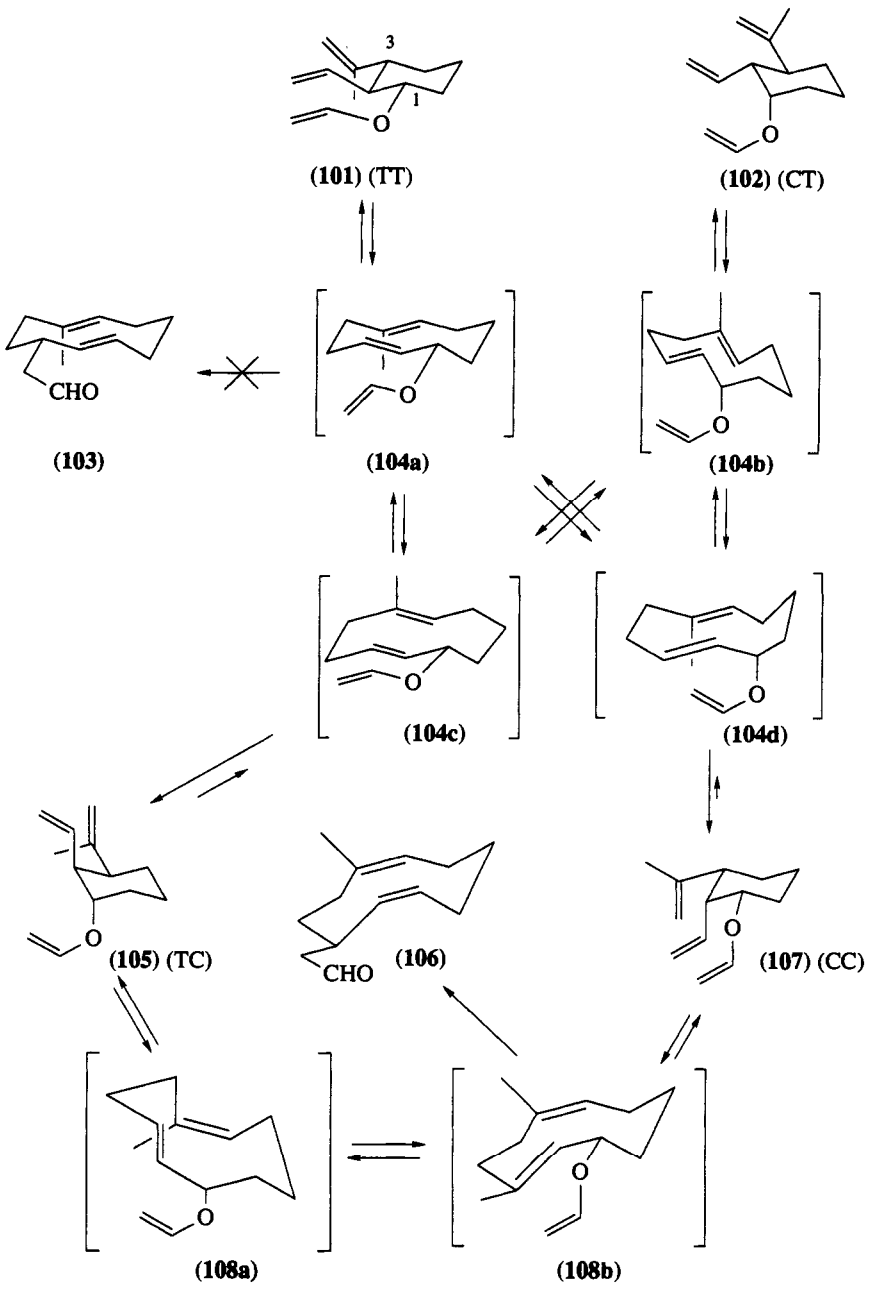


(96) (97) (98) (14)

(99) (100)

The tandem Cope–Claisen rearrangement provides an excellent opportunity to transform *trans*-2,3-divinylcyclohexanes *via* the less stable (*E,E*)-1,5-cyclodecadienes to (*E,E*)-1,6-cyclodecadienes (equation 15). When the two *trans*-divinylcyclohexanes, (**101**) (TT) and (**102**) (CT), are independently thermolyzed at ~300 °C, the (*Z,Z*)-1,6-cyclodecadiene (**106**), not the (*E,E*)-isomer (**103**), is formed. In the transformation (**101**) to (**104a**) to (**103**), the activation energy of the Claisen rearrangement is higher than that of the Cope rearrangement. At lower temperature (255 °C) interconversion of (**101**) and (**102**) occurs through the reversible Cope rearrangement. The interconversion is channeled through the crown conformations (**104a**) and (**104b**) of the intermediate (*E,E*)-1,5-cyclodecadiene. This process can be viewed as a stepwise 180° rotation of the ring double bonds passing through conformations (**104c**) and (**104d**) without entering the *cis* manifold. At the higher temperature this barrier is breached and the (*Z,Z*)-1,6-cyclodecadiene (**106**) is formed *via* the *cis*-1,2-divinylcyclohexanes (**105**) (TC) and (**107**) (CC). This view is supported by facile conversion of *cis*-1,2-divinylcyclohexane (**105**) (TC) to (*Z,Z*)-cyclodecadiene (**106**) at 255 °C, conditions that only interconvert (**101**) (TT) and (**102**) (TC). Reversible Cope isomerization of (**105**) (TC) to (**107**) (CC) occurs at 207 °C without Claisen rearrangement to (**106**).

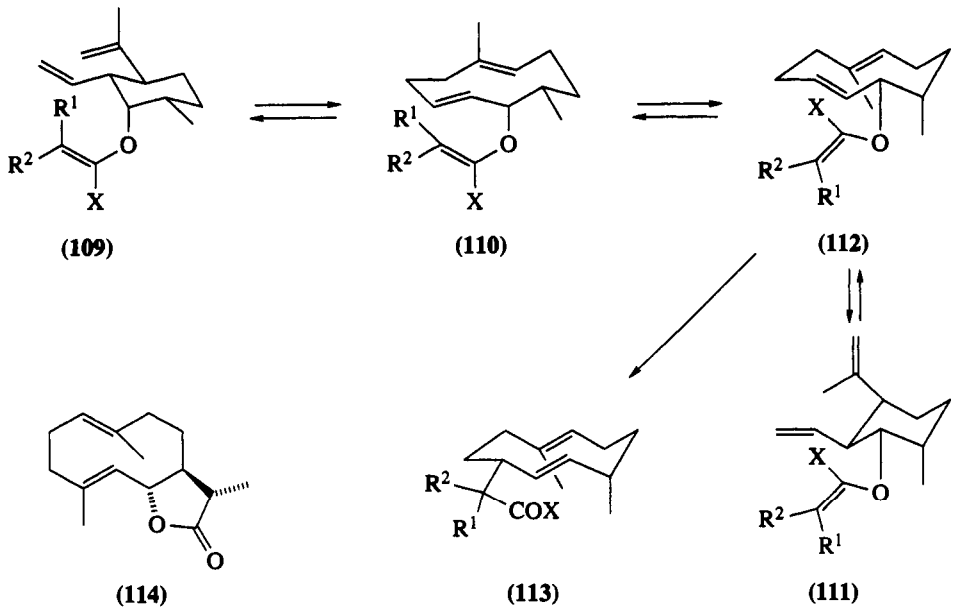
The success of this tandem Cope–Claisen rearrangement requires the lowering of the activation energy of the Claisen rearrangement below that of the Cope rearrangement. Recognizing that the Claisen rearrangement of *O*-silyl ketene acetals occurs more rapidly than vinyl ethers and that propionate- and isobu-



(15)

tyrate-derived *O*-silyl ketene acetals rearrange faster than those derived from acetate,[20] Raucher[21] has examined the reaction with the series of chiral 2,3-divinylcyclohexane *O*-*t*-butyldimethylsilyl ketene acetals (**109a**) to (**109c**) derived from (*S*)-(–)-carvone (equation 16). Thermolysis of (**109a**) at 205 °C effects equilibration with (**111a**) *via* the conformers (**110a**) and (**112a**) of the (*E*,*E*)-1,5-cyclodecadienes; in addition, the products of *O*- to *C*-silyl migration of (**110a**) and (**111a**) are also formed. The rearrangement of (**109b**) gives a mixture of three inseparable carboxylic acids; ^{1}H NMR spectroscopy indicates the presence of an (*E*)-disubstituted double bond. Rearrangement of the isobutyrate-derived silyl ketene acetal (**109c**) provides the desired acid (**113d**) in 51% yield. The problem of *O*- to *C*-silyl migration is obviated by use of the triisopropylsilyl ester (TIPS), which permits the preparation of the ester (**113b**) in 30% yield. This substance has been transformed into the 10-membered ring lactone, (+)-dihydrocostunolide (**114**).[22]

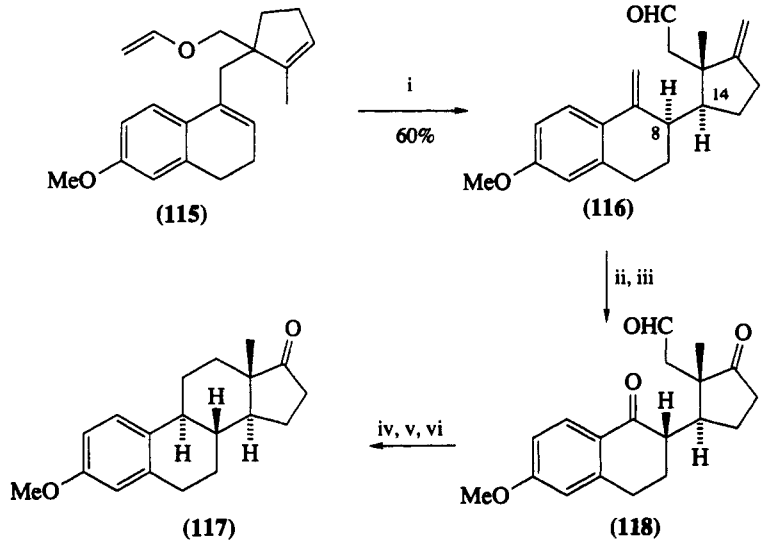
The functionality and stereochemistry provided by aldehyde (**100**) have led to the use of the tandem Cope–Claisen rearrangement for the synthesis of estrone methyl ether (**117**)[23] and steroid synthons.[24] Thermolysis of triene (**115**; Scheme 8) provides aldehyde (**116**) as the major component of a 2/1 mixture;



(16)

a: R^1, R^2 = H, H; X = $OSiMe_2Bu^t$
b: R^1, R^2 = H, Me; X = $OSiMe_2Bu^t$
c: R^1, R^2 = Me, Me; X = $OSiMe_2Bu^t$
d: R^1, R^2 = Me; X = OH
e: R^1 = H, R^2 = Me; X = $OSiPr^i_3$
f: R^1 = H, R^2 = Me; X = OMe

the minor component is isomeric with (**116**) at the quaternary center. The stereochemistry of the C(8)–C(14) bond is the result of a chair-like transition state in the Cope rearrangement, a stereochemistry that is incorrect for construction of the steroid nucleus. This difficulty is corrected by ozonolysis of diene (**116**) and equilibration of the resultant tricarbonyl (**118**) to provide an intermediate that is amenable to reductive ring closure and subsequent transformation to (**117**).

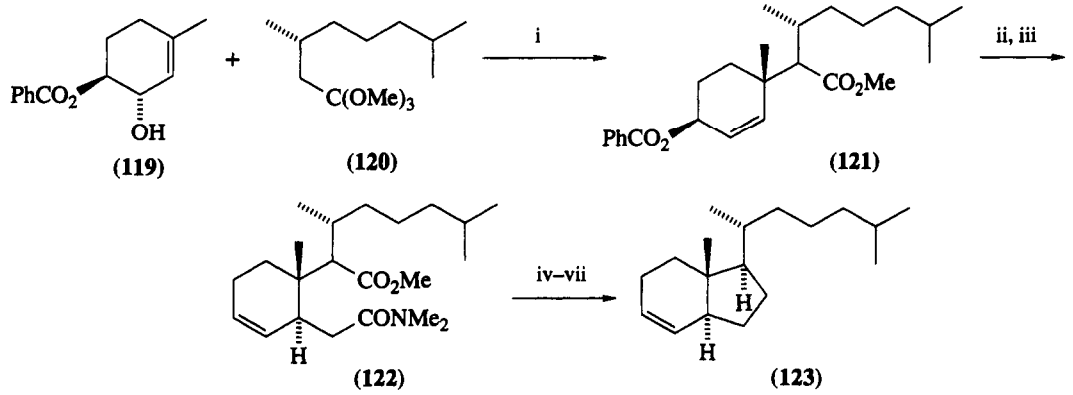


i, 370 °C, 20 s; ii, O_3; iii, MeONa, MeOH; iv, $TiCl_3$, Zn/Ag, DME; v, K/NH_3; vi, CrO_3

Scheme 8

7.3.2.1.3 Claisen–Claisen

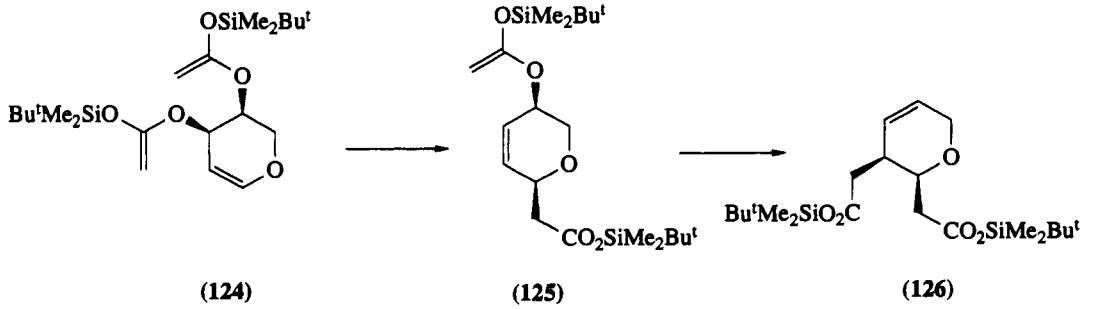
The use of two consecutive Claisen rearrangements has been accomplished in both the sequential and tandem modes. A noteworthy example of the former method has been applied creatively to syntheses in the vitamin D area by Lythgoe and his coworkers (Scheme 9).[25] (*R*)-Methyl orthodihydrocitronellate (**120**) is subjected to an orthoester Claisen rearrangement[13] with allylic alcohol (**119**) to produce esters (**121**). To avoid the formation of diastereomers, (**119**) must be used as the enantiomer shown, not as its racemate or other enantiomer. Although the stereochemistry at the stereogenic center bearing the ester group is not controlled, it is of no consequence in subsequent steps. Because benzoate (**121**) is allylic, its derived allylic alcohol is readily subjected to a second Claisen rearrangement *via* the Eschenmoser procedure[26] providing amide (**122**); subsequent Dieckmann cyclization affords the vitamin D synthon (**123**). The stereochemistry of each oxygen function in (**119**) dictates the eventual stereochemistry of each side chain introduced into (**122**).



i, xylene, reflux, cat. $EtCO_2H$; ii, NaOH; iii, $MeC(OMe)_2NMe_2$, xylene, reflux; iv, KOH; v, CH_2N_2; vi, NaH, DMSO; vii, H_3O^+

Scheme 9

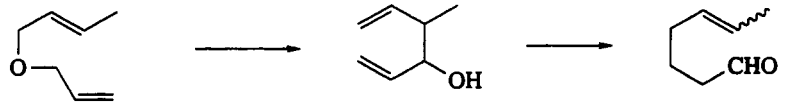
During preliminary studies on the synthesis of the pseudomonic acids, Curran[27] uncovered a rate enhancement attributable to the presence of the ring oxygen in the Claisen rearrangement of di-*t*-butyldimethylsilyl ketene acetal (**124**) to monoester (**125**). At 60 °C, the first Claisen rearrangement is an order of magnitude faster than the subsequent rearrangement of (**125**) to (**126**); however, the process can be accomplished effectively as a tandem rearrangement.



7.3.2.2 [2,3]–[3,3] Rearrangements

Nakai and his collaborators have explored in detail the stereochemistry of the [2,3] Wittig rearrangement of diallyl ethers and propargyl ethers and have applied the rearrangement in both the sequential and tandem modes with other sigmatropic rearrangements.[28] Preferential metalation of ether (**127**) at the methylene group of the allyl residue effects a [2,3] Wittig rearrangement to the versatile 1,5-hexadien-3-ol (**128**; equation 17), which is a 4:1 *threo*/*erythro* mixture.[29] The *threo*- and *erythro*-dienes (**128**) undergo oxy-Cope, anionic oxy-Cope,[30] or silyloxy-Cope rearrangement to afford aldehydes (**129**) with

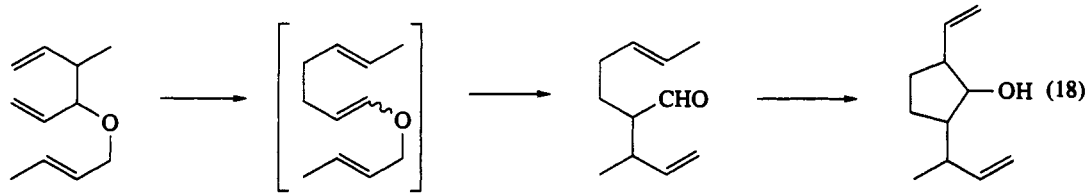
67–95% (*E*)-alkene selectivity. The oxy-Cope is more (*E*)-alkene selective in nonpolar than in polar solvents, and reflects the high end of the selectivity range.



(17)

(127) (128) (129)

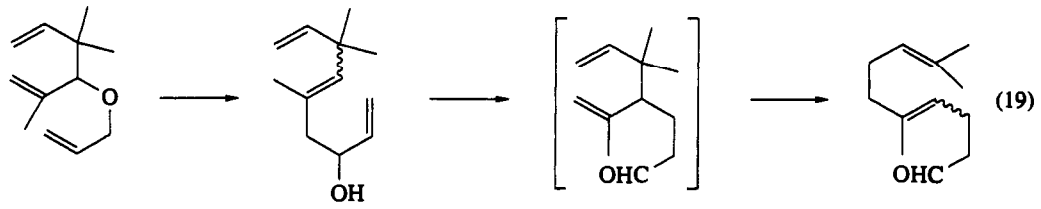
When converted to their (*E*)-2-butenyl ethers (**130**), dienols (**128**) serve as precursors for additional tandem processes. Thermolysis of the trienes (**130**) at 250 °C induces an initial oxy-Cope rearrangement to an allyl vinyl ether (**131**) that suffers irreversible Claisen rearrangement affording aldehyde (**132**; equation 18). While the diastereoselectivity of the reaction has not been determined, the geometry of the disubstituted double bond is exclusively of the (*E*)-configuration, a result that requires the secondary methyl group of triene (**130**) to be equatorial in the oxy-Cope transition state. Extended reaction time produces cyclopentanol (**133**), the product of an intramolecular oxy–ene reaction, at the expense of aldehyde (**132**). Trienes (**93**) and (**130**) differ in the relative positions of the oxygen and adjacent methylene group; accordingly, the products, (**95**) and (**132**), respectively, interchange the position of the aldehyde group and the proximate double bond.



(18)

(130) (131) (132) (133)

Not only are the trienes (**130**) suitable for consecutive [3,3] sigmatropic rearrangements, but, as diallyl ethers, are candidates for an additional [2,3] Wittig rearrangement. Because the diallyl ethers (**130**) are prepared from diallyl ether (**127**), and metalation occurs preferentially at the methylene adjacent to the oxygen rather than the methine,[31] the methodology adumbrates the opportunity for iterative processes. This concept is practised, in part (equation 19), by the [2,3] Wittig rearrangement of diallyl ether (**134**) to trienols (**135**), which is followed by a tandem oxy-Cope/Cope rearrangement to aldehyde (**136**); the aldehydes are isolated as a 2/1 mixture of (*E*)- and (*Z*)-isomers, respectively.



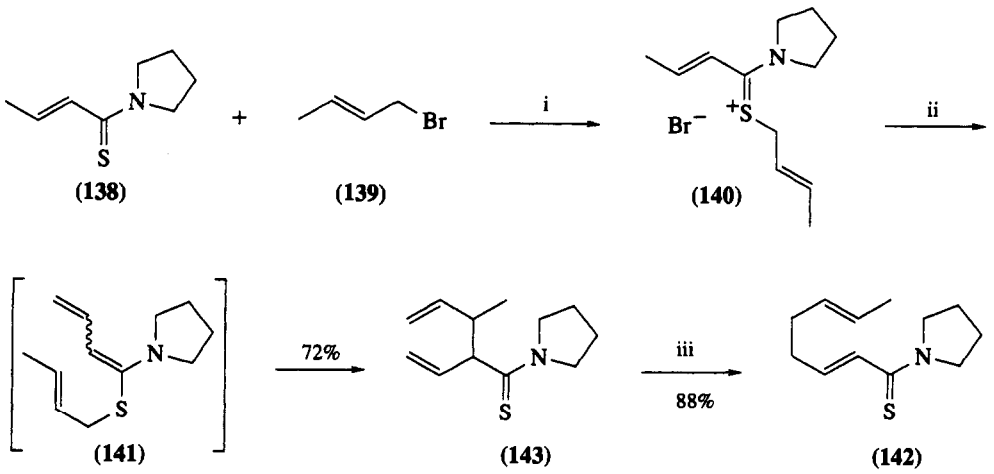
(19)

(134) (135) (137) (136)

7.3.2.3 Sulfur-based Rearrangements

The nucleophilicity of sulfur and its ability to stabilize α-carbanions provide sulfur compounds with unique opportunities for sigmatropic processes; consecutive rearrangements are no exception. The formation of salt (**140**) *via* S_N2 alkylation of (*E*)-2-butenyl bromide (**139**) followed by deprotonation leads to the intermediate allyl vinyl ether (**141**) which, under the conditions of the deprotonation, undergoes a thio-Claisen rearrangement to afford thioamide (**143**; Scheme 10).[32] Thermolysis of (**143**) at elevated temperature affords the Cope product (**142**) in addition to some of its deconjugated isomer. Several unique characteristics of the thio-Claisen sequence should be noted: first, the heteroatom–allyl bond is made in the alkylation step, this connection being not normally practised in the parent Claisen reaction;

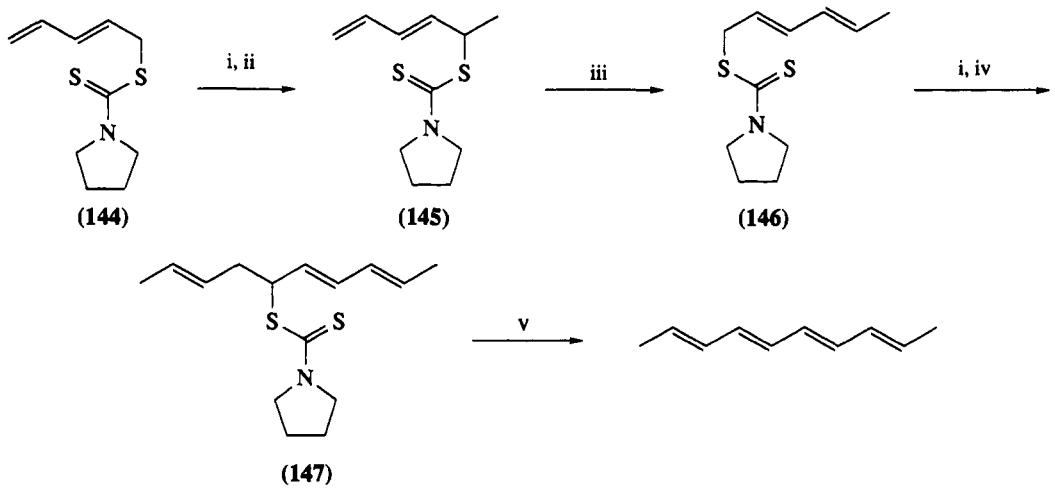
and secondly, the direct α-alkylation of (**138**), or any of its congeners, would not be expected to give the S_N2' butenyl unit of thioamide (**143**).



i, Bu^{t}OH, r.t.; ii, Bu^{t}OH, DBU, r.t.; iii, tetralin, reflux

Scheme 10

The ability of sulfur to stabilize carbanions is exemplified in the following cases. The pentadienyldithiocarbamate (**144**; Scheme 11) can be alkylated at the methylene group to afford the methylated product (**145**).[33] At 110 °C, the dithiocarbamate unit 'walks' its way to the other end of the pentadienyl chain *via* tandem [3,3] sigmatropic rearrangements. The formation of (**146**) is thermodynamically controlled as the more-substituted pentadienyl unit is formed. Dithiocarbamate (**146**) can be alkylated and eventually transformed into sulfur-free products; the sequence giving (**148**) from (**146**) is but one of these processes.

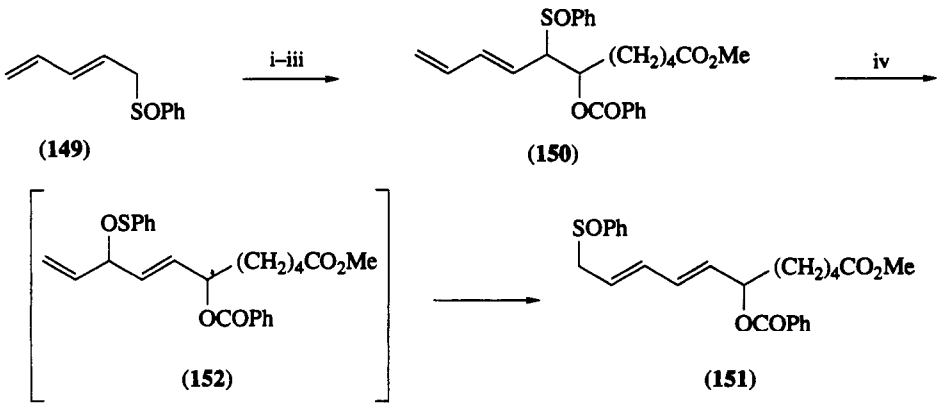


i, LDA, THF, –78 °C; ii, MeI; iii, toluene, reflux; iv, (**139**); v, MeI, LiF, Li_2CO_3, DMF

Scheme 11

A close relative of the previous tandem [3,3]–[3,3] sigmatropic rearrangement invokes its tandem [2,3]–[2,3] counterpart: the allylic sulfoxide–sulfenate rearrangement.[34] As a key step in the synthesis of 5-deoxyleukotriene D, Corey[35] applied the sequence of transformations illustrated in Scheme 12. The anion of allylic sulfoxide (**149**) undergoes 1,2-addition to methyl 5-formylpentanoate followed by low temperature benzoylation. Upon warming the reaction mixture to ambient temperature, a facile sulfox-

ide–sulfenate–sulfoxide rearrangement occurs that provides the thermodynamically more stable sulfoxide (**151**). By virtue of the Pummerer rearrangement, the dienyl sulfoxide unit of (**151**) is transformed into a 2,4-dienaldehyde, thereby allowing the dienyl sulfoxide (**149**) to function as an equivalent of the 4-formyl-(*E,E*)-1,3-butadienyl anion. In the examples of Schemes 11 and 12, the thermodynamically more stable (*E,E*)-diene is formed.



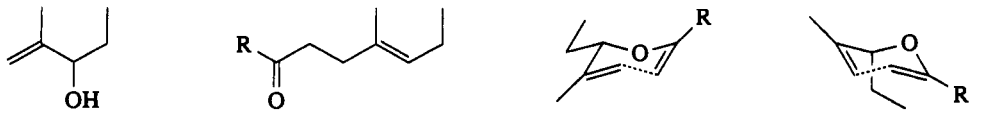
i, Bu^nLi, THF, –78 °C; ii, $OHC(CH_2)_4CO_2Me$; iii, PhCOCl, –40 °C; iv, 25 °C, 3 h

Scheme 12

7.3.3 ITERATIVE REARRANGEMENTS

7.3.3.1 Linear Processes

Faulkner and Petersen[36] have examined the effect of C(2)-substituents of ethyl vinyl ethers on the alkene geometry of the resultant Claisen product. The rearrangement of secondary allylic alcohol (**153**) as its vinyl ether provides a 90:10 ratio of (*E/Z*)-isomers (**154a**). The use of the Eschenmoser variant, *i.e.* dimethylacetamide dimethylacetal, affords a 99.4/0.6 ratio of the (*E/Z*)-amides (**154b**). Similarly, the application of 2-methoxypropene gives rise to the methyl ketone (**154c**) without any detectable (*Z*)-isomer. Based upon the assumption that the chair-like transition state is operative, transition state (**155**), having the ethyl substituent equatorial, encounters fewer pseudo-1,3-diaxial interactions than its counterpart (**156**). This effect is more pronounced when the R substituent is larger than hydrogen.



(**153**) (**154**) (**155**) (**156**)

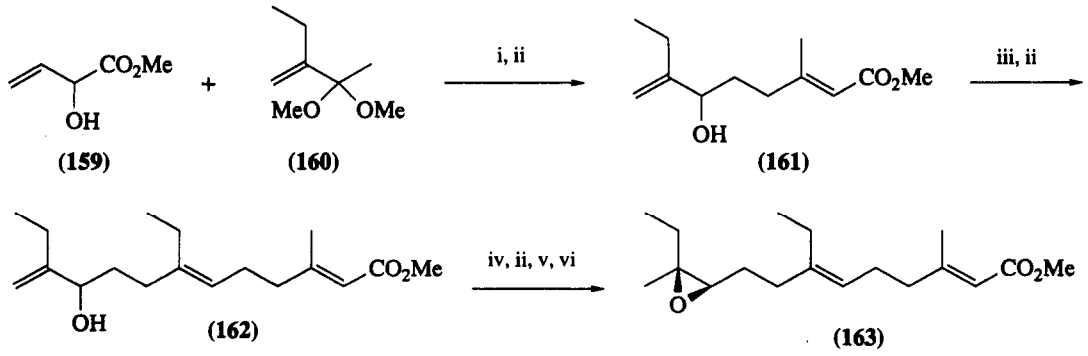
a: R = H
b: R = NMe_2
c: R = Me

When 2-methoxy-3-methyl-1,3-butadiene and alcohol (**153**) are the reacting partners, the unsaturated ketone (**157**) results. In this instance, the R group is isopropenyl, and the stereochemistry of the isolated double bond is of the (*E*)-configuration. Reduction of the ketone (equation 20) provides a new secondary allylic alcohol (**158**) that can undergo iterative rearrangements. Each rearrangement introduces the equivalent of an isoprene unit in a head-to-tail fashion.

This strategy has been applied to the synthesis of the C_{18} *Cecropia* juvenile hormone (JH) (**163**; Scheme 13) using the ketal (**160**) rather than an alkoxy butadiene.[37] Surprisingly, an α,β-unsaturated ester is obtained as an ~3:1 mixture from which the undesired (*E*)-isomer can be separated by fractional distillation. The iterated allylic alcohol (**163**) is transformed into its isomeric allylic alcohol which is subsequently reduced to an alkene and epoxidized to realize the target (**163**). The scheme also lends itself to

(157) (158) (20)

the synthesis of the enantiomers of JH by utilizing the enantiomers of 3-chloro-2,2-dimethoxy-3-methylpentane[38a] and 3-hydroxy-2,2-dimethoxy-3-methylpentane.[38b]

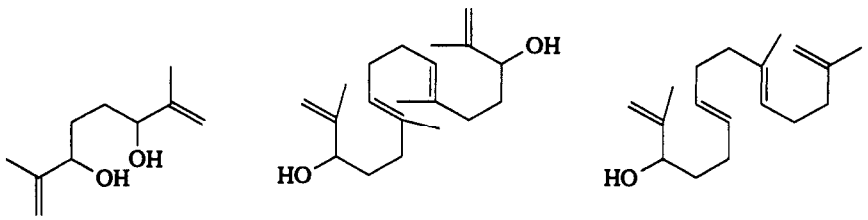


(159) (160) (161) (162) (163)

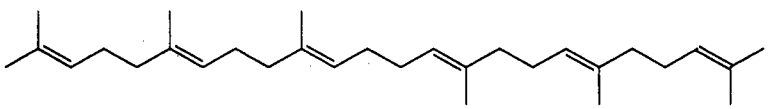
i, cat. 2,4-dinitrophenol, toluene, 110 °C; ii, $NaBH_4$; iii, cat. 2,4-dinitrophenol, toluene, 110 °C + (**160**); iv, $SOCl_2$; v, aq. NBS; vi, K_2CO_3

Scheme 13

Diol (**165**)[39] is an intermediate in the synthesis of the symmetrical triterpene, squalene (**167**). Succindialdehyde serves as the central four carbons followed by bidirectional synthesis through diol (**164**). The transformation of diol (**164**) into its higher homolog (**165**) requires several operations: (i) orthoacetate rearrangement[13] to a diester; (ii) reduction to a diol; (iii) oxidation to a dialdehyde; and (iv) addition of isopropenyllithium. A more convergent approach employs 3,3-dimethoxy-2-methylbut-1-ene in conjunction with diol (**164**), a sequence that only requires reduction of the resultant isopropenyl ketone after rearrangement to realize diol (**165**).[37]



(164) (165) (166)

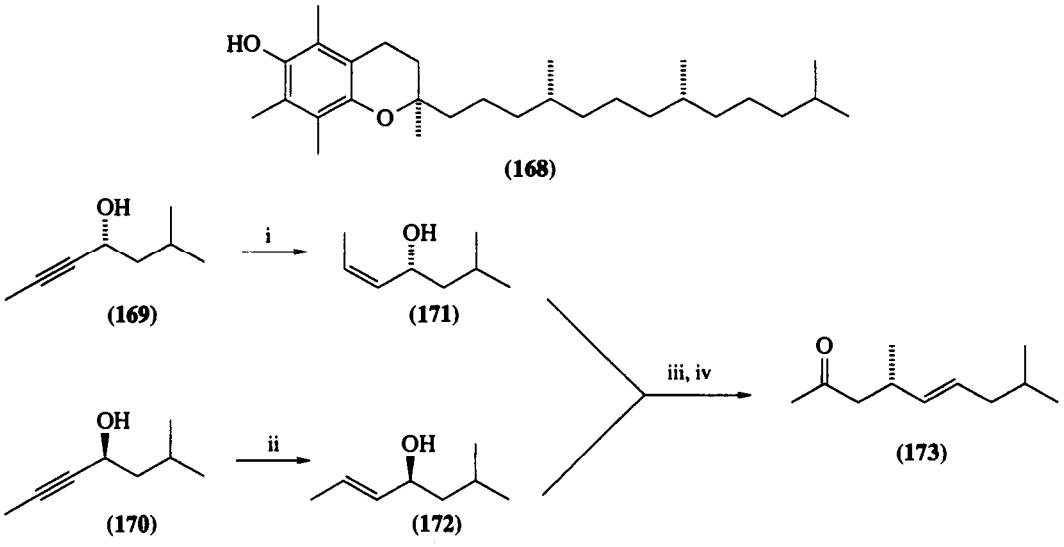


(167)

Allylic alcohol (**166**) is the product of 'right-to-left' linear iteration by this process. Not only is the trisubstituted alkene accessible with high stereochemical control, but also the (*E*)-disubstituted alkene is readily prepared. These linear polyenes play an important role in the biomimetic synthesis of steroids and higher terpenes.[40]

Vitamin E (α-tocopherol, **168**) bears two secondary methyl groups at the stereogenic centers in its side chain. An ingenious solution to the synthesis of this chain has been realized employing iterative Claisen

rearrangements in a scheme that is enantioconvergent (Scheme 14).[41] Readily accessible 6-methyl-2-heptyn-4-ol, prepared by the addition of propynylmagnesium bromide to isovaleraldehyde, is resolved *via* the hemiphthalate α-methylbenzylamine salt to its (*R*)- and (*S*)-enantiomers, (**169**) and (**170**), respectively. Lindlar reduction of the (*R*)-enantiomer provides the (*R*)-(*Z*)-allylic alcohol (**171**), while dissolving metal reduction affords the (*S*)-(*E*)-enantiomer (**172**). Claisen rearrangement of either allylic alcohol, after exchange with ethyl vinyl ether, gives rise to (*S*)-(*E*)-unsaturated aldehyde (**173**). The rearrangement is also successful with the Eschenmoser,[26] Johnson[13] and Ireland[20] variants of the Claisen rearrangement.



i, Lindlar cat., H_2; ii, Na/NH_3; iii, $EtOCH{=}CH_2$, $Hg(OAc)_2$; iv, PhH, reflux, 12 h

Scheme 14

Figure 1 illustrates the stereochemical control elements (*R/S; E/Z*) that are operative in this reaction. The *x*-axis (*R,S*) reflects the chair transition states for the enantiomers (**174**/*ent*-**174**; **175**/*ent*-**175**) of the vinyl ethers of the (*E*)- and (*Z*)-alcohols; the *y*-axis reflects the change of alkene geometry of a given absolute configuration. Passage from one quadrant to a contiguous one results in the opposite enantiomer of

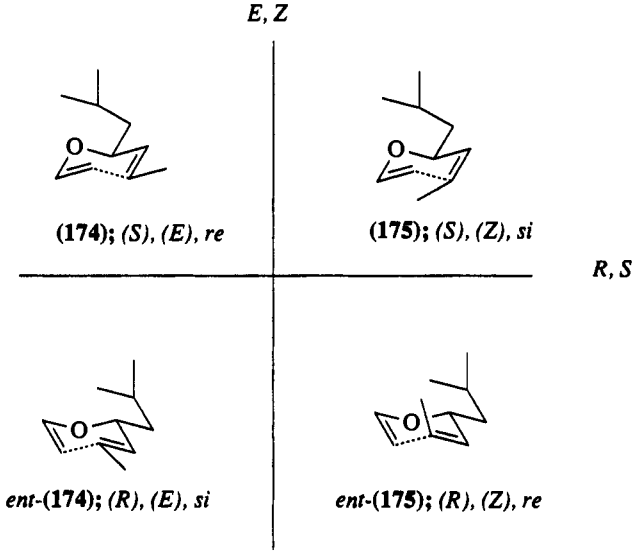
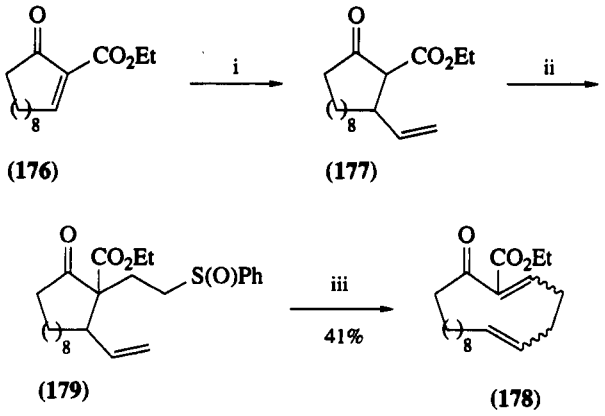


Figure 1



i, H_2C=CHMgCl, CuI; ii, NaH, CH_2=CHS(O)Ph; iii, 250 °C, 10^{-3} Torr

Scheme 15

the Claisen rearrangement product being formed; passage through two quadrants provides the same enantiomer. That is to say, change of an even number of control elements provides the same enantiomer; change of an odd number gives the opposite enantiomer. Thus, the quadrants corresponding to (**174**) and *ent*-(**175**) afford aldehyde (**173**), while the quadrants corresponding to (**175**) and *ent*-(**174**) provide *ent*-(**173**).

The second iteration is accomplished by the addition of propynylmagnesium bromide to aldehyde (**168**); the 1:1 mixture of diastereomers is separated and treated as in Scheme 14.[42]

7.3.3.2 Ring-forming Processes

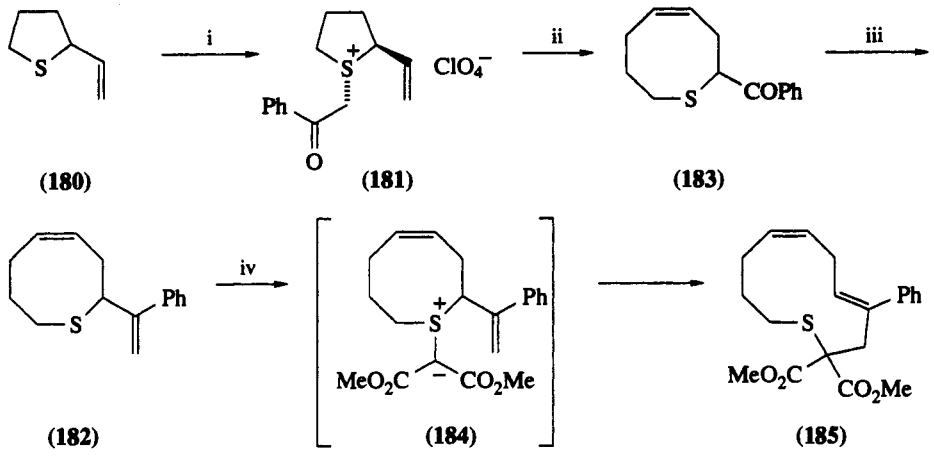
Iterative sigmatropic processes have been developed that achieve ring expansion or the formation of polycyclic structures. Schmid and coworkers[43] have investigated the iterative ring expansion shown in Scheme 15. The double bond of cycloalkylidene β-keto ester (**176**) is appended with a nucleophilic vinyl unit and an electrophilic vinyl group, the latter in the guise of phenyl vinyl sulfone. Thermolysis of (**179**) achieves elimination and Cope rearrangement, the two reactions constituting a tandem process, to afford the 16-membered cycloalkylidene β-keto ester (**178**), the product of a four-atom ring expansion, as a mixture of geometric isomers. The product (**178**) of the rearrangement renews the functionality of (**176**), and it is ready for a second ring expansion.

Vedejs[44] and Schmid[45] have independently developed an iterative ring expansion process that employs the [2,3] sigmatropic rearrangement of sulfur ylides (Scheme 16). Base-catalyzed rearrangement of the *trans*-substituted sulfonium salt (**181**) *via* the carbonyl-stabilized ylide gives rise to the (*Z*)-alkene (**183**) (67%) in addition to 5% of the more strained (*E*)-isomer. Wittig methylenation of (**183**) provides a new allylic sulfide (**182**), which upon treatment with dimethyl diazomalonate in the presence of copper undergoes a second, three-atom ring expansion to malonate (**185**) which bears a new (*Z*)-alkene.

While the minor component, (*E*)-(**183**), of the rearrangement of the *trans*-substituted sulfonium salt (**181**) may be rationalized by the chair-like transition state *trans*-(*E*)-(**186**), the related transition state *trans*-(*Z*)-(**186**) does not account for the formation of the major product (**183**), because the bond-forming carbon atoms are too remote from one another (equation 21). Alternatively, an isomerization of the *trans*-substituted sulfonium salt to its *cis* counterpart *via* several possible pathways[46] permits the formation of (**183**) *via* transition state *cis*-(*Z*)-(**186**), or (*E*)-(**183**) through the twist transition state *cis*-(*E*)-(**186**). While the formation of a *cis*-alkene is highly favored in the 8-membered ring, the 11-membered ring favors the formation of a *trans*-alkene.

The foregoing methods have been successfully applied to the synthesis of carbocyclic cytochalasans[47] and the macrolide methynolide (**191**; equation 22).[48] Iterative ring expansion of the five- and eight-membered ring sulfonium salts (**187**) and (**189**) leads to the 11-membered ring sulfur heterocycle (**190**). Sulfonium salt (**189**) is a 1:1 mixture of stereoisomers that gives (**190**) with 16:1 selectivity in 76% yield.

Schmid[45] has successfully transformed the five-membered ring sulfonium salt (**192**) into the 17-membered ring sulfur thiacycle (**197**) in four iterations (Scheme 17). The products (**194**), (**193**) and (*E*)-(**194**) are formed in a ratio of 67:27:6. The presence of tetrahydrothiophene (**193**) is the result of ylide formation at the more-substituted allylic site of salt (**192**) followed by [2,3] sigmatropic rearrangement. The

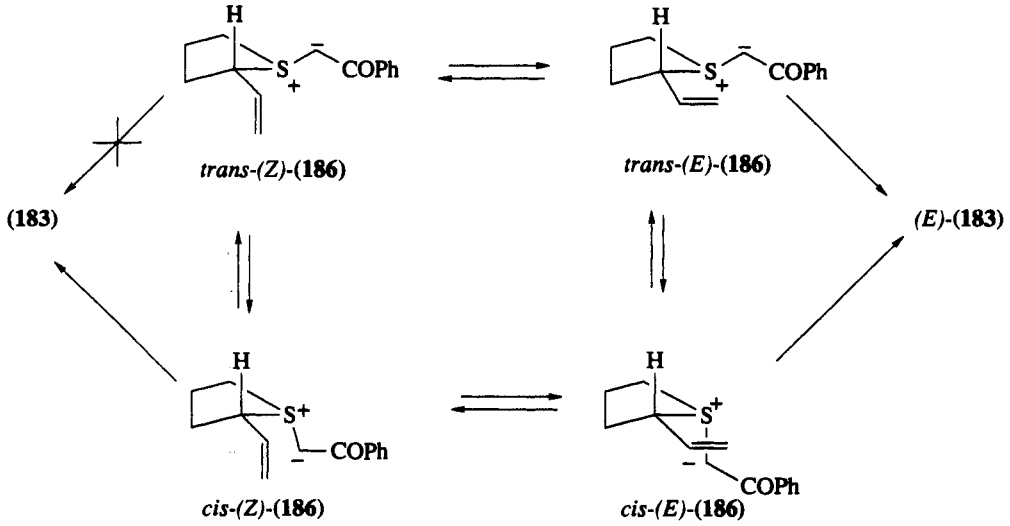


(180) (181) (183)

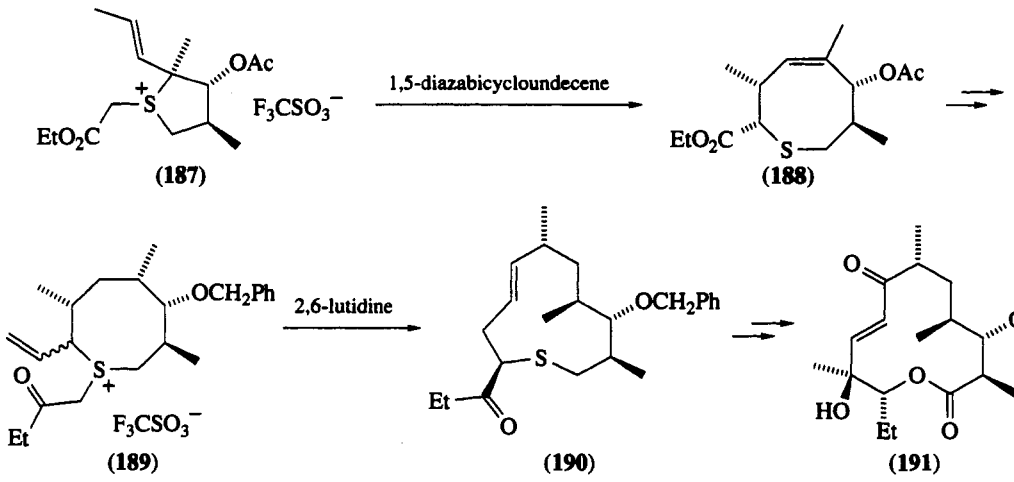
(182) (184) (185)

i, $PhCOCHN_2$, 60% $HClO_4$, MeCN: ii, DBU, toluene, 90 °C;
iii, Ph_3PCH_2; iv, $N_2C(CO_2Me)_2$, copper bronze, 100 °C

Scheme 16

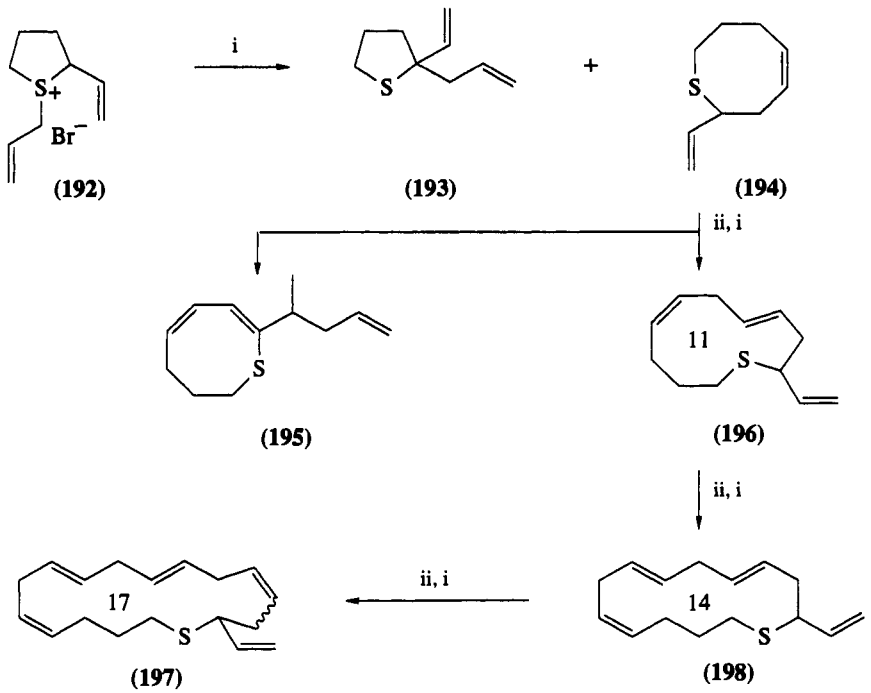


(21)



(22)

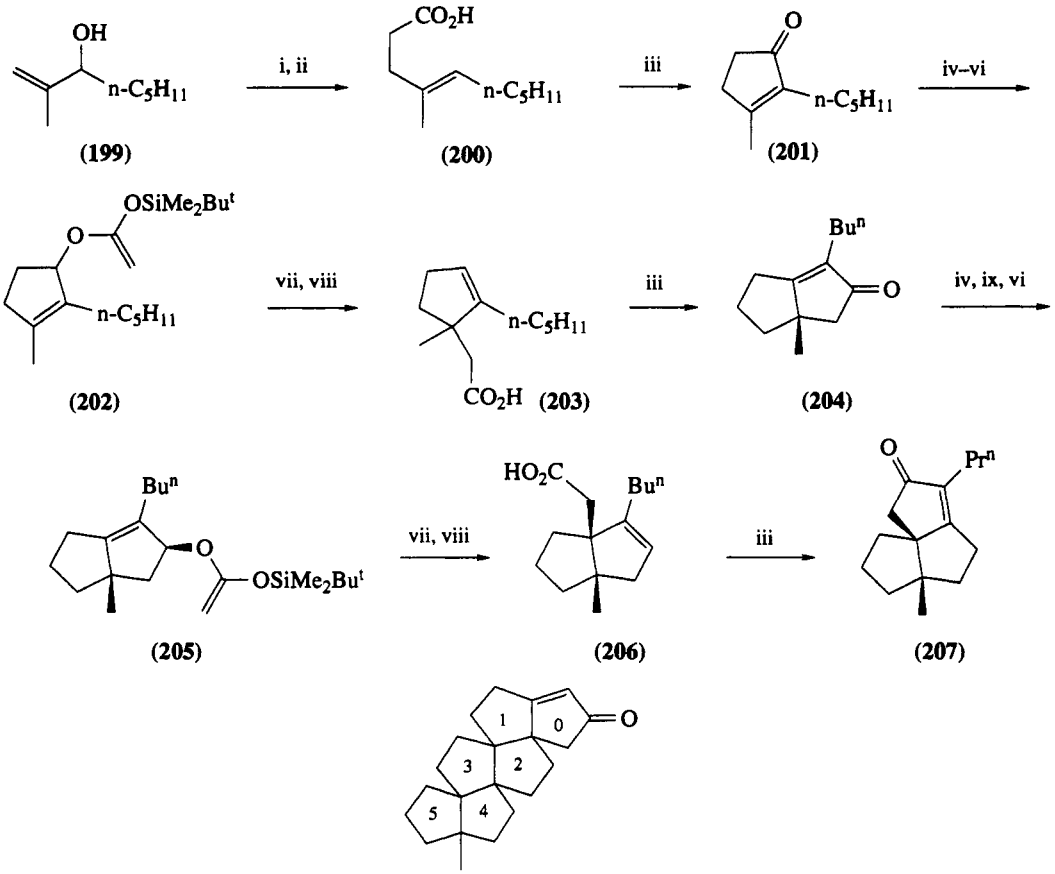
(*Z*)-thiacyclooctene (**194**) undergoes a successful [2,3] sigmatropic rearrangement to provide the 11-membered (*E,Z*)-triene (**196**) (76%) and triene (**195**) (11%), which arises from isomerization of the double bond of the vinyl group into conjugation with the sulfur atom in the intermediate sulfonium salt and subsequent thio-Claisen rearrangement. The third iteration to form the 14-membered ring (**198**) also introduces the alkene in the (*E*)-configuration; however, expansion to the 17-membered ring affords a 2:1 ratio of (*Z,E,E,Z*)-(**197**) and (*E,E,E,Z*)-(**197**), respectively. The rearrangements of Scheme 17 proceed in greater than 80% yield.



i, KOH, H_2O–pentane, 23 °C; ii, $H_2C{=}CHCH_2Br$, F_3CCH_2OH

Scheme 17

An iterative cyclopentannulation process invokes a series of Claisen rearrangements coupled with polyphosphoric acid mediated ring closures of the Claisen products (Scheme 18). The lithium aluminum hydride reduction of cyclopentenone (**204**) to the allylic alcohol gives the α-alcohol which requires inversion *via* the Mitsunobu procedure to achieve the desired β-configuration. As each successive ring is added, the alkyl chain is shortened by one carbon. Thus, structure (**208**) represents the extent to which annulation may be carried with a five-carbon chain; the numbers in the rings indicate the length of the carbon chain as each ring is formed. The possibility exists for alkylation of the cyclopentenone ring of (**208**) and continued annulation.



i, $MeC(OEt)_3$, $EtCO_2H$, 135 °C; ii, KOH, aq. MeOH, reflux; iii, PPA, 110 °C; iv, $LiAlH_4$; v, Ac_2O, Py, DMAP; vi, LICA, THF/HMPA, Bu^tMe_2SiCl, –78 °C; vii, 60 °C; viii, AcOH; ix, AcOH, DEAD, Ph_3P, C_6H_6

Scheme 18

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8.1
Rearrangements of Vinylcyclopropanes and Related Systems

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8.1.1 INTRODUCTION

Perhaps it is appropriate that this review be written some 100 years after the report of the first syntheses of cyclopropane derivatives by von Baeyer[1] and Perkin[2] and the formulation of the 'theory of ring strain' by von Baeyer.[1] The chemistry of small ring compounds has risen to prominence in the last 30 years. The popularity especially of the three-membered rings as intermediates in synthetic transformations has been due primarily to their latent energy content and to the almost endless number of chemical transformations in which these compounds and their derivatives can participate. New applications and novel permutations of the basic systems continue to appear at a fast pace. The fascinating chemistry

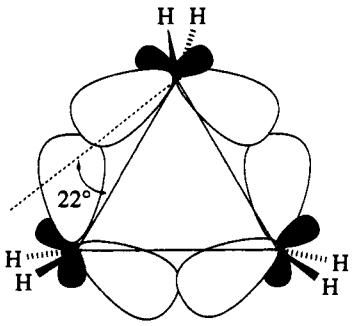
associated with the strain of these intermediates continues to find wide applicability in the field of synthetic methodology and in the total synthesis of complex molecules.

The following discussion will highlight those transformations of vinylcyclopropanes and their derivatives that are selective with regard to regio- and stereo-chemistry. The discussion of such transformations is done from the position of a synthetic practitioner interested in their actual use. Omitted from this chapter are transformations likely to be covered in other parts of this volume (*e.g.* Cope rearrangements of divinylcyclopropanes). A guide to reviews dealing with the preparation of cyclopropane derivatives is provided. At the end of this chapter a survey of useful and general methodologies based on the title transformations is provided along with a tabular compilation of total syntheses featuring these rearrangements as key steps.

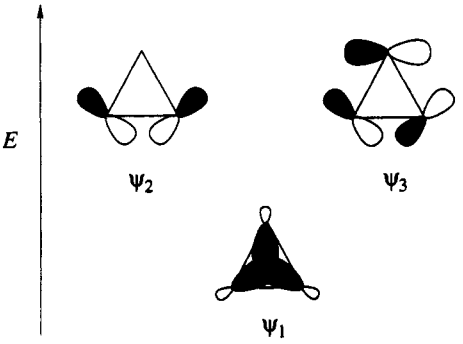
8.1.2 THEORETICAL AND MECHANISTIC CONSIDERATIONS OF THE VINYLCYCLOPROPANE SYSTEM

8.1.2.1 Bonding and Energetics of Cyclopropane Systems

The bonding in cyclopropane requires that the sp^3 hybrids be misaligned by approximately 22° from the imaginary line connecting the carbon atoms. The result is the so-called 'bent' bond having about 20% less orbital overlap than the corresponding bond in ethane. The Coulson–Moffitt[3] model (**1**) and the Walsh[4] model (**2**) use three sp^3-hybridized CH_2 groups and three sp^2-hybridized CH_2 groups, respectively. The overall hybridization of cyclopropane carbon–carbon bonds is thus $sp^{2.3}$; this greater *p*-character can be invoked in rationalizing the similarity of cyclopropane chemistry to that of alkenes. Because the bond angles are considerably less than the ideal 109.5°, cyclopropane suffers from significant angular (Baeyer) strain, as well as from torsional (Pitzer) strain from eclipsed carbon–hydrogen bonds.



(1)



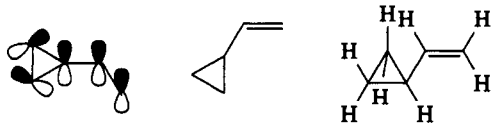
(2)

A unique treatment of cyclopropane has been advanced by Dewar,[5] who introduced the concept of σ-aromaticity, which explains some of the anomalous chemical and physical properties of cyclopropane. The notion of σ-conjugation implies that three σ-bonds form a cyclic system of six electrons; thus cyclopropane is aromatic by the $(4n + 2)$ rule. This explanation well accounts for the strain energy of cyclopropane. The actual value (27.5 kcal mol^{-1})[6] is much lower than the predicted value of 104 kcal mol^{-1} (1 cal = 4.2 J), calculated from the C—C—C bending force constants obtained spectroscopically.[5,7] A similar comparison for cyclobutane (antiaromatic by the above notion and the $4n$ rule) underestimated the strain energy.[5] σ-Aromaticity also accounts for such observations as ^1H NMR chemical shifts and the reactivity of cyclopropane toward electrophiles.

The cyclopropane ring is subject to a number of chemical transformations that are only possible because of its unique bonding and high energy content. It is the energy content (27.5 kcal mol^{-1}) that drives the diradical opening of cyclopropane, especially so if one (or both) of the resulting radicals becomes a part of a delocalized allylic system, as in the case of vinyl- or divinyl-cyclopropanes. Such resonance stabilization energy of an allylic radical system (12.6 kcal mol^{-1})[8] can be used to explain the lower activation energy for reactions involving vinylcyclopropane (34–55 kcal mol^{-1}) compared with the activation energy for reaction resulting from diradical processes that involve only the cyclopropane ring (59–66 kcal mol^{-1}).[9–13]

The vinylcyclopropane unit contains the strain energy of the cyclopropane ring (27.5 kcal mol^{-1}), and it is this energy content that will be primarily responsible for its reactive options. Thermal ring fission can occur by any one of three mechanisms: [1,5] sigmatropic hydrogen shift, $[2\sigma_s + 2\pi_s]$ concerted reorganization to cyclopentene, or a diradical fission followed by further reactions of the diradicals (recombination or hydrogen abstraction). This discussion has received considerable attention in both the mechanistic and the synthetic sense and has been the subject of several recent reviews.[9–21]

The bonding in vinylcyclopropane (**3**) is such that an *s-trans–gauche* conformational equilibrium exists to allow for maximum orbital overlap of the asymmetric component of cyclopropane orbitals with the π- or π^*-orbitals of the ethylene unit, as shown in (**3a**). From thermochemical studies it appears that conjugation of an alkene with cyclopropane stabilizes the system by 1.2 kcal mol^{-1}.[22,23] The conformational equilibrium for vinylcyclopropane was shown to consist of an *s-trans* minimum (**3b**) and two *gauche* conformers that are equal in energy and destabilized by 1.43 kcal mol^{-1} with respect to the *s-trans* conformation. The barrier to interconversion has been determined to be 3.92 kcal mol^{-1}.[24]



(3a) (3) (3b)

The details of bonding and spectroscopic properties of cyclopropane derivatives have recently been reviewed.[13,23,25] In addition, the properties and energetics of cyclopropyl cations, anions, radicals, anion radicals and cation radicals have been amply reviewed, and comparisons have been made with their corresponding alkenic counterparts.[13,23,26]

8.1.2.2 Reactive Tendencies

To a synthetic chemist the analogy between cyclopropanes and alkenes is indeed an appropriate one. Virtually every reaction that an alkene undergoes has its counterpart in the repertoire of transformations possible with cyclopropanes. Thus conjugation of a cyclopropane to an alkene makes it possible to invoke a number of reaction modes and reactive intermediates that can be compared directly to their alkenic counterparts.

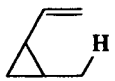
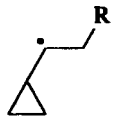
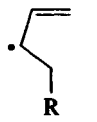
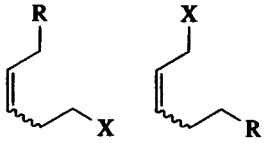
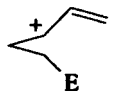
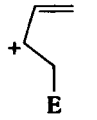
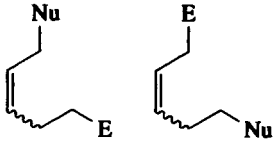
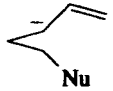
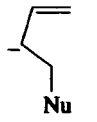
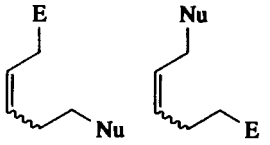
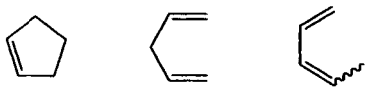
How a particular vinylcyclopropane will be electronically perturbed toward a specific mode of reactivity depends on the substitution of either the cyclopropane or the vinyl portion. All of the principal reactions of vinylcyclopropanes proceed *via* transition states that require stabilization by activating groups and/or release of the ring strain. To understand and to alter the reactive tendencies of substituted vinylcyclopropanes, we must understand the components of the possible transition state and the probable reactive intermediates involved. Table 1 shows the principal reaction pathways of the vinylcyclopropane system in the context of their intermediates, products, and alkenic equivalents.

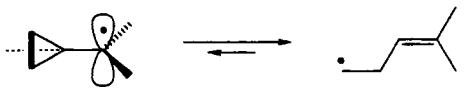
The cyclopropylcarbinyl radical (**4**), the cyclopropylcarbinyl cation (**5**) and the cyclopropylcarbinyl anion (**6**) all dominate the expected reactivity of vinylcyclopropanes since one of these forms will be expected to be a major contributor to either a radical or a polar transition state. It is important to consider the various reactive subunits in some detail in order to understand the 'big picture' reactivity of a vinylcyclopropane system, especially as perturbed by additional substituents.

The dominant contributor to the reactivity of vinylcyclopropanes in any radical reaction is the form (**4a**), the cyclopropylcarbinyl radical system. The opening of a cyclopropylcarbinyl radical to a butenyl radical is among the fastest radical processes known, with a rate constant of 1.3×10^8 sec^{-1}.[27,28] The various stereoelectronic effects of this rearrangement have been reviewed.[29,30] The structure of (**4a**), deduced from its ESR spectrum[31,32] and in agreement with calculations (STO-36 basis set),[33] is in the bisected conformation shown, predicted to be 1.4 kcal mol^{-1} more stable than its perpendicularly oriented counterpart. Above −100 °C only the butenyl radical (**4b**) can be detected. Substituent effects do not seem to operate here when the substituents are on the cyclopropane (*i.e.* product stabilization).[34] The cyclopropylcarbinyl cation and anion have structures similar to (**4a**), bisected conformations (**5**) and (**6**), respectively. A concise summary of solvolytic and mechanistic data for system (**5**) has recently appeared.[23] Reviews of cyclopropylcarbinyl anions and carbenes are also available.[12,13]

To understand how substituents, especially heteroatoms, will change the reactivity of these systems, the basic transformations shown in Table 1 should be kept in mind. The number of possibilities is limitless, especially upon the recognition that, depending on the substituents, any one of the above contribut-

Table 1 Principal Reaction Modes of Vinylcyclopropanes

Reaction type	*Reactive intermediate*	*Alkenic counterpart*	*Product(s)*
[1,*X*] Sigmatropic migration	 [1,5 shift]		
Radical addition	 **(4)** (cyclopropylcarbinyl radical)		
Electrophilic addition			
Nucleophilic addition			
Radical cleavage			

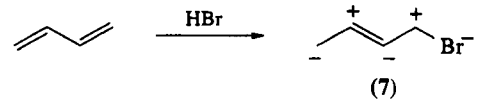


(4a) (4b)

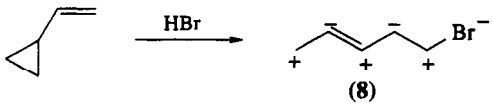
(5) (6)

ing structures (**4**), (**5**), or (**6**) can become operational on the mode of subsequent rearrangement of the vinylcyclopropane when such rearrangements occur from the homolytic or heterolytic manifolds. The question of concerted rearrangements, or the $[2\pi_s + 2\sigma_s]$ processes, is more difficult to address. Evidence exists on both sides of the argument with no clear-cut rules for or against a universally accepted mechanism. The next section will present the debate concerning this topic in more detail.

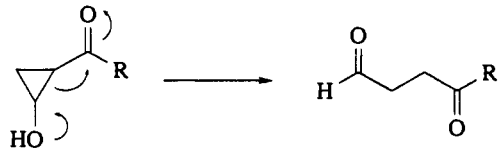
In terms of retrosynthetic or disconnective reasoning, cyclopropane is an ideal molecular building block. Because it can be expected to act as an alkene, all of the standard reactions can be performed with it. As it has an extra carbon, however, it serves as a marvelous 'synthetic wedge tool'[12] that can be used to either disrupt existing symmetry or consonance or to introduce it to the target. The concepts of synthetic consonance and dissonance formulated by Evans[35] or the 'cyclopropane trick' analogy of Seebach[36] are ideal in understanding the synthetic utility of cyclopropanes. Thus, for example, equilibrium addition of HBr across 1,3-butadiene yields 1-bromo-2-butene (**7**; equation 1), in which the halide enjoys an allylic relationship with the alkene. Similar addition to a vinylcyclopropane (equation 2) will, on the other hand, produce 1-bromo-3-pentene (**8**) where the same relationship is homoallylic. One can immediately see that the charge parity in the product alkenes has been inverted by the introduction of the odd carbon, and thus inverted reactivity of such alkenes can be expected in subsequent synthetic steps. This criterion is extremely important in synthetic schemes involving long range planning and placement of functional groups. This property of cyclopropane has been exploited in the pioneering efforts of Wenkert, who developed 1,4-dicarbonyl compound synthesis based on the ability of oxycyclopropylcarbinyl systems such as (**9**) to act as pseudo enols (equation 3).[20,37,38]



(7) (1)



(8) (2)



(9) (3)

Finally the introduction of cyclopropane or vinylcyclopropane into organic compounds provides an opportunity to cross the odd/even manifolds in further synthetic steps aimed at the preparation of compounds of increased molecular complexity. Traditionally, any synthesis that involves intermediates with an odd number of atoms is more difficult because proper charge parity or consonance cannot be observed. A cyclopropane unit then functions as a topological operator in those cases where such crossover is desired.[39–41]

The most fascinating features of vinylcyclopropane reveal themselves upon the introduction of not only substituents but heteroatoms. The number of possible permutations of molecular connectivity in a system such as (**10**; Figure 1) is virtually limitless. (Consider the series of connectivity operations for a

chemical system composed of an odd number of atoms with an external operator X (Figure 1). Whereas there is only one way to connect A and X, there are now six ways to connect X through the ring opening of the three-membered ring system (**i**) and 120 such different connections in the ring opening of the heterovinylcyclopropane (**ii**) and its interactions with X.[42]) The complexity of connectivities of (**10**) with an external operator X is related through the factorial (!) function and becomes even greater when the presence or the position of substituents in (**10**) or the complexity of X are added for consideration. The success in predicting the reactivity of a system such as (**10**) depends on the nature of component atoms, substituents, electronic perturbations, and the preference of some mechanistic pathways over others. To consider selective transformations of a system that has in excess of 120 possibilities may seem frivolous; fortunately there exists a number of simplifying parameters that provide for surprising selectivity as well as predictability of the rearrangements of any hetero-substituted system of type (**10**).

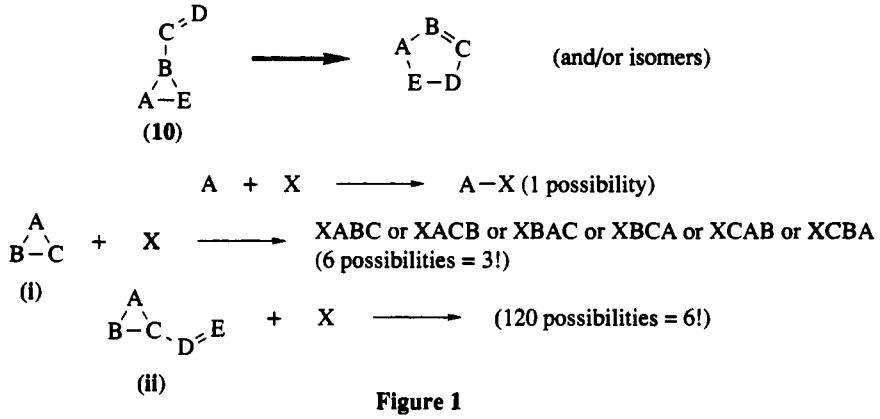
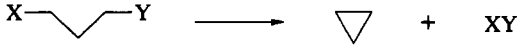


Figure 1

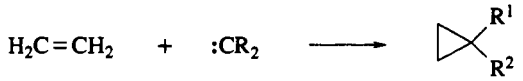
The substituent effects have been quantitatively addressed in the context of specific transformations, for example the vinylcyclopropane–cyclopentene rearrangement, and will be discussed in the appropriate sections. The donor/acceptor principles have been applied to thermal, heterolytic and transition metal catalyzed rearrangements and have been reviewed.[16,21] These principles take into account the possible intermediate structures listed in Table 1 and are used to explain the reactivity of a particular cyclopropane system. In the discussion that follows emphasis will be given to the processes that are uniformly selective with regard to regio-, stereo- and enantio-chemical integrity of the products.

8.1.2.3 Guide to Preparation

The inherent energy content of the cyclopropane ring demands that the method of introduction of a cyclopropyl subunit itself relies either on highly reactive intermediates or on irreversible or energetically, if not entropically, favored processes. Thus the synthesis of cyclopropane derivatives can be classified into three major categories: 1,3 bond forming sequences (equation 4);[43–45] carbene or carbenoid routes (equation 5);[46–50] and rearrangement pathways (equations 6 and 7).[51–54]

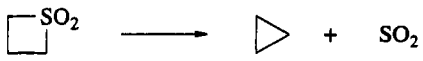


(4)



(5)

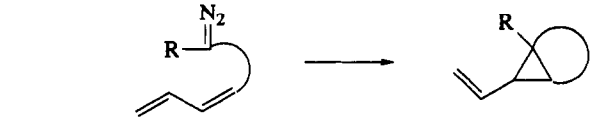
(6)



(7)

The procedures for the synthesis of cyclopropane derivatives, especially by the carbenoid route[43,45–49,55–57] or the ylide route (1,3-displacement),[19,20,45,58,59] have been amply reviewed. Equally well reviewed are the reactions of cyclopropanes and their use in synthetic methodology.[9,12,13,15–21,41] For the preparation of the more common cyclopropane derivatives, the use of suitably functionalized cyclopropyl building blocks that are commercially available would be recommended.

Vinylcyclopropanes are most easily prepared by one of the following methods: (i) cyclopropanation of conjugated dienes (inter- and intra-molecular) (equation 8);[41] (ii) permutations of the reactions of allylic ylides with Michael acceptors (equation 9);[19,20,45] (iii) ring opening of oxaspirocyclopentanes (equation 10);[19,20] (iv) additions of vinyl diazo compounds to alkenes (equation 11);[60] (v) indirect methods of formation, *e.g.* Wittig reaction of acylcyclopropanes and rearrangement pathways;[44,45] and (vi) in certain specific cases where the vinylcyclopropanes are immediately reacted further, by thermolysis of 1,4-dienes *via* [1,5] shift sigmatropic reactions.[41,61] The preparations of vinyloxiranes, vinylaziridines, cyclopropylcarbonyls and cyclopropylimines have been reviewed in different contexts (addition of ylides to carbonyl compounds, interaction of azides or diazo compounds with alkenes, *etc.*), but their preparations have not been summarized under a common heading. However, any reference dealing with the use of these compounds will provide a guide to one or more methods of their synthesis.



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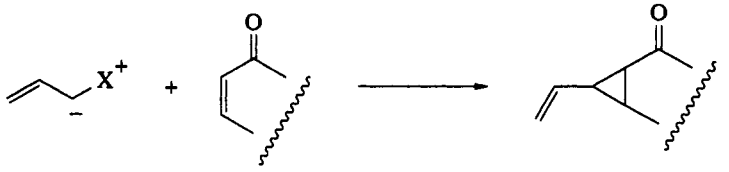
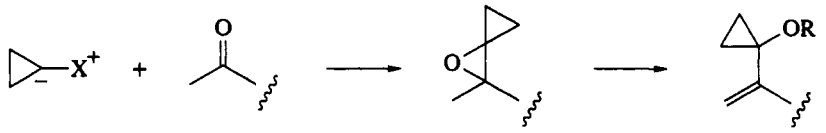
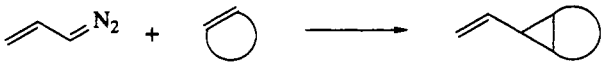


(9)



(10)



(11)

8.1.3 REARRANGEMENTS OF VINYLCYCLOPROPANES

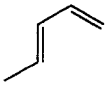
The vinylcyclopropane system is subject to a wide variety of transformations ranging from thermolysis and photolysis to nucleophilic and electrophilic ring opening and transition metal catalysis. A common trait in all such transformations is the release of the ring strain and further reaction of the intermediates thus generated. Until recently the most commonly recognized transformations of vinylcyclopropanes were those resulting from thermally induced bond reorganizations. There are two major pathways available to vinylcyclopropanes on thermolysis: rearrangement to cyclopentene and ring opening to alkenes or dienes. The ability to predict which of these transformations is the most likely depends to a great extent on the substituents and on the precise conformational definitions and the orientation of the π-system of the vinyl group to the cyclopropane. As will be seen in further discussion, some element of control is available. The thermal cleavage of vinylcyclopropane can in principle provide any of the products depicted in Scheme 1. The analysis of the mechanistic pathways has been reviewed, but a great deal of uncertainty exists regarding the precise distinction between radical, zwitterionic or the concerted nature of these processes.[62]

E_a = 57.3 kcal mol^{-1}
log A = 14.4

(3)

E_a = 49.6 kcal mol^{-1}
log A = 13.5

E_a = 56.2 kcal mol^{-1}
log A = 13.9

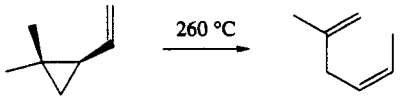


E_a = 53.6 kcal mol^{-1}
log A = 13.0

Scheme 1

8.1.3.1 [1,5] Shift Pathways

Under some circumstances the [1,5] sigmatropic shift of hydrogen from an alkyl group oriented *cis* to the vinyl group is the lowest energy pathway available to a vinylcyclopropane.[10,11,61] The classic experiments that led to the understanding of this process were performed by Winstein[63] and Frey.[61,64,65] The rearrangement of vinylcyclopropane (**11**) proceeded at 260 °C to furnish only the *cis*-alkene (**12**; equation 12).[64] This rearrangement usually proceeds with an activation energy of 30–35 kcal mol^{-1},[9–11] and is thought to involve a chair-like (**13**) rather than a boat-like (**14**) transition state. Most of these rearrangements are stereospecific, yielding only the *cis*-alkene.



(12)

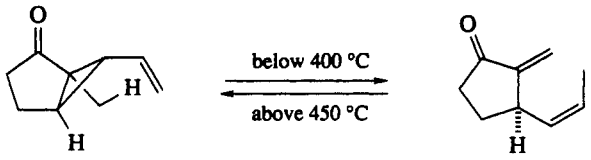
(**11**) (**12**)

chair: 4.5 kcal mol^{-1} more stable [65, 68] boat

(**13**) (**14**)

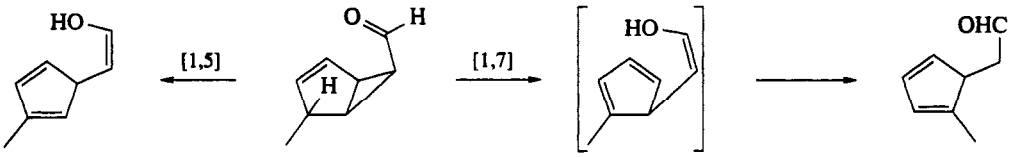
The transformation has been shown to be reversible by careful study of the temperature profiles of flash vacuum pyrolysis of either *cis*-methylvinylcyclopropane (**15**) or diene (**16**; equation 13).[66] Only above 400 °C did the vinylcyclopropane show the expected tendency toward diradical cleavage, a process that requires a substantially higher activation energy (15–20 kcal mol^{-1} higher) than the concerted [1,5] shift. This rearrangement also occurs stereospecifically in endocyclic vinylcyclopropanes such as (**17**; equation 14).[67] The migration of the hydrogen atom is governed by the principles of sigmatropic rearrangements, *i.e.* the pathway of the hydrogen atom is suprafacial.[68] The effect of substituents and their stereochemistry in this rearrangement was investigated.[69]

The fact that suitably sterically biased *cis*-alkylvinylcyclopropanes participate in these types of reactions attests to the ability of the cyclopropane ring to transfer conjugative properties and to act as a pseudo ene unit. Competing pathways of higher order may become dominant in those cases where the transition state is stabilized by extended conjugation, as in the case of (**18**) and its predominant [1,7] hydrogen shift (Scheme 2).[70]



(15) (16) (13)

(17) (14)



9% (18) 91%

Scheme 2

Oxygen, nitrogen and carbon atoms can equally well participate in the 'vinyl' system. Table 2 provides a survey of some synthetically useful rearrangements of this type. In all cases the formation of the alkene is regioselective and in most cases it is stereospecific as well, according to the principles outlined above. The distinction between boat and chair transition states depends on the precise conformation of the reacting system, and this factor can be somewhat manipulated experimentally.

The synthetic utility of this process can be seen by evaluating the examples in Table 2. For example, because the cyclopropane serves as a pseudo alkene and because the [1,5] shift requires a six-membered transition state, it relates conceptually to the Cope and Claisen rearrangements. The γ,δ-unsaturated carbonyl compounds in Table 2 are those that would otherwise be obtained *via* Claisen or orthoester Claisen rearrangements, which are normally effected under strongly acidic or strongly basic conditions (Scheme 3).

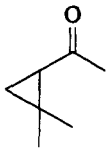
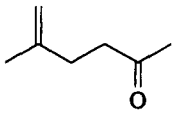
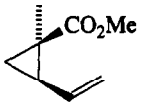
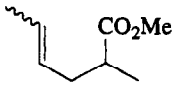
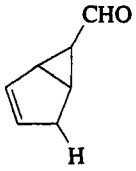
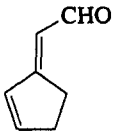
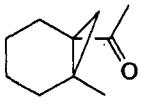
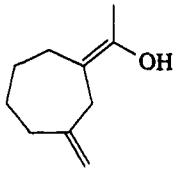
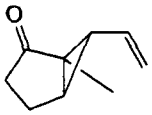
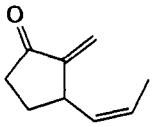
For compounds of small molecular weight, the [1,5] shift pathway may therefore be superior in the ease of preparation, simplicity and cost. In those instances where 1,4-dienes are easily constructed with the alkene predisposed *cis*, the resulting conversion to vinylcyclopropanes may in fact be superior to the use of carbenoid-based reagents in those instances where the resulting vinylcyclopropanes need not be isolated (Scheme 4). The retro-ene reaction of 1,4-dienes requires temperatures which induce immediate further reactive options in the vinylcyclopropane as soon as it is generated.[66]

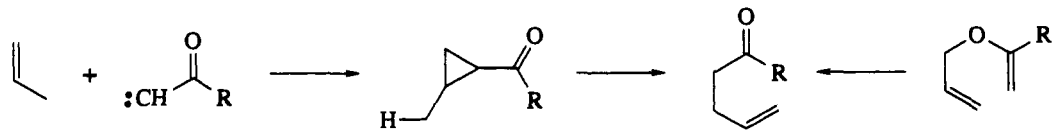
Two examples that show selectivity in synthetic applications are the synthesis of cycloheptanone (**19**),[75] which involves ring expansion *via* a [1,5] hydrogen shift, and the synthesis of sarkomycin (**20**; Scheme 5).[66,76] In both of these protocols, the intermediate cyclopropyl ketone or vinylcyclopropane system could be rearranged to dihydrofurans or cyclopentenes respectively by the appropriate adjustments in the experimental conditions.[9,41]

8.1.3.2 Vinylcyclopropane–Cyclopentene Rearrangement

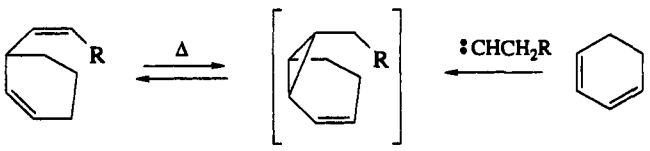
The thermal rearrangement of vinylcyclopropanes to cyclopentenes is probably the most recognized mode of reactivity of the vinylcyclopropyl system and one that has received the most attention. Discovered by Neureiter in 1959,[77] it was scrutinized in detail during the 1960s. The fundamental issue at that time revolved around the concerted $[2\pi_s + 2\sigma_s]$ *versus* diradical nature of the rearrangement. No resolution of this question materialized as both mechanisms were invoked to explain specific cases.[9–13] The experimental evidence in the majority of cases studied, however, supports a diradical-type cleavage of the vinylcyclopropane system and a reclosure of the allylic diradical with an average activation energy of about 45 kcal mol^{-1}, or approximately 15 kcal mol^{-1} higher than the competing [1,5] shift pathway discussed in the previous section. What is puzzling is the apparent stereospecificity of the rearrangement of optically pure vinylcyclopropanes such as (**21**; equation 15).[78] The presence of 'forbidden' products, (–)-(**23**) and (+)-(**23**), would suggest a biradical mechanism, but the high degree of retention of optical purity

Table 2 Thermal Rearrangements of *cis*-Alkylvinylcyclopropanes

Cyclopropane	*Temperature* (°C)	*Alkene*	*Yield* (%)	*Ref.*
	300		—	65, 71
	150		89.4	72
	280		82.5 *(trans)* 17.5 *(cis)*	72
	120		—	70, 73, 74
	200		80	75
	360		80	66



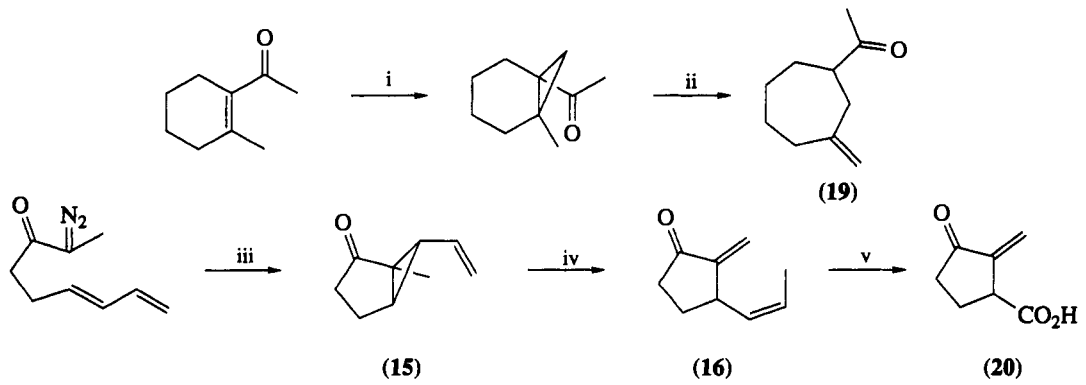
Scheme 3



not isolated

Scheme 4

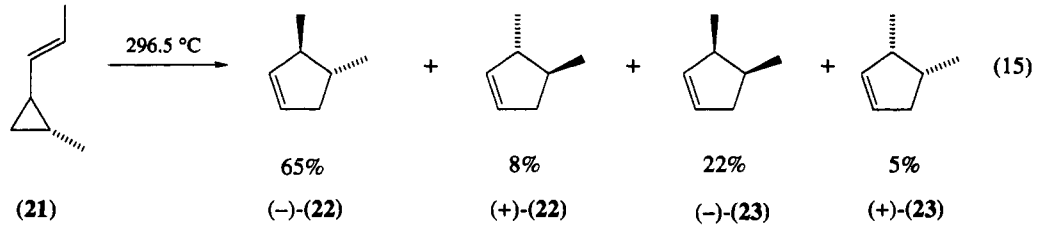
(80.1 ± 0.4% at 60 °C, 68.8 ± 0.5% at 120 °C) would rule out any freely rotating diradical species.[62,78] This observation implies that if the regiochemistry of the rearrangement is controlled, the stereo- and enantio-chemical consequences will follow.



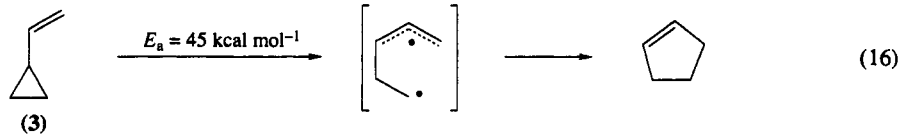
(15) (16) (19) (20)

i, $LiAlH_4$; Simmons–Smith cyclopropanation, Collins oxidation; ii, 200 °C, 2 h;
iii, $Cu(acac)_2$, PhH, Δ; iv, 450 °C, Pyrex; v, O_3, CH_2Cl_2, Me_2S; Jones oxidation

Scheme 5



The molecular topology of this rearrangement is fascinating in its potentially limitless permutations. As indicated in Section 8.1.2.2, any one of the five atoms in the vinylcyclopropyl system may be replaced with almost any other atom (C, Si, P, N, O, S, *etc.*) and the overall reorganization to an unsaturated five-membered ring system remains operational. Thus cyclopropyl aldehydes, imines, ketones and esters yield the corresponding heteroatom analogs of cyclopentene, as do vinyloxiranes, vinylaziridines and vinylthiiranes. When electronegative elements are contained within the vinylcyclopropane framework, the mechanism may change from a diradical to a dipolar one.



In the parent system (**3**), only one bond is activated toward a cleavage that produces an allylic radical (equation 16). In more-substituted cases, however, different degrees of activation may exist, and these will control the rate as well as the regiochemistry of the rearrangement. Some rather drastic differences in the conditions and the rate of the rearrangement can be seen in Table 3.

In general, increased carbon substitution, extended conjugation, or the presence of heteroatoms lowers the activation energy for the reorganization to cyclopentene. In some cases changes in carbon substitution cause the reaction pathway to deviate from the cyclopentene rearrangement entirely. Thus, in the rearrangement of keto vinylcyclopropanes of type (**24**; equation 17), only bond **a** is activated toward radical scission as a result of the electron-withdrawing effect of the carbonyl group.[41,97] No products that would result from scission of bonds **b** or **c** are observed until a higher order of substitution exists at the β-carbon, as in the case of (**26**), where the competition between the tertiary (bond **c**) and the secondary α-keto radical (bond **b**) clearly favored product (**27**) in several instances (equation 18).[98] Once the α-position was substituted, as in (**28**), the normal cyclopentene rearrangement took place (equation 19), indicating that a tertiary α-keto radical is favored over a tertiary radical.[41,99]

Activation by electron-donating heteroatoms accomplishes similar regioselective ring cleavage. It has been shown during the era of mechanistic investigations that heteroatom substitution of the cyclopropane moiety lowers significantly the activation energy of rearrangement, whereas similar substitution on the alkenic unit has little effect.[9] Several examples of this principle are shown in Table 3. In all of the cases,

Table 3 Substituent Effects in the Vinylcyclopropane–Cyclopentene Rearrangement

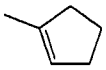
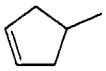
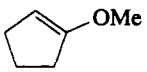
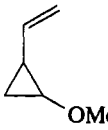
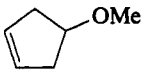
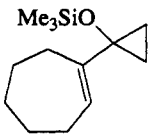
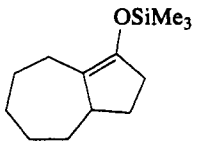
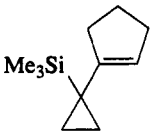
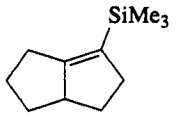
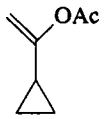
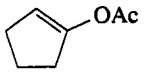
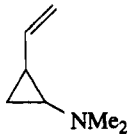
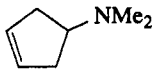
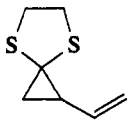
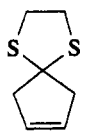
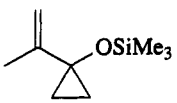
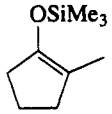
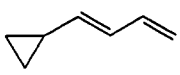
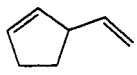
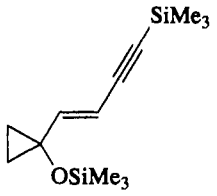
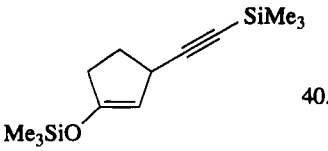
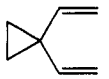
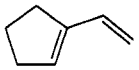
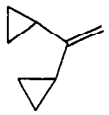
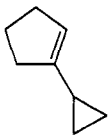
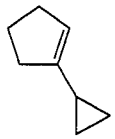
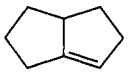
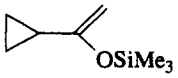
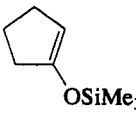
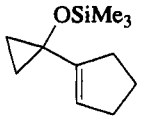
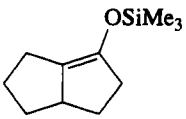
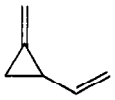
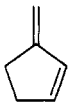
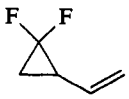
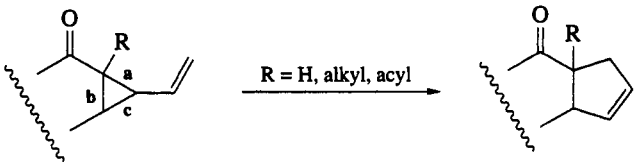
Vinylcyclopropane	*Cyclopentene*	E_a (kcal mol^{-1})	*Ref.*
		49.7	79–81
		49.4	82, 83
		48.7	65, 83
		44.7	20, 84
		38.7	20, 84
		42	85
		—	81
		—	86
		31.2	87
		—	88
		—	89
		44.5	11

Table 3 *(continued)*

Vinylcyclopropane	*Cyclopentene*	E_a (kcal mol^{-1})	*Ref.*
		40.5	90
		39.6	91
		51.1	92
		51.3	92
		51.3	15, 83, 93
		44.3	83
		25.8	94
		41.5	
	a		
		37.9	95, 96
	b		
	a:b = 4:96		

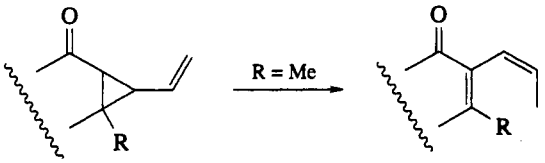
the cleavage of the cyclopropane ring occurs regioselectively in such a way as to provide a diradical that is contained in an allylic system on one side and α to the heteroatom on the other, or both, as shown in equations (20) and (20a). When directly attached to the cyclopropane, oxygen, sulfur and nitrogen all

exhibit the accelerating effect, whereas silicon retards the rearrangement.[15,81] Fluorine has been shown to destabilize vinylcyclopropanes by 12–14 kcal mol^{-1}.[95,96]



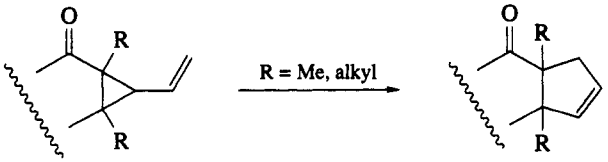
(17)

(24) (25)



(18)

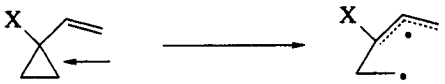
(26) (27)



(19)

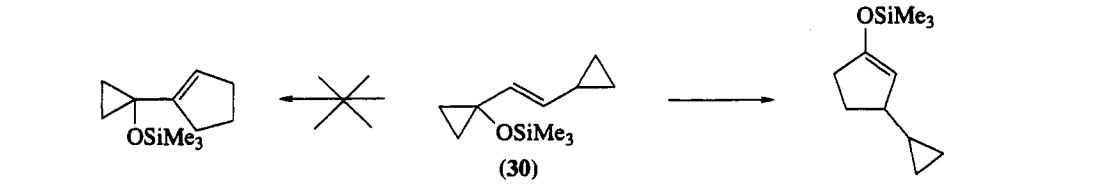
(28) (29)

(20)



(20a)

The following examples further illustrate the selectivity that can emerge from this analysis (Scheme 6). Divinylcyclopropane (**30**) underwent exclusively the cleavage of the siloxy-substituted ring[83] with activation enhancement of *ca.* 5 kcal mol^{-1}, whereas the silyl-substituted counterpart (**31**) preferred the cleavage of the carbon-substituted ring due to the decelerating effect of silicon.[81]

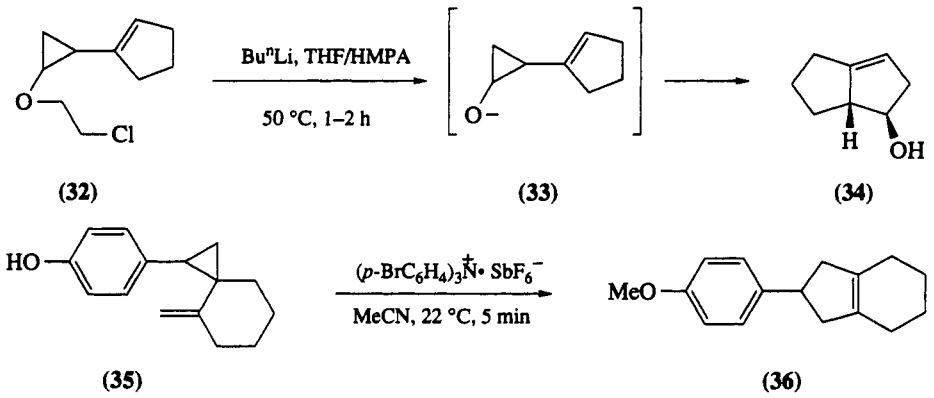


(30)

(31)

Scheme 6

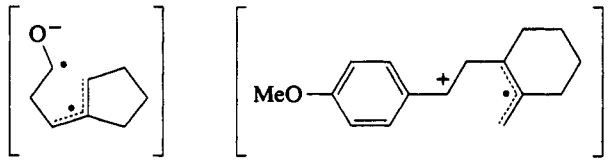
Examples of rearrangements where odd electron species may be intermediates include the concerted (and stereospecific) rearrangements of alkoxides such as (**33**), generated from β-chloro esters (**32**) with *n*-butyllithium at low temperature[100] and the cation radical accelerated rearrangement of (**35**; Scheme 7).[101] The exact mechanism of either of these transformations is not known. A concerted ring closure of an anion radical (**37**) was proposed in the former case, whereas either a stepwise isomerization of a trimethylene cation radical (**38**) or a concerted rearrangement involving an odd electron pericyclic transition state was invoked for the latter. The rate enhancement in the rearrangements of vinylcyclopropanes such as (**35**) has been estimated to be $>10^9$ as compared to the thermal reorganization that occurred only above 200 °C.[101] It should be noted that odd electron species do not subscribe to the normal rules concerning symmetry forbidden reactions and that ample precedent is available concerning accelerating effects in such reactions by creating odd electron intermediates.[102]



(**32**) (**33**) (**34**)

(**35**) (**36**)

Scheme 7

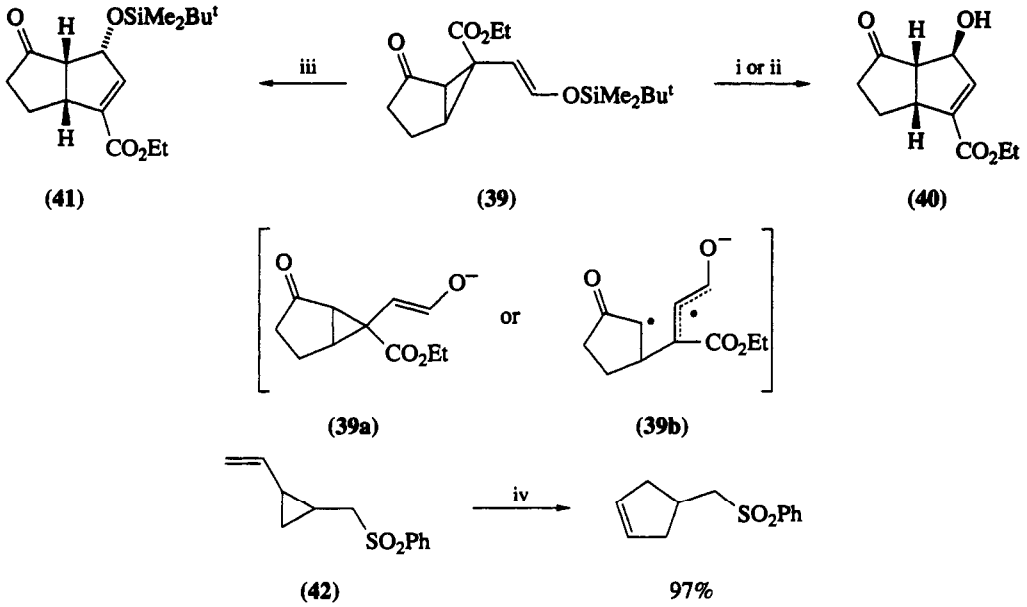


(**37**) (**38**)

A similar acceleration has most recently been observed in the rearrangement of vinylcyclopropanes of type (**39**; Scheme 8).[103] This fluoride-mediated vinylcyclopropane–cyclopentene isomerization proceeds at −78 °C to give (**40**) in 85% yield; this is to date the mildest condition available. Two possible intermediates, the enolate anion (**39a**) or the diradical anion (**39b**), may be responsible for such acceleration in analogy to the enolate anion accelerated divinylcyclobutane rearrangement recently reported.[104] The mechanism of this transformation is unclear but may involve anion acceleration similar to that observed in the rearrangement of sulfonyl anions derived from (**42**; Scheme 8).[105] By comparison the thermolysis of (**39**) produced exclusively the *endo* isomer of (**41**) at 580 °C.[103]

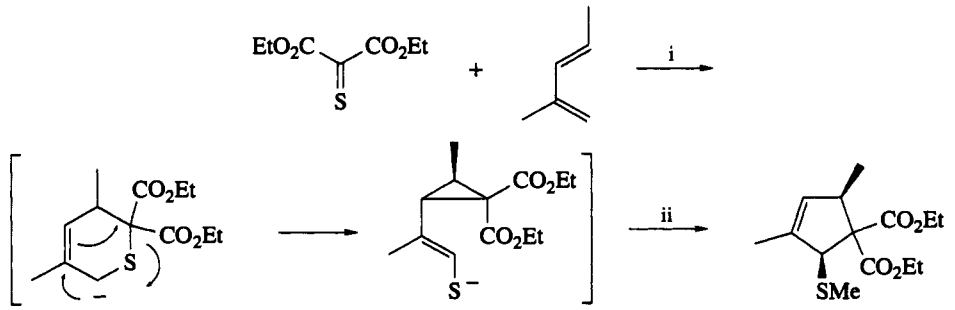
Most recently, a vinylcyclopropane rearrangement that appears to involve anion acceleration was reported to take place during an interesting [4 + 2 − 1] annulation, depicted in Scheme 9. Following the [4 + 2] cyclization of the thiocarbonyl compound, the [2,3] sigmatropic ring opening of the anion generates a thioenolate anion-terminated vinylcyclopropane, which rearranges at low temperature and is trapped with an alkylating agent. The stereoselectivity of this ring closure was reported to favor *syn* substitution by 13:1.[106] This process is similar in concept to the rearrangement of vinylcyclopropane (**39**).

Photochemical rearrangements of vinylcyclopropanes have been reported under both direct and sensitized conditions; the field has been reviewed on several occasions.[9,12,14] In 1962 the investigation of the addition of photochemically generated methylene diradical to butadiene led to speculations regarding the possibility of direct 1,4-addition of a carbene to a diene.[107] Such direct additions, however, have been found operating only in the cases of sterically constricted dienes such as (**43**) or (**44**).[108] A photochemical vinylcyclopropane–cyclopentene rearrangement taking place during the reaction can account for the observed products. The sensitized conditions generate triplet species with $E_T = 80$ kcal mol^{-1}, far above the activation barrier for the vinylcyclopropane cleavage, and thus promote other, competing pathways. Both diradical and zwitterionic species (and sometimes carbenes) have been proposed as intermediates in



i, KF, 18-crown-6, THF, –78 °C; ii, Bu^n_4NF, H_2O, THF, –10 °C; iii, 580 °C, $PbCO_3$/Vycor; iv, Bu^nLi, THF, HMPA, –78 to –30 °C

Scheme 8

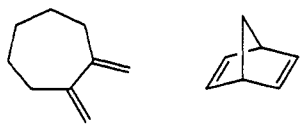


i, $LiNPr^i_2$ or $KN(Me_3Si)_2$, THF, –78 °C; ii, MeI

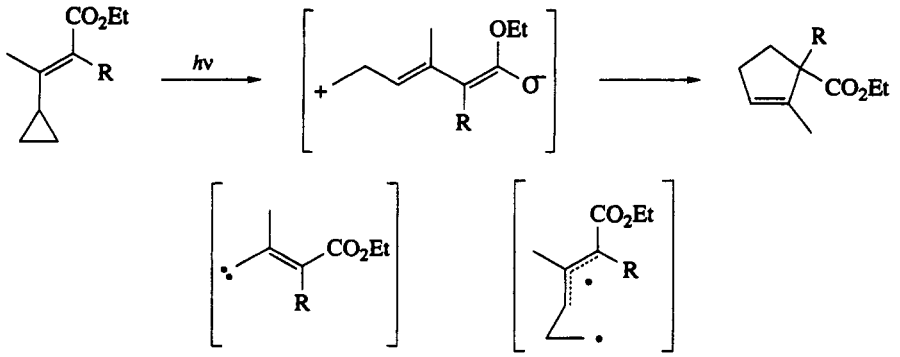
Scheme 9

transformations of this type.[109] The example in Scheme 10 illustrates such intermediates.[109] Photolytic rearrangements of vinylcyclopropenes such as (**45**) lead to cyclopentadienes *via* diradical recombination, bicyclo[2.1.0]pentane diradicals or carbene intermediates (equation 21).[110]

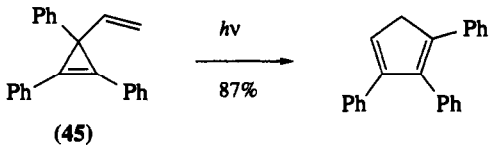
Rearrangements of endocyclic vinylcyclopropanes under direct irradiation lead to useful yields of ring-contracted products as the examples in Table 4 illustrate. Some regioselectivity is observed in the rearrangements of unsymmetrical vinylcyclopropenes, which lead to cyclopentadienes (**46**) and (**47**) (equation 22).[114] A similar rearrangement of a cyclopropene ester, where the carbonyl serves as a vinyl equivalent, produced furan (**48**) with similar regioselectivity (equation 23).[115] For additional examples of vinylcyclopropene rearrangements consult Section 8.1.7.



(**43**) (**44**)

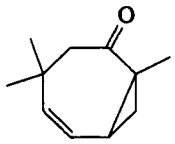
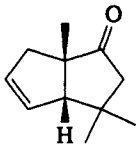
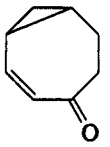
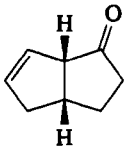
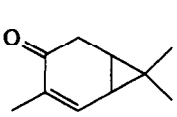
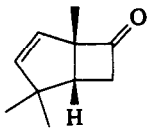
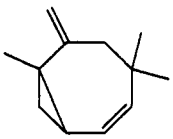
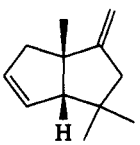


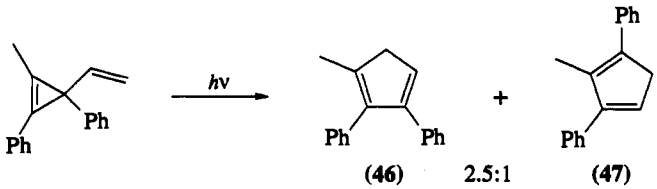
Scheme 10



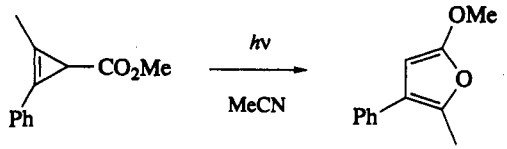
(45) (21)

Table 4 Photochemical Vinylcyclopropane–Cyclopentene Rearrangements

Vinylcyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	*hν*, MeOH		56	111
	*hν*, acetone		82	112
	*hν*, TFA		—	113
	*hν*, MeOH		56	112



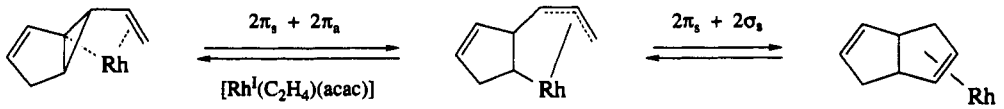
(46) 2.5:1 (47) (22)



(48) (23)

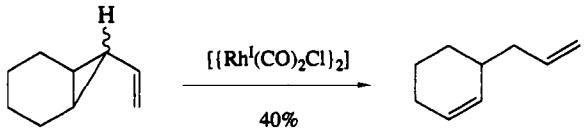
The photochemical transformations of vinylcyclopropanes are of mechanistic interest, but because of the high energy of the reaction intermediates, especially in the triplet manifold, practical applications are scarce. The regio- and stereo-selective aspects are, however, similar to those of the thermal processes. Additional methods that provide for the cyclopentene rearrangement involve the degenerate photochemical rearrangements observed by Wender during meta-photocycloaddition of arenes and alkenes and utilized extensively in the synthesis of triquinane sesquiterpenes.[41,116,117] (See Section 8.1.9 or ref. 41 for a recent summary.)

Transition metal catalyzed rearrangements have received considerable attention because of the mild conditions required for these rearrangements. The interaction of the vinylcyclopropanes with metal catalysts is accompanied by ligand insertion in most cases. This topic has recently been reviewed.[118] Rhodium-catalyzed rearrangements of vinylcyclopropanes (**49**) have been studied (Scheme 11),[119,120] and found to yield diquinanes (**50**) in an apparent $[2\pi_s + 2\pi_a]/[2\pi_s + 2\sigma_a]$ process.[119] It appears that the presence of an additional ligand in vinylcyclopropane (**49**) is necessary for the rearrangement.[119,121,122] In contrast, both isomers of vinylcyclopropane (**51**) give diene (**52**) in a process involving stereospecific β-hydride elimination (equation 24). No cyclopentene formation was observed. In one case, a carbonyl was thought to assume the function of an additional alkenic ligand. Vinylcyclopropane (**53**) gave exclusively triquinane (**54**; equation 25), whereas the pyrolytic conditions led to a mixture of *cis-anti-cis* and *cis-syn-cis* isomers in a 6:1 ratio.[122] Few examples exist where simple vinylcyclopropanes (without the additional ligand) rearrange to cyclopentenes; rather they rearrange to dienes. In the case of divinylcyclopropylethylene (**55**) it can be argued that the nonparticipating cyclopropane serves the function of this additional ligand (equation 26).[121]

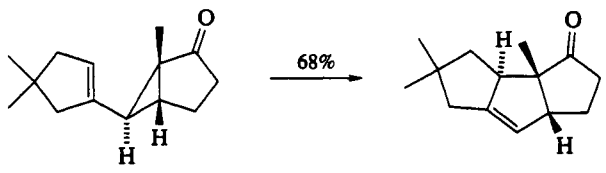


(**49**) (**50**)

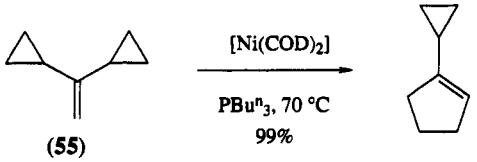
Scheme 11



(**51**) (**52**) (24)

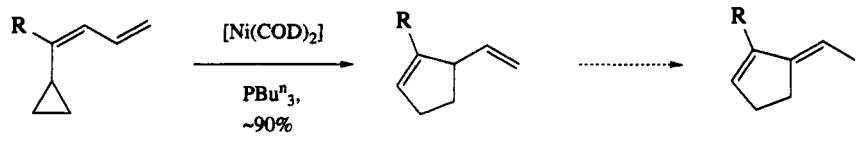


(**53**) (**54**) (25)



(**55**) (26)

The presence of additional unsaturation in vinylcyclopropane (**56**) was invoked as an explanation for its facile nickel(0)-catalyzed rearrangement to vinylcyclopentene (**57**) in excellent yield (Scheme 12).[121] The geometry of the diene in (**56**) turned out not to be important as the ring opening led to the equilibration of (*E*)- and (*Z*)-isomers prior to the final closure. The reaction was therefore stereoselective, but cyclopentene (**57**) suffered, in some cases, isomerization to (**58**) under the reaction conditions.[121]

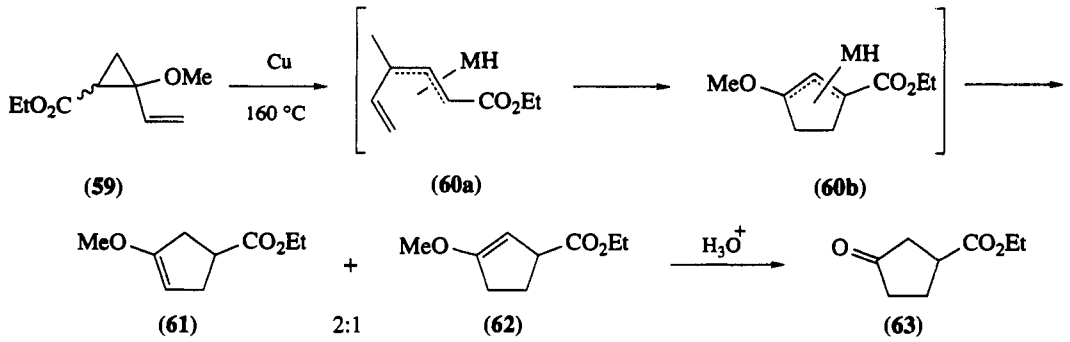


(**56**) (**57**) (**58**)

R = Me, alkyl, Ph

Scheme 12

The copper-catalyzed rearrangement of vinylcyclopropane (**59**) was thought to involve the π-allyl systems (**60a**) and (**60b**) (Scheme 13). The regioselectivity of this rearrangement was only two-fold; however, both enol ethers (**61**) and (**62**) can be hydrolyzed to the 1,4-dicarbonyl system (**63**). Platinum- and rhodium-catalyzed decomposition of (**59**) yielded dienes.[123]

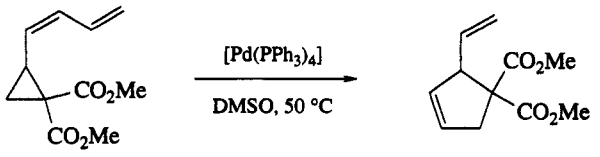


(**59**) (**60a**) (**60b**)

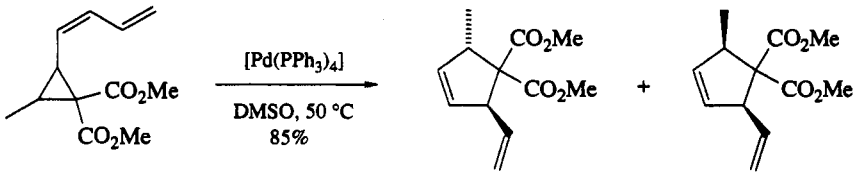
(**61**) 2:1 (**62**) (**63**)

Scheme 13

Palladium-catalyzed rearrangements of dienylcyclopropanes have also been reported. Vinylcyclopropane (**64**) gave cyclopentene (**65**) without regard to the (*E*)/(*Z*) composition of the diene (equation 27).[124] Similar results with respect to (*E*) and (*Z*) mixtures were also observed in the more-substituted case of (**66**) with moderate stereoselectivities (3:1) observed upon reclosure (equation 28). It has been suggested that the palladium-catalyzed rearrangement is in fact a nucleophilic-like opening followed by reclosure. Such transformations are discussed in Section 8.1.3.4 in the context of the stepwise opening of activated vinylcyclopropanes with iodide and other nucleophiles.



(**64**) (**65**) (27)

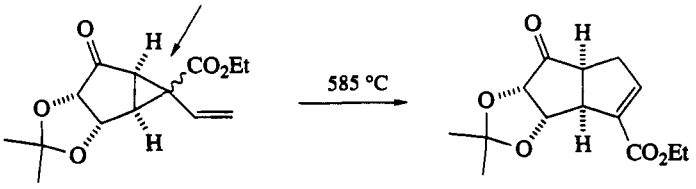


(**66**) (**67**) 3:1 (28)

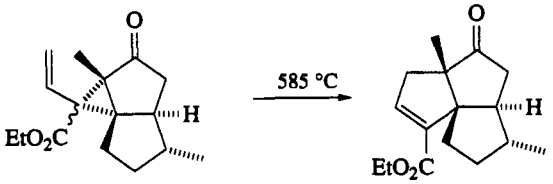
In summary, the regio- and stereo-chemical course of the vinylcyclopropane–cyclopentene rearrangement can be predicted by analyzing the donor/acceptor qualities of the substituents and by considering the nature of the intermediates in the incipient ring closures. It can be concluded that, based on the discussion above, only one bond in a vinylcyclopropane system will be predominantly activated toward regioselective cleavage. The stereochemical outcome will then be governed by the energetics of the corresponding substituted cyclopentene, which is formed from a cisoid conformation of a biradical such as (**68**; equation 29). It should be noted that, if such a conformation cannot be reached for steric reasons (the size of $R_2 >> R_3$, for example), then processes other than cyclopentene formation will predominate.[125] In functionalized cyclopentenes the stereoselectivity would be expected to be dominated by the *endo* effect, which governs the radical closures.[41,126,127] In fused systems, either the kinetic *endo* effect or the relative energetics of *cis versus trans* fusion will determine the stereochemistry at the ring junction. In the field of polycyclopentenoids, for example, this issue is relatively unimportant as all ring junctions prefer to be in the thermodynamically more stable *cis* form.

(68) (69) (29)

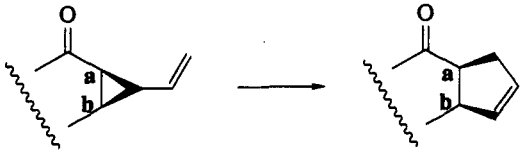
The stereochemistry of those rearrangements involving concerted processes can be rationalized with the results of Baldwin's experiment[78] for those vinylcyclopropanes that contain no resident chirality other than at the centers that become diradicals. Rearrangements of optically active vinylcyclopropanes that contain set chirality at centers remote to the rearrangement site, such as vinylcyclopropanes (**70**; equation 30) and (**72**; equation 31), lead to the retention of 100% optical purity in the products.[128,129] Although the enantioselective preparation of cyclopentenes by this method is not routine, save isolated examples,[41] it should be expected that in optically pure vinylcyclopropanes of type (**74**; equation 32), the rearrangement would proceed with complete retention of optical configuration since center **b** is not involved in the rearrangement. The increased use of such processes awaits the development of a suitable methodology for the generation of optically pure vinylcyclopropanes.



(70) (71) (30)



(72) (73) (31)

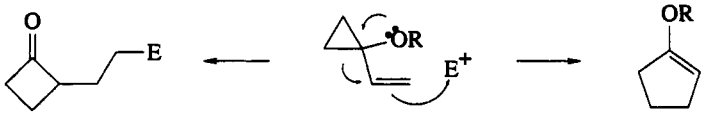


(74) (32)

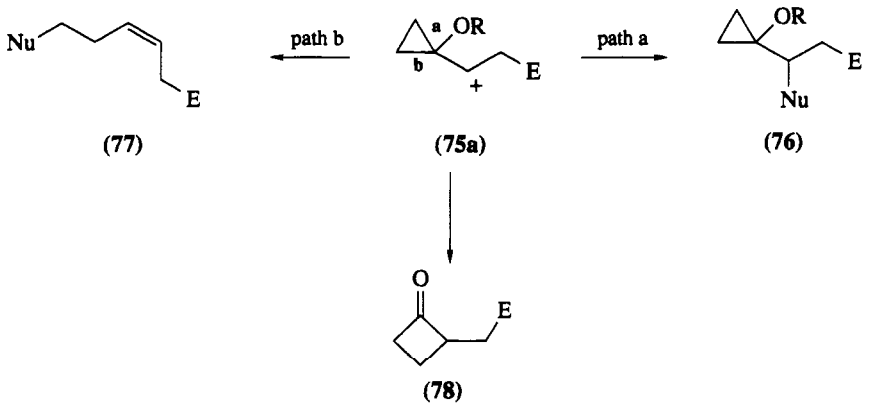
A summary of the synthetic methods based on the vinylcyclopropane rearrangements appears in Section 8.1.8. The listing of total syntheses featuring this rearrangement and its heteroatom variants is compiled in Section 8.1.9.

8.1.3.3 Ring Expansions of Oxyvinylcyclopropanes

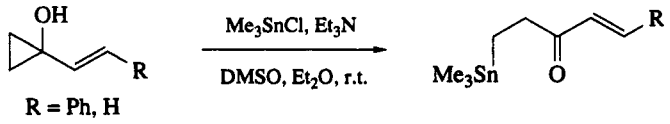
Vinylcyclopropanes substituted with oxygen (or sulfur or selenium) are susceptible to ring expansion to the corresponding cyclobutanone derivative in addition to the expected cyclopentene rearrangement (Scheme 14). The oxycyclopropane can be viewed as a pseudo enol in those interactions with electrophiles that would involve the vinyl group. The resulting cyclopropylcarbinyl system (**75**) will interact with nucleophiles either directly (path a) or through ring opening (path b; Scheme 15). The participation of either bond **a** or **b** in this opening will depend on the precise conformation of (**75**), which is in turn dependent on the nature of the cation and its solvation, as well as on the tendency of the cyclopropylcarbinyl cation (**75a**) to unravel. When proper orbital overlap exists, one of these bonds will participate in opening the cyclopropane to yield (**77**) or it will act as an internal nucleophile in its migration (and concomitant ring expansion to **78**). This latter process has been developed and extensively utilized by Trost in spirocyclobutanone annulation.[19,20] A less common reaction of oxyvinylcyclopropanes would involve normal electrophilic opening of the oxycyclopropane, as, for example, that occurring in the generation of the β-stannyl enone (equation 33).[15]



Scheme 14



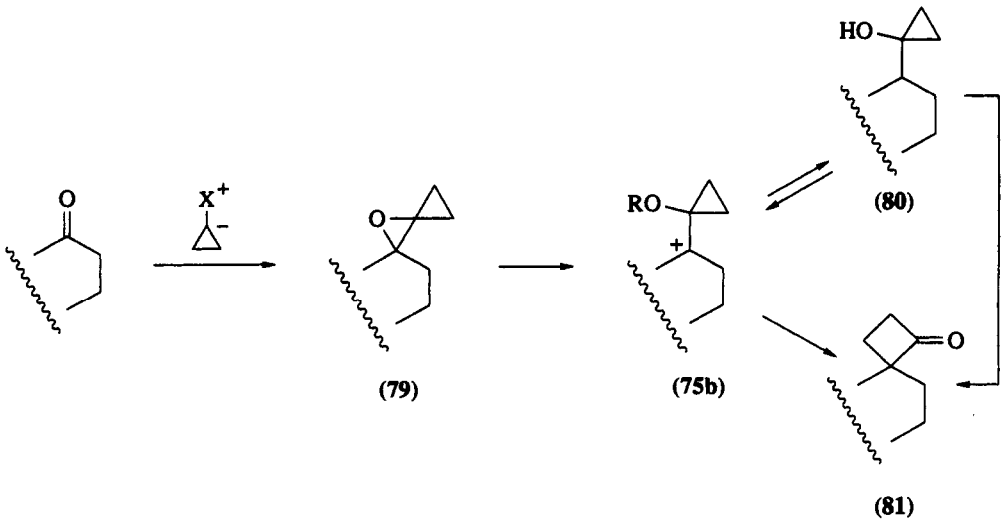
Scheme 15



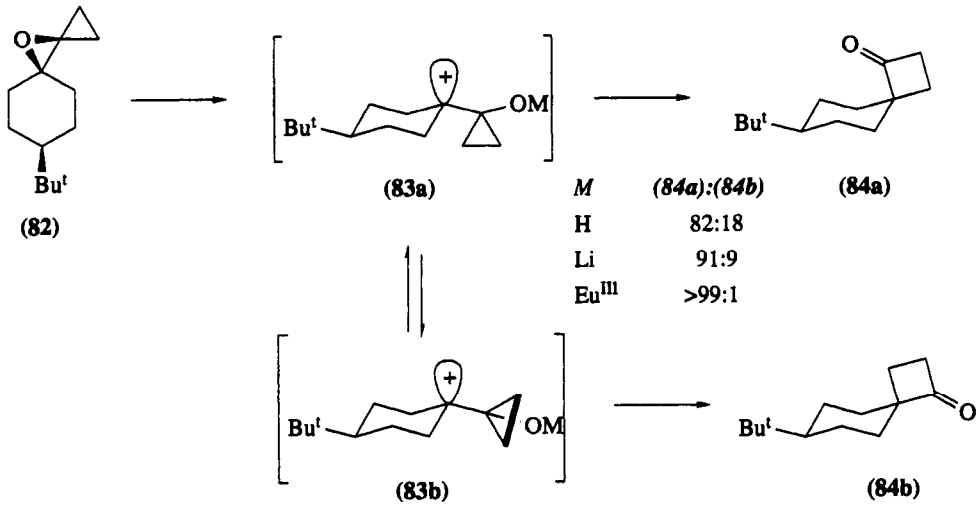
(33)

The ylide-based methodology of oxaspirocyclopentanes in synthesis provided the elements of control shown in Scheme 14. The oxaspirocyclopentane system (**79**), prepared from the corresponding cyclopropyl and carbonyl compounds, can be eliminated by a variety of methods to vinylcyclopropane (**80**), which can be used in cyclopentene annulation or be rearranged to spirocyclobutanone (**81**; Scheme 16).[20] When treated with acid, vinylcyclopropane (**80**) generates cations of type (**75b**), which collapse to cyclobutanones whose stereochemistry depends on the precise conditions and the solvating properties of the acid used. For example, treatment of epoxide (**82**) with protic acids resulted in approximately 80:20 selectivity in the formation of (**84a**; Scheme 17).[130] When the equilibrium of (**83a**) and (**83b**) was retarded by the use of counterions that accelerated the migration by rendering the oxygen more electron releasing

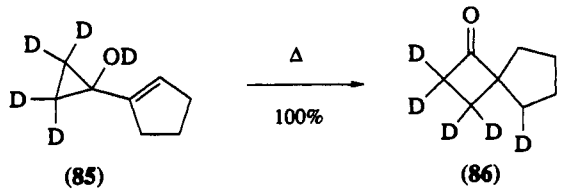
(and also prevented the rotation leading to the more stable conformer **83b**), only (**84a**) was observed. The rearrangement occurs with inversion of configuration at the migrating center; this would be consistent with a thermally allowed [$2a + 2a + 2s$] concerted process, which has been invoked to explain the formation of cyclobutanones during pyrolysis of vinylcyclopropanols such as (**86**; equation 34).[15,20] The stereochemistry of this rearrangement has been shown to involve the intramolecular *cis* addition of H (or D) to the double bond *via* the transition state (**87**), which is not consistent with a concerted process.[131,132]



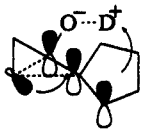
Scheme 16



Scheme 17

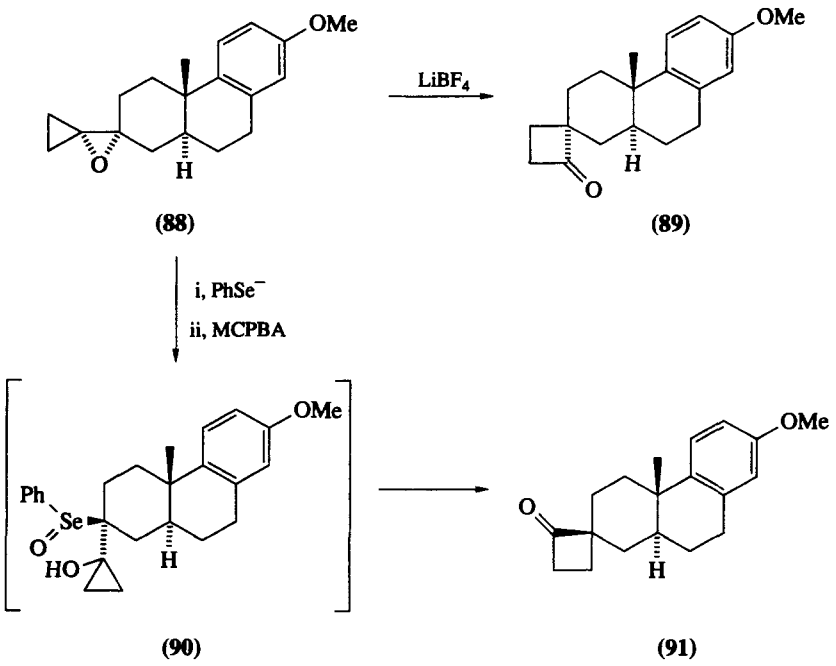


(34)



(87)

Finally the stereochemistry of cyclobutanone is subject to complete control by adjusting the experimental conditions of the reaction, which can lead to either a single or a double inversion at the migrating center. Thus $LiBF_4$-catalyzed opening of epoxide (**88**) leads (through inversion) to cyclobutanone (**89**), whereas phenyl selenide opening (inversion) followed by oxidation to a selenoxide leaving group leads, through a second inversion, to the diastereomer (**91**) (Scheme 18).[20,133] Table 5 illustrates the utility of cyclobutanone annulation in the preparation of spirocyclic ketones from oxygen- and sulfur-substituted vinylcyclopropanes.



Scheme 18

Vinylogous modes of this rearrangement are also possible. Complex systems can be attained by utilizing a built-in electrophile in an intramolecular ring expansion/alkylation, as shown in equation (35). This kind of cyclization is applicable to seven- and eight-membered carbocyclic ring synthesis and proceeds with approximately 12:1 stereoselectivity, which is due to the more stable, parallel conformation depicted in equation (35).[140]

Thus by recognition of the reactive options of the basic system (**75**) and the possibilities involving either further conjugation of functional groups or substitution possibilities, virtually limitless methodology is available. Recent reviews of this topic[15,20] point out the vast number of ring systems and substitution patterns available.

8.1.3.4 Reactions with Nucleophiles (Normal and Vinylogous Modes)

When a vinylcyclopropane is substituted with an electron-withdrawing group, donor/acceptor symmetry causes the electrons to flow in one particular direction. Such a system, for example (**92**), is susceptible to nucleophilic opening by either external agents (Nu^-) or by causing additional electrons to flow from heteroatom X to the cyclopropane weakened by electron withdrawal. The latter process usually takes place under acid catalysis and after substantial development of carbonium ion character at the site of the heteroatom. As the agency of a heteroatom lone pair can be considered in the same light as an external nucleophilic attack, this process will also be mentioned briefly in this section. Control of regiochemistry among the four possible modes of opening is available by careful consideration of stereoelectronic effects and choice of experimental conditions.

The opening of activated cyclopropanes with nitrogen nucleophiles has been widely applied to the synthesis of pyrrolizidine and pyrroline alkaloids by Danishefsky; this subject has been reviewed.[12,141] A number of pyrroline annulations have been based on this principle, illustrated in equation (35a).[12,141–143] Similar opening can be accomplished with halides, cuprates, and sulfur or selenium nucleophiles.[12,16,21]

Table 5 Cyclobutanone Synthesis

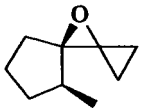
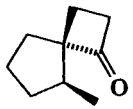
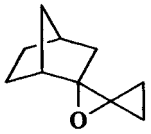
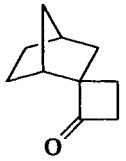
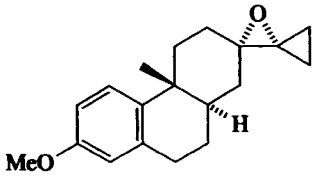
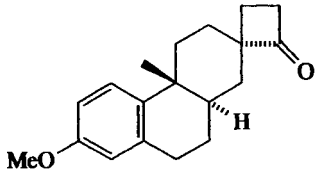
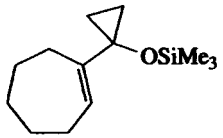
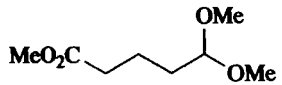
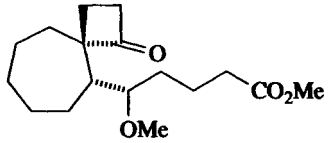
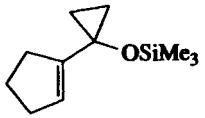
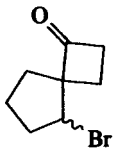
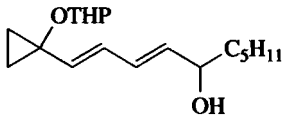
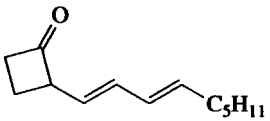
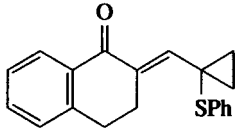
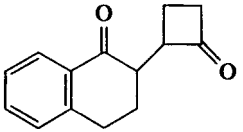
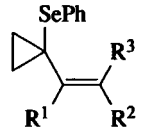
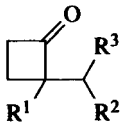
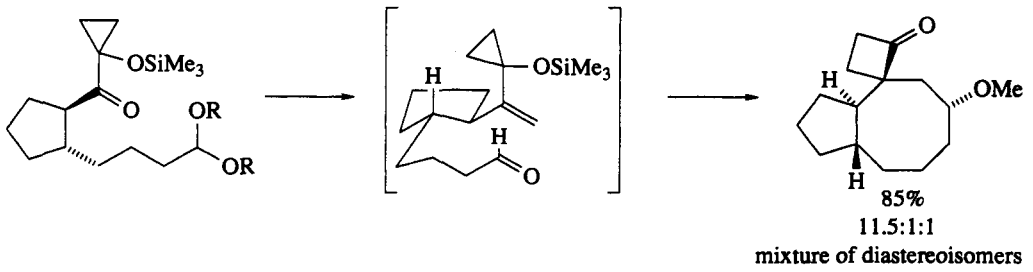
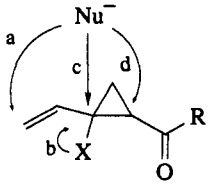
Vinylcyclopropanol or oxaspirocyclopentene equivalent	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	$LiBF_4$, PhH, r.t. to reflux	 (96:4)	61	133
	$LiBF_4$, PhH, r.t. to reflux	 (91:9)	92	130
	$LiBF_4$, PhH, r.t. to reflux		70–75	134
	 $Me_3SiOSO_2CF_3$ (cat.)		95	135
	dioxane, Br_2		84	136

Table 5 *(continued)*

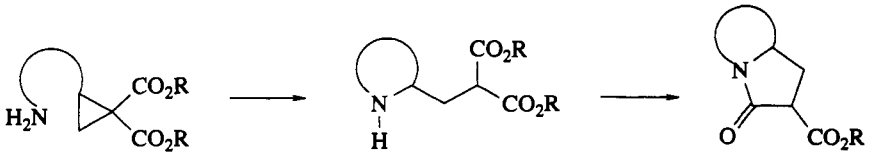
Vinylcyclopropanol or oxaspirocyclopentene equivalent	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	PPTS, EtOH 95%		83	137
	50% aq. TFA		95	138
 R^1, R^2, R^3 = H, alkyl	$TsOH, H_2O$, PhH, Δ		63–90	17, 139



(35)

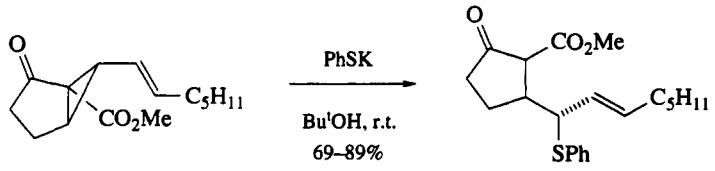


(92)



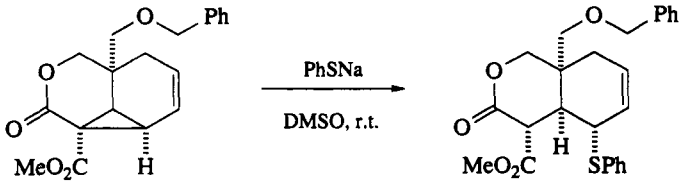
(35a)

With vinylcyclopropanes such ring opening can still occur without the participation of the alkene and with inversion of configuration at the reacting center. The opening of cyclopropyl keto ester (**93**) has been used in an approach to prostanoids (equation 36),[144,145] whereas the opening of tricyclic systems (**95**)[146] and (**97**)[147] served in the synthesis of vernolepin and vernomenin (equations 37 and 38). Similarly, vinylcyclopropane (**99**) reacted with Me_2CuLi to give stereoselectively propellane (**100**) in an approach to modhephene (equation 39).[148]



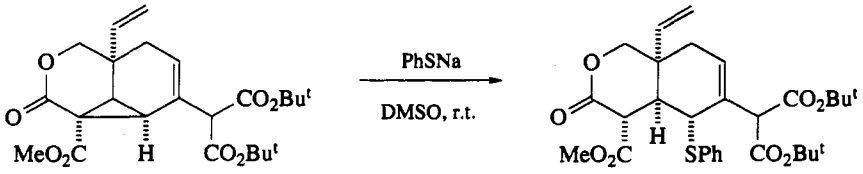
(93) (94)

(36)



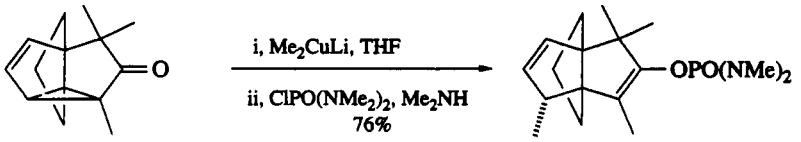
(95) (96)

(37)



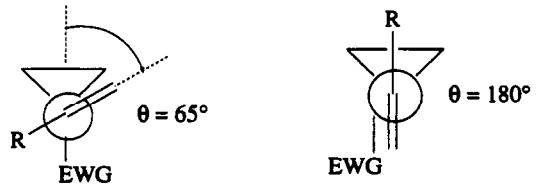
(97) (98)

(38)

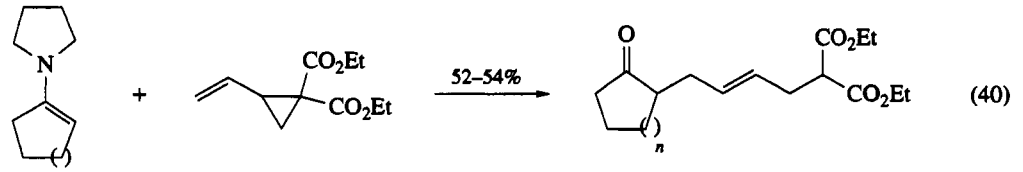


(99) (100) (39)

The vinylogous mode of opening depends to a great extent on the conformation of the vinylcyclopropane. Of the two conformations (**101a**) and (**101b**), the *s-trans* or antiperiplanar arrangement in (**101b**) is preferred (1.17 kcal mol^{-1}) and cannot be reached in a cyclic or conformationally rigid system.[149] Vinylcyclopropanes such as (**102**) react with enamines in refluxing *p*-cymene to furnish, after hydrolysis, ketones (**103**) through the vinylogous mode of opening (equation 40).[150]

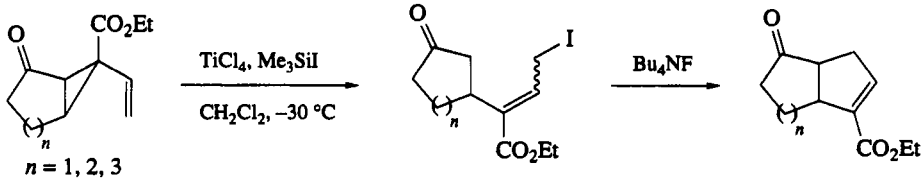


(**101a**) Synclinal *(gauche)* (**101b**) Antiperiplanar



$n = 1, 2$ (**102**) (**103**) (40)

The opening of cyclopropyl ketones, investigated by Miller,[151] has been adapted to vinylogous opening of vinylcyclopropanes in the development of a milder procedure for cyclopentene annulation.[152] In the presence of Lewis acids, the (*E*):(*Z*) selectivity in the formation of allylic iodides (**105**) was 80:20, whereas only marginal selectivity (60:40) was observed with TMSI alone (Scheme 19).[128,152] Similar results were also obtained with tosyl iodide[153] and, under some circumstances, with LiI at higher temperatures.[154] A recent review summarizes the reactivity and the synthetic utility of vinylogous modes of opening as well as the preparation of activated donor/acceptor-functionalized vinylcyclopropanes and their behavior in nucleophilic and electrophilic addition reactions.[45]

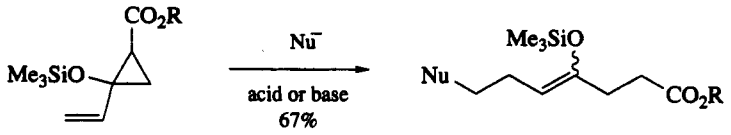


$n = 1, 2, 3$

(**104**) (**105**) (**106**)

Scheme 19

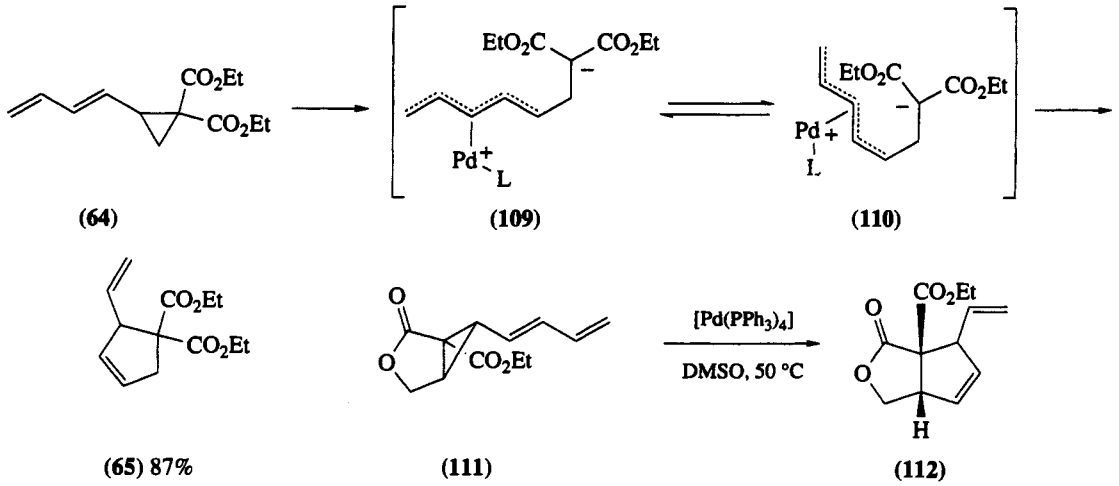
Donor- or acceptor-substituted vinylcyclopropanes such as (**107**) afford products of vinylogous opening (**108**) with a wide variety of nucleophiles (equation 41).[16] The palladium(0)-catalyzed ring opening of vinyl- or dienyl-cyclopropanes such as (**64**) and (**111**) is thought to involve a nucleophilic attack to form zwitterion (**109**), which collapses to a vinylcyclopentene (and not cycloheptadiene) through the preferred W-conformation (**110**; Scheme 20).[45,122] The mechanism of these openings has been studied.[155,156]



(41)

(107) (108)

$Nu^- = MeNO_2$, MeOH, PhSH, Et_2NH, $PhSO_2H$, HF

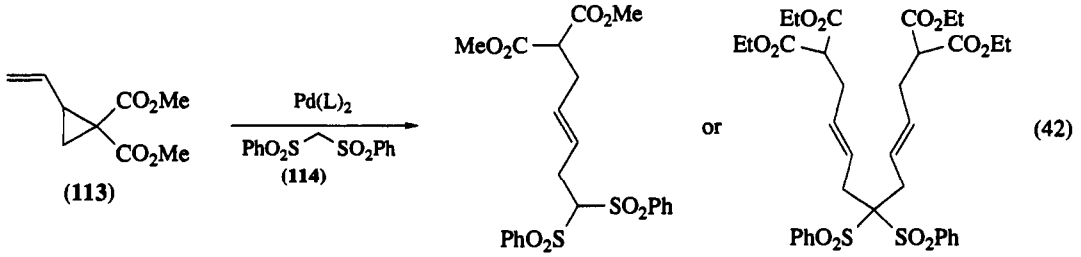


(64) (109) (110)

(65) 87% (111) (112)

Scheme 20

Addition of carbon nucleophiles to doubly activated vinylcyclopropanes has also been reported. Increasing the vinylcyclopropane ratio to two equivalents led to the isolation of doubly alkylated product (**116**) selectively (equation 42).[157,158] All of the reactions discussed in this section, as well as their various permutations, have been the subject of an excellent review.[45]



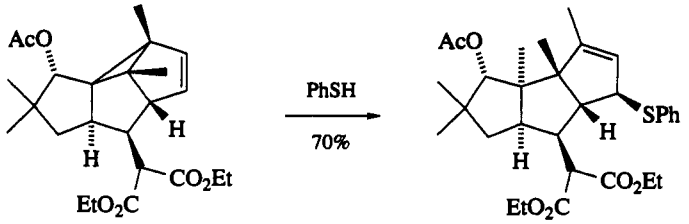
(113) (114) (115) 94% (116) 96%

(42)

8.1.3.5 Radical Reactions or Cycloadditions

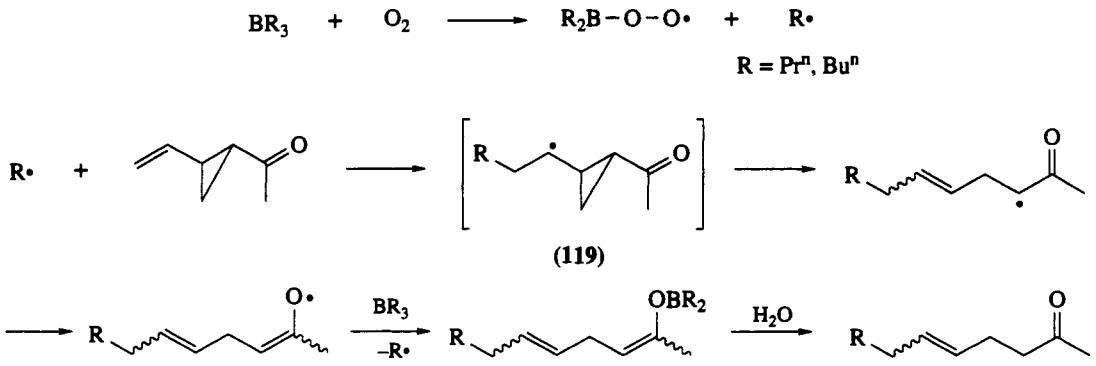
Addition of free radical species to vinylcyclopropane results either in the abstraction of hydrogen from the cyclopropane or ring opening through the agency of the cyclopropylcarbinyl radical generated upon the initial addition.[12] The latter process has found some synthetic applications, for example, in the ring opening of triquinane (**117**) with benzenethiol (equation 43).[124]

Alkylboranes undergo free radical 1,6-addition to keto vinylcyclopropanes, as shown in Scheme 21. The mechanism postulated involves the generation and ring opening of cyclopropylcarbinyl radical (**119**).[159] Free radical polymerization of substituted vinylcyclopropanes through both 1,2- and 1,5-type additions has also been reported.[160] A recent application of these types of procedures to synthetic methodology has been demonstrated in the cyclopentane annulation depicted in equation (44). The stereo- and regio-selectivity in the formation of cyclopentanes (**120**) is acceptable. (*Syn* orientation of the alkenic substituent with the vinyl group was observed, and there was about a 3:1 preference for *cis* substitu-

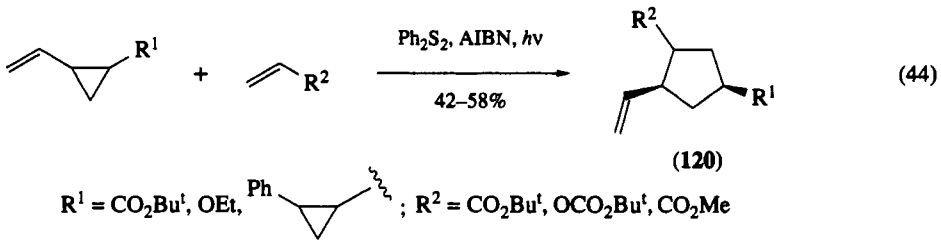


(117) (118) (43)

tion.)[161] Similar technology was applied to the preparation of tetrahydrofurans from vinyloxiranes (see Section 8.1.4.1).[162] Vinylcyclopropanes such as (**121**) also undergo radical addition with PhSH or Bu_3SnH to afford functionalized enol ethers (**122**), which are hydrolyzed to ketones, thus eliminating the stereochemical problems of alkene geometry (Scheme 22).[16]

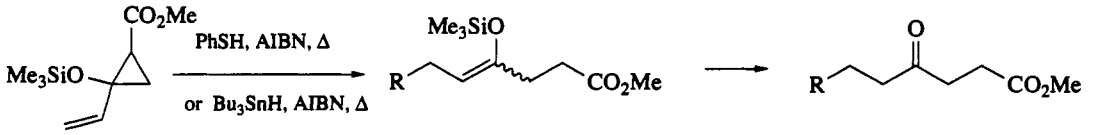


Scheme 21



(**120**) (44)

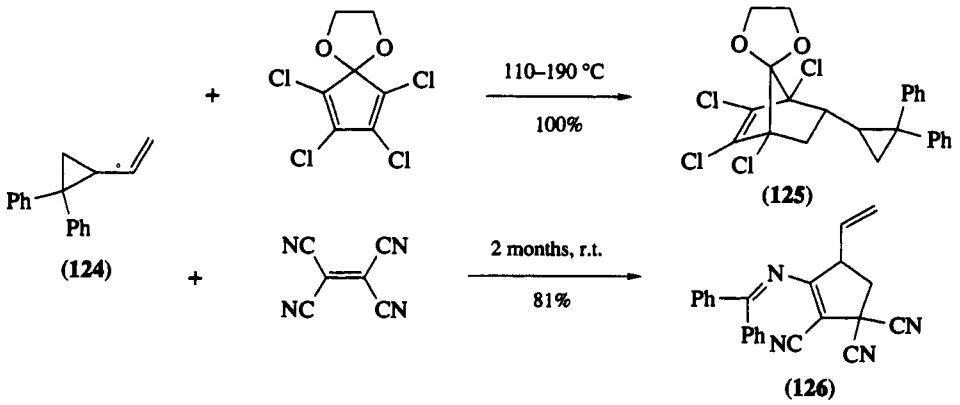
$R^1 = CO_2Bu^t$, OEt, Ph ; $R^2 = CO_2Bu^t$, OCO_2Bu^t, CO_2Me



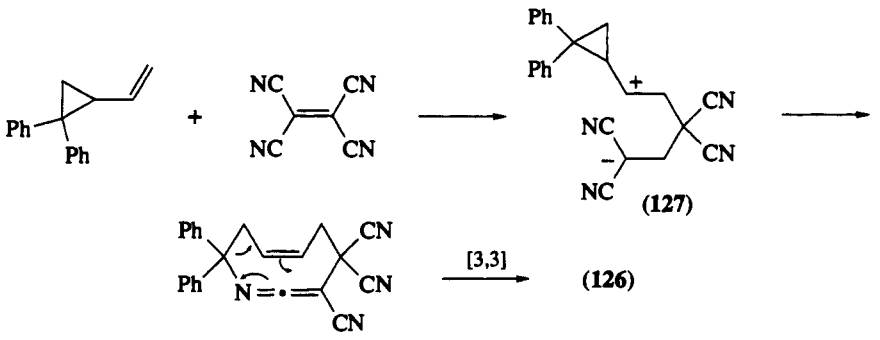
(**121**) (**122**) R = SPh, 30%; $SnBu_3$, 85% (**123**)

Scheme 22

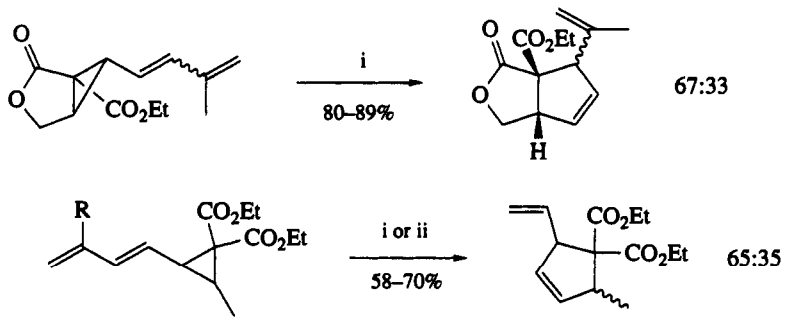
Cycloadditions of vinylcyclopropanes have also been studied.[163] For example, vinylcyclopropane (**124**) gave the Diels–Alder adduct (**125**), presumably as a single (*endo*) stereoisomer (Scheme 23). On the other hand, the reaction of (**124**) with tetracyanoethylene took a different course, resulting in the formation of cyclopentene (**126**). A possible mechanism involves the transformation shown in Scheme 24. It should be noted that the norphenyl derivative of (**124**) gave the corresponding cyclopropylcyclobutane supporting the intermediacy of the proposed zwitterion (**127**). A tin-promoted free radical opening of dienylcyclopropanes has recently been reported, but unfortunately the stereoselectivity of the radical closure was modest (Scheme 25).[164]



Scheme 23



Scheme 24

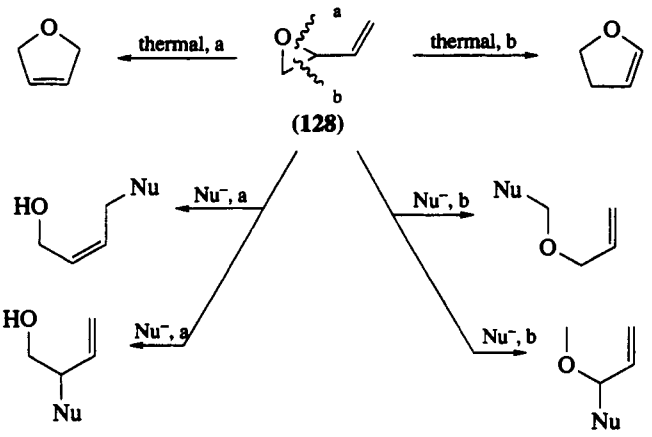


i, Ph_3SnH or PhSH, AIBN, 80 °C; ii, Ph_3GeH or Bu^n_3SnH, AIBN, 80 °C

Scheme 25

8.1.4 REARRANGEMENTS OF VINYLOXIRANES

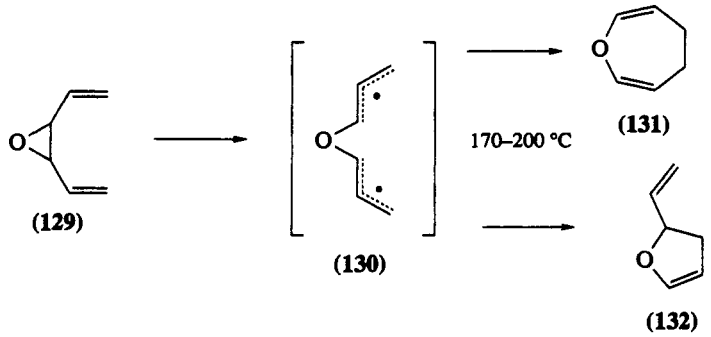
Rearrangements of vinyloxiranes proceed by analogy with the corresponding vinylcyclopropane reorganization with two notable exceptions: first, they generally require lower activation energy and therefore take place under milder conditions, and, second, most of the thermal rearrangements proceed through zwitterionic or ylide-like intermediates, which are uncommon in carbocyclic cases. The nucleophilic opening of systems such as (**128**) is more complex because of the coordinative abilities of oxygen and the increased number of nucleophilic interactions that are possible (Scheme 26). Nevertheless, some parallel behavior and predictability in vinyloxirane rearrangements are available.



Scheme 26

8.1.4.1 Thermal Isomerization

The study of benzene oxide–oxepin tautomerism, reviewed in the late 1960s, revealed a competing pathway in the rearrangements of *trans*-divinyloxiranes of type (**129**; Scheme 27).[165,166] The corresponding *cis* isomer gave only oxepin (**131**), whereas the *trans* isomer gave a 7:3 mixture of dihydrofuran (**132**) and oxepin (**131**). The activation parameters implied that the intermediate was biradical (**130**) (*cis*-oxide: $\Delta H^{\ddagger} = 24.6$ kcal mol^{-1}, $\Delta S^{\ddagger} = -11.3$ cal deg^{-1} mol^{-1}; *trans*-oxide: $\Delta H^{\ddagger} = 36$ kcal mol^{-1}, $\Delta S^{\ddagger} = -0.4$ cal deg^{-1} mol^{-1}).[165] These values indicate processes far lower in energy than those operating in the vinylcyclopropane rearrangement, while their difference (11 kcal mol^{-1}) led to the conclusion that the rearrangement was concerted for the *syn* isomer and biradical for the *trans* compound.

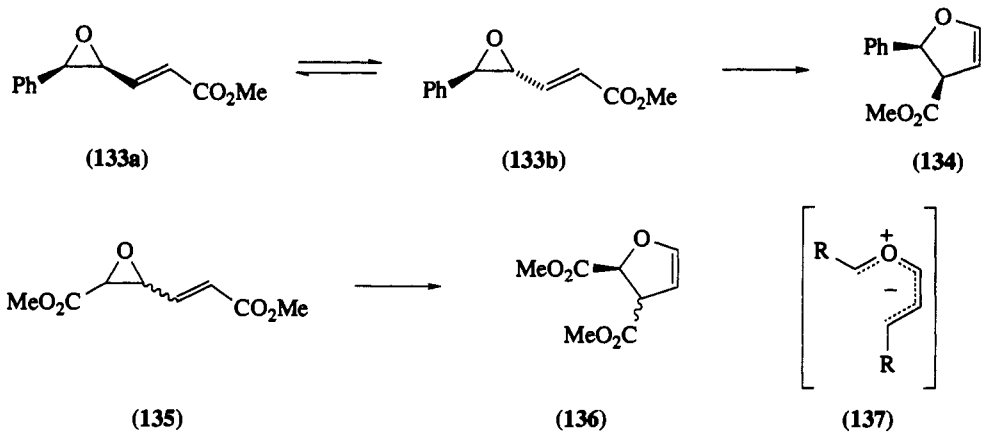


Scheme 27

The mechanism has since been studied on a number of occasions, and it is generally agreed that concerted, electrocyclic closures of ylides are operating in the formation of either oxepins or vinylfurans.[167,168–171] The rate of racemization of optically pure vinyloxiranes has been shown to be six times faster than the isomerization to the dihydrofuran.[167] Alternatively, cleavage of a vinyloxirane to a carbon–oxygen diradical pair or to a carbene–carbonyl pair has been considered for processes that do *not* usually lead to the formation of dihydrofuran[167,169,172] (though there is a notable exception[172]). Corresponding [1,5] shift pathways are also known for those oxiranes that contain a *cis*-oriented alkyl group with at least one hydrogen.[169]

The regio- and stereo-selectivity of this rearrangement has been addressed and found to be excellent.[168] Thus either isomer of vinyloxirane (**133**) yielded dihydrofuran (**134**) stereoselectivity, whereas the rearrangements of vinyloxiranes (**135**) led to a mixture of *cis* and *trans* isomers (Scheme 28). (*Cis*/*trans* isomerization was also accomplished photochemically.)[173] The results were rationalized by involving ylides of type (**137**) and their allowed $[2\pi_s + 2\sigma_a]$ or $[2\pi_a + 2\sigma_s]$ closures for the former case and biradicals for the latter, although the epimerization may have taken place after the rearrangement because of the presence of an acidic proton.[168]

A number of substituents can be placed on the periphery of the vinyloxirane system. For example, extensively studied were alkynyl- and dienyl-oxiranes of the general structures represented by (**138a**) to

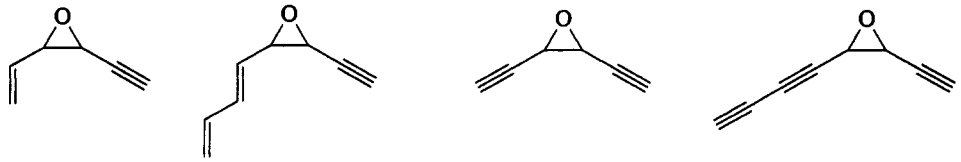


(133a) (133b) (134)

(135) (136) (137)

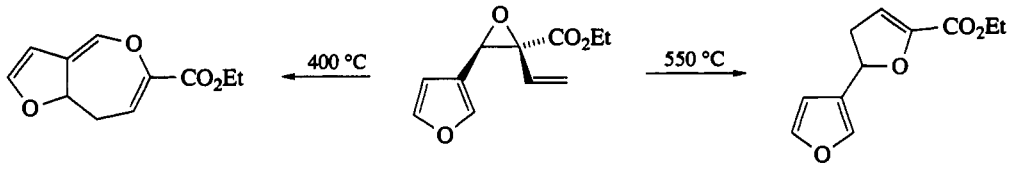
Scheme 28

(**138d**). Their isomerization to various oxidation states of oxepins competed in some cases with the formation of the corresponding vinylfurans.[168,169,171,174,175]



(138a) (138b) (138c) (138d)

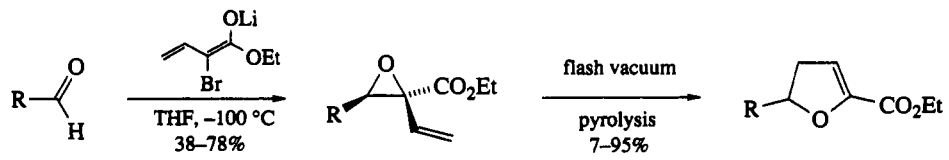
The control of furan *versus* oxepin manifolds has been addressed recently. Vinyloxiranes of type (**139**) yielded oxepins (**140**) at lower temperatures, whereas higher temperatures gave dihydrofurans (**141**; Scheme 29),[176] indicating that the Cope-type rearrangement of *cis*-divinyloxirane may be controlled by precisely defining the temperature profile of the flash vacuum pyrolysis.[176,177]



(140) (139) (141)

Scheme 29

A [2 + 3] dihydrofuran annulation methodology was recently developed based on this rearrangement. Divinyloxiranes (**142**) were generated by the stereospecific addition of the lithium dienolate of ethyl α-bromocrotonate to aldehydes, and the subsequent pyrolysis to dihydrofurans (**143**; Scheme 30) occurred in excellent isolated yields (except for R = Bu^n, Pr^i).[176]



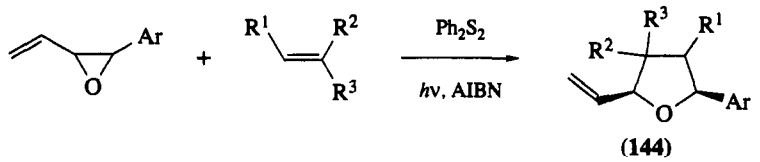
(single isomer)

(142) (143)

R = Bu^n, Pr^i, Ph, CH_2=CH, 2-furyl, 3-furyl

Scheme 30

Radical addition of alkenes to vinyloxiranes to yield tetrahydrofurans was reported in analogy to the similar reaction of vinylcyclopropanes (equation 45),[161] with the same regio- and stereo-selectivity (with a predominance of *syn* isomers having the regiochemistry indicated in **144**).[162] Radical polymerization of vinyloxiranes has also been reported.[178] The rearrangements of vinylthiiranes proceed in a similar fashion to those of vinyloxiranes. The general field of thermal rearrangements of three-membered heterocycles containing oxygen, sulfur or nitrogen has recently been reviewed.[179] A vast majority of the literature on the rearrangements of vinyloxirane systems deals with those cases where Cope-like rearrangements of the divinyloxiranes are possible. The expansions of such systems to oxepins and further rearrangements and transmutations of, for example, vinylalkynyloxiranes to vinylcyclopropyl aldehydes have also been studied and reviewed.[175,177,179] Some of the reactivity patterns of vinyloxiranes and their derivatives are shown in Table 6.



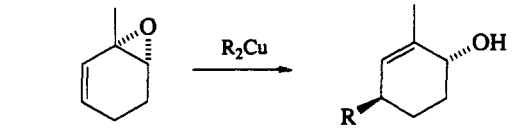
(144) (45)

8.1.4.2 Nucleophilic Opening

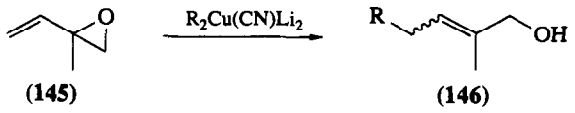
Vinyloxiranes react with nucleophiles in three regiochemically distinct ways: with α, β and vinylogous modes of opening. The subject has been of considerable interest in the context of acyclic stereoselection and generation of allylic alcohols in an iterative fashion.

Cyclic vinyloxiranes react with organocuprates with inversion of configuration (*anti*) and in a vinylogous mode (equation 46), not by the expected S_N2 reaction that simple oxiranes are known to undergo. This subject has recently been summarized.[185]

The conformation of vinyloxirane is restricted in such cases, whereas the acyclic vinyloxiranes, like vinylcyclopropanes, enjoy a conformational equilibrium, which determines the (*E*):(*Z*) ratio of the allylic alcohols that result from interactions with nucleophiles. For example, vinyloxirane (**145**) gave a 4:1 (*E*):(*Z*) ratio of allylic alcohols (**146**; equation 47) with $Ph_2Cu(CN)Li_2$, but a 7:2 ratio when $(2\text{-}C_5H_5NCH_2)_2Cu(CN)Li_2$ was used (Scheme 31).[186]

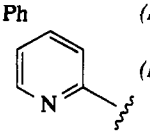


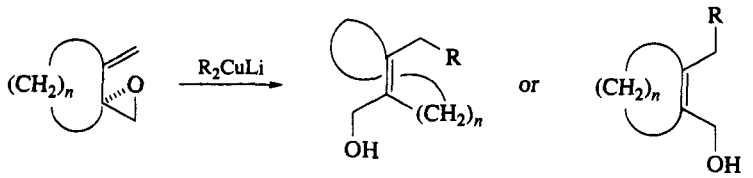
(46)



(145) (146) (47)

R = Ph (*E*):(*Z*) = 3.4:1

R =  (*E*):(*Z*) = 7:2



(48)

n	*ee* (%)	*trans*:*cis*
10, 12	82–92	99:1
14	racemization	89:11

Table 6 Rearrangements of Vinyloxiranes and Related Compounds

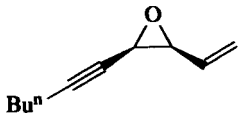
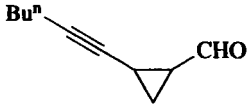
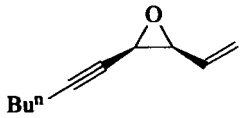
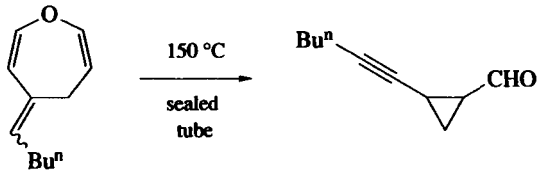
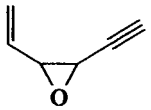
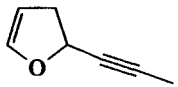
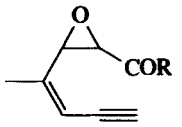
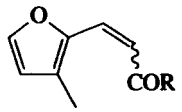
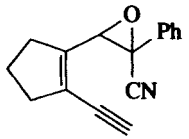
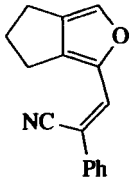
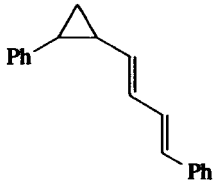
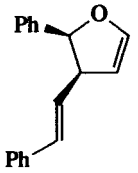
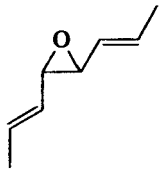
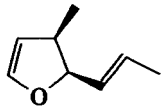
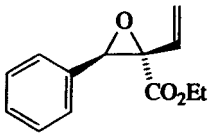
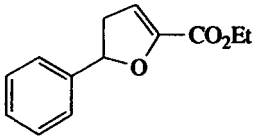
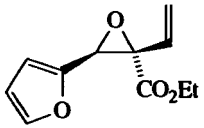
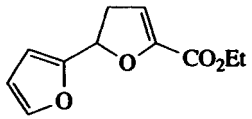
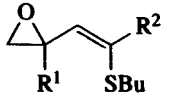
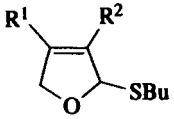
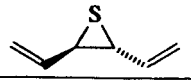
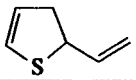
Vinyloxirane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	335 °C, gas phase		83	175
	150 °C, CCl_4, sealed tube		90	175
	405 °C		87	180
	350 °C	 *(E):(Z)* = 11:1	70–80	172
	170 °C	 *(Z):(E)* = 9:1	85	170

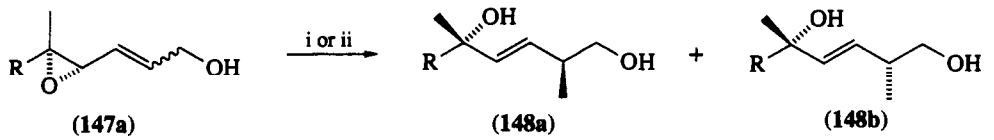
Table 6 *(continued)*

Vinyloxirane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	170 °C		100	181
	210–250 °C		70–80	182
	500 °C, 0.02 mmHg		95	176
	500 °C, 0.02 mmHg		69	176
	$HgSO_4$, H_2O		—	183
	340–360 °C		—	184

Stereoselective S_N2' addition of cuprates has been documented for vinyloxiranes such as (**147a**) and (**147b**). The pairs (**148**) and (**149**) are enantiomeric, so this selectivity also reflects a controlled access to all four enantiomers of these alcohols. The normal S_N2 opening or elimination pathways were suppressed in these systems.[185] The selectivity increased with (*Z*)-isomers in all cases studied. The stereochemistry of the cuprate additions to optically pure macrocyclic (and exocyclic) vinyloxiranes has also been investigated (equation 48).[187]

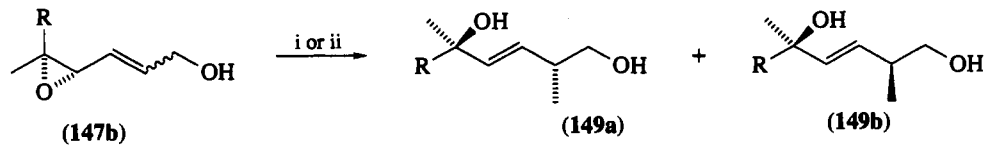
Palladium-catalyzed nucleophilic opening of vinyloxiranes received much attention and led to the development of a methodology for *cis*-hydroxylation, as shown in Scheme 32. In this procedure the normally expected distal approach of the oxygen nucleophile is suppressed by intramolecular trapping with carbonate.[188]

Carbon as well as amine nucleophiles add to vinyloxiranes in a vinylogous sense with palladium(0) catalysis. In all such cases the initial nucleophilic attack on the vinyloxirane probably proceeds as depicted in Scheme 25, and its success would be governed by the usual steric effects. Some useful examples are shown in Table 7.



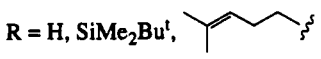
(**147a**) (**148a**) (**148b**)

(147a)	*(148a):(148b)*	*Yield* (%)
(E)	84:16	81
(Z)	1:99	88



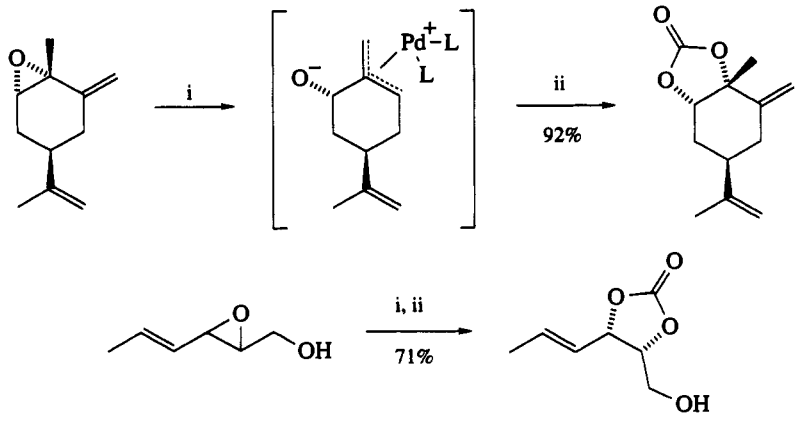
(**147b**) (**149a**) (**149b**)

(147b)	*(149a):(149b)*	*Yield* (%)
(E)	14:86	95
(Z)	97:3	95



i, $LiMe_2Cu$, THF/Et_2O (4:1), 0 °C; ii, LiMeCuCN, Et_2O, 0 °C

Scheme 31



i, $[Pd\{P(OPr^i)_3\}_4]$, 30 min, THF, r.t; ii, CO_2

Scheme 32

Table 7 Addition of Nucleophiles to Vinyloxiranes

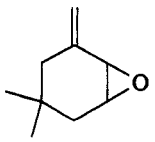
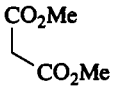
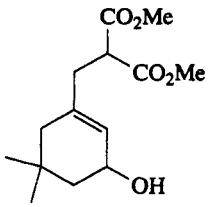
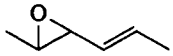
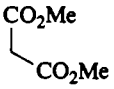
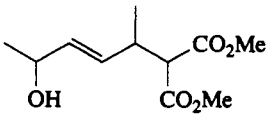
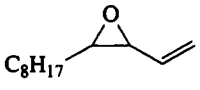
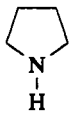
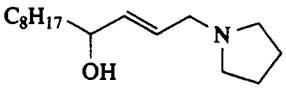
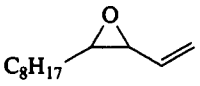
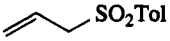
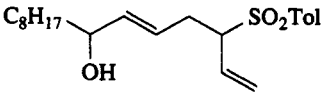
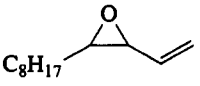
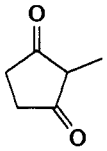
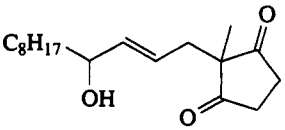
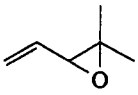
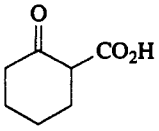
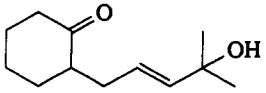
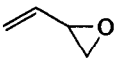
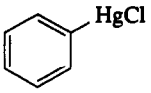
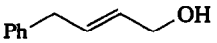
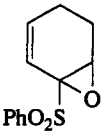
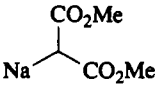
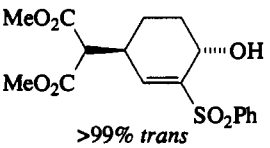
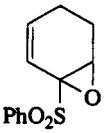
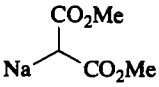
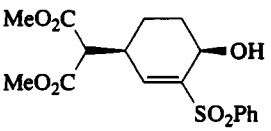
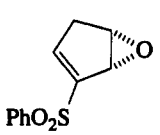
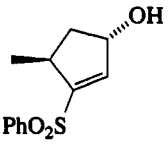
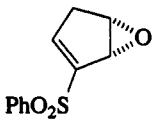
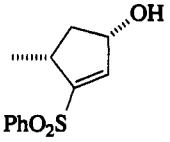
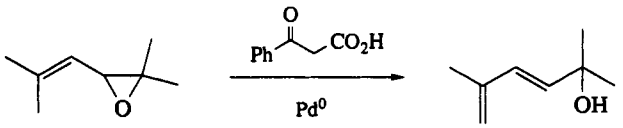
Vinyloxirane	*Nucleophile*	*Catalyst*	*Product*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$		85	189
		$[Pd(PPh_3)_4]$		76	189
		$[Pd(PPh_3)_4]$		92	190
		$[Pd_3(TBAA)_3]$		64	190
		$[Pd(PPh_3)_4]$	 *(E):(Z)* = 98:2	91	190
		$[Pd(PPh_3)_4]$		54	191
		Li_2PdCl_4		76	192
		(no catalyst)	 >99% *trans*	89	193
		$Pd(DBA)_2$		85	193

Table 7 *(continued)*

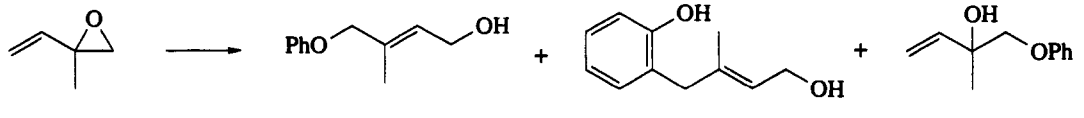
Vinyloxirane	*Nucleophile*	*Catalyst*	*Product*	*Yield (%)*	*Ref.*
	Me_2CuLi	Me_3Al	 *trans:cis* = 92:8	80	194
	MeLi	$LiClO_4$	 *cis:trans* = 95:5	81	194

For the sake of comparison, the regio- and stereo-selectivity of some nucleophilic openings of vinyloxiranes with organometallic reagents derived from copper, lithium, sodium and other metals indicate the control available under some conditions. Complete control of diastereoselectivity in the opening of cyclic vinyloxiranes is available, for example by utilizing palladium(0)-catalyzed conditions in the reaction of the sodium salt of dimethyl malonate with cyclic vinyloxiranes.[193,194] Increased substitution on the vinyl portion of the vinyloxirane leads to isomerization with opening, as in the case of the disubstituted vinyloxirane (**150**; equation 49).[191]



(**150**) (49)

Other nucleophilic reagents effect the opening of vinyloxiranes in a similar fashion. Sodium phenoxide reacts with vinyloxiranes as illustrated in Scheme 33, with some control of regiochemistry.[195] Vinylaluminum reagents give S_N2' products exclusively,[196] whereas alkynides of titanium open epoxides such as (**151**) regioselectively by an S_N2 process.[197] Vinyloxiranes react with allylstannanes in the presence of Lewis acids with excellent regioselectivity, as shown in Scheme 34. Similar selectivity for the internal substitution was observed for allylsilanes.[198] In contrast, Grignard or cuprate reagents favor the S_N2' opening leading to (**153b**) in 70:30 and 80:20 ratios, respectively. Rhodium(I)-catalyzed rearrangements of vinyloxiranes yield α,β-unsaturated aldehydes and ketones.[199]



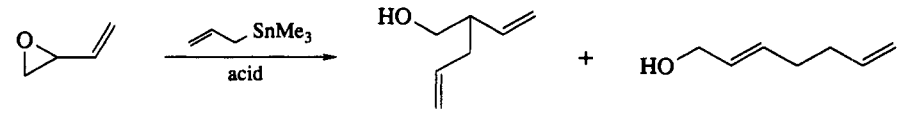
(**151**) (**152a**) (**152b**) (**152c**)

Conditions	*(152a) (%)*	*(152b) (%)*	*(152c) (%)*	*% yield*
PhONa, DMSO	–	–	100	61
PhONa, Et_2O	6	45	49	43
PhONa, CF_3CH_2OH	4	76	20	53

Scheme 33

Cyclic vinyloxiranes were opened with *t*-butyldimethylsilyl cyanide to yield isonitriles, as shown in equation (50).[200] The opening of vinyloxiranes like (**142**) with TMS-I, TMS-I/$TiCl_4$ and SmI_2 was attempted in an effort to provide a topographical option for the [2 + 3] dihydrofuran annulation. While the 2,5-substitution pattern inherent in (**143**) is furnished through thermolytic rearrangements, the 2,3-isomer would result from an S_N2' opening of (**142**) to allylic iodide (**154**), which would cyclize to 2,3-function-

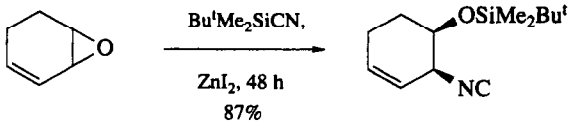
alized dihydrofuran (**155**; Scheme 35).[128] Only marginal results were obtained under conditions adapted from similar opening of vinylcyclopropanes with trimethylsilyl iodide and titanium tetrachloride.[128] However, SmI_2 opening consistently gave the regioisomer (**156**),[201] albeit in poor yields perhaps because of the reducing properties of this reagent.[202]



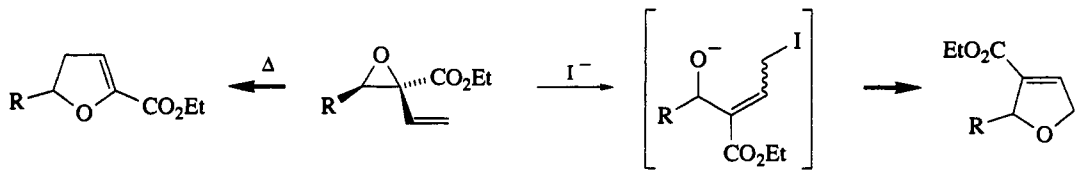
(**153a**) (**153b**)

Acid	*(153a)* (%)	*(153b)* (%)
BF_3	91	0
$AlCl_3$	52	0
$TiCl_4$	14	0

Scheme 34

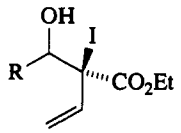


(50)



(**143**) (**142**) (**154**) (**155**)

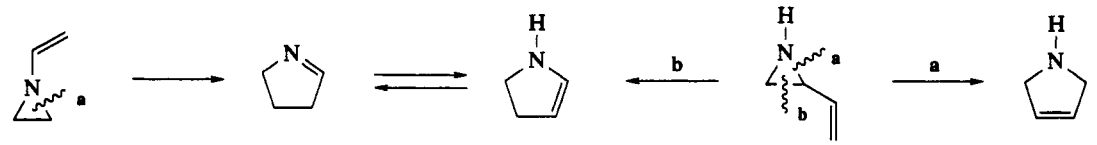
Scheme 35



(**156**)

8.1.5 REARRANGEMENTS OF VINYLAZIRIDINES

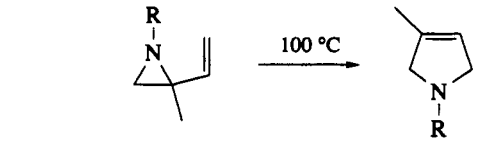
Like vinyloxiranes, vinylaziridines are subject to a number of rearrangements that parallel the pathways available to vinylcyclopropanes. Unlike vinyloxiranes, however, vinylaziridines undergo extremely well controlled nucleophilic opening to furnish pyrrolines under nonthermolytic conditions. They are easily prepared from alkenes and azides *via* triazolines.[203] Because of the valency of nitrogen there are two topographical isomers possible (**157** or **159**), each leading to a different tautomer of pyrroline (**158** or **160**), and an additional isomer, 3-pyrroline (**161**), available through cleavage of bond **a** in (**159**; Scheme 36). This remarkable property of vinylaziridines translates into selective preparation of all possible isomers of pyrroline, 1-, 2- and 3-pyrroline, by careful 'tuning' of the reactivity of (**157**) and (**159**) through substituent effects and the knowledge of probable reaction intermediates. Much of the thermal and photochemical behavior of vinylaziridines may be rationalized through either diradical or zwitterionic (azomethine ylide) intermediates. This subject has been thoroughly summarized.[41,179,204]



(**157**) (**158**) (**160**) (**159**) (**161**)

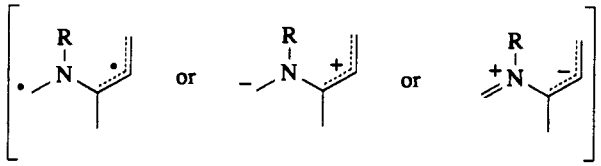
Scheme 36

Vinylaziridines such as (**162**) have been rearranged thermally to 3-pyrrolines (equation 51),[205,206] presumably through one of the species (**164**). Substituents play an important role in the likelihood of these intermediates.[207] The energy of activation for carbon–nitrogen bond cleavage has been estimated to be 12–14 kcal mol^{-1} (compared with 27 kcal mol^{-1} for cyclopropane).[208] Vinylaziridines of type (**165**; R = alkyl) furnish 1-pyrrolines (**166**) or, if X is another heteroatom, the corresponding heterocyclopentenes (equation 52; Section 8.1.7).[206,209]

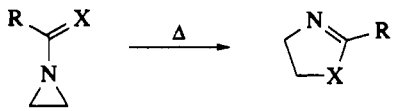


(51)

(**162**) (**163**)



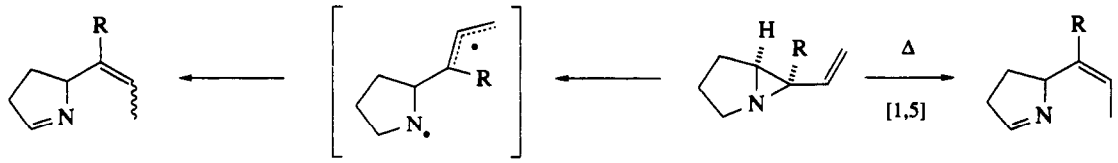
(**164**)



(52)

(**165**) (**166**) X = CR_2, O, S, NR

The competing reaction involves the formation of imines (presumably *via* diradicals and hydrogen migration), as proposed by Logothetis to account for the formation of imines in the thermolysis of aziridines.[210] Imine formation is sometimes observed as a competing pathway in the thermolysis of *N*-substituted vinylaziridines,[211] and can also be rationalized by a process analogous to a [1,5] homodienyl shift.[179,212,213] In cyclic systems having proper stereochemistry (*endo*) this process may predominate, as evidenced by the isolation of only the (*E*)-alkene (**168**; R = CO_2Et; Scheme 37).[212,213]



(**168**) (**167**) R = H, CO_2Et (**168**)

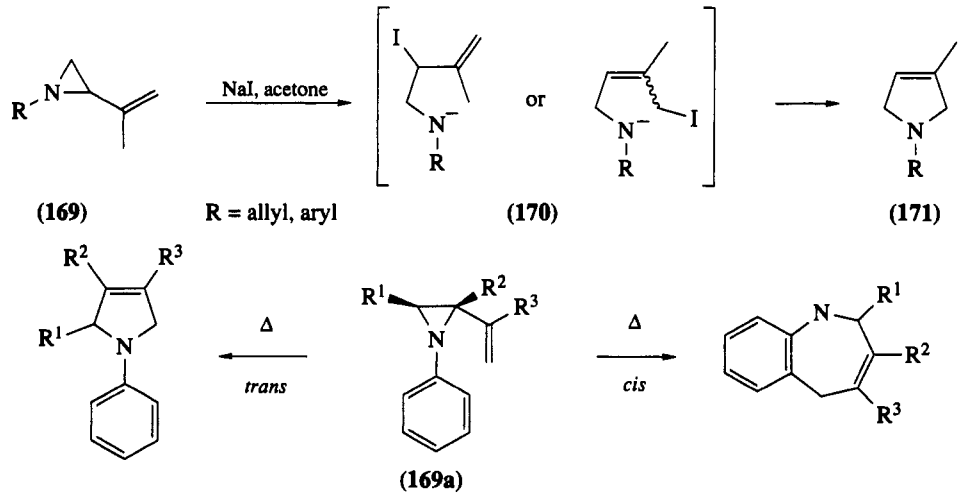
Scheme 37

Reaction of vinylaziridines (**169**) with NaI in refluxing acetone led to 3-pyrrolines (**171**; Scheme 38).[214,215] When the *N*-substituent contains an additional alkene as in the case of (**169a**), the possibility of an intervening Cope-like rearrangement will complicate pyrroline formation. The selectivity between these two pathways usually depends on the stereochemistry of the vinylaziridine and the temperature of the rearrangement. (Higher temperatures favor the pyrroline formation as the Cope rearrangement is frequently reversible.) No *cis/trans* isomerization was observed in the case of (**169a**).[216] The divinylaziridine rearrangement as well as the [1,5] shift pathways of vinylaziridines can be controlled according to the principles found valid with vinylcyclopropanes or vinyloxiranes. Some aspects of the rearrangements of vinylaziridines have been reviewed.[179,180]

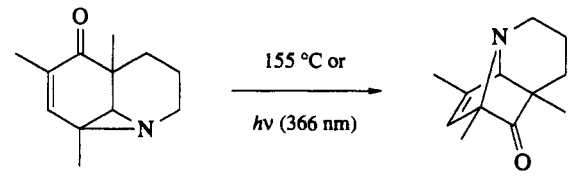
Photochemical rearrangements have also been reported, as shown in equation (53).[217,218] Transition metal catalyzed rearrangement [palladium(0)] of a dienylaziridine has been reported in one case,[219] and a radical opening of a dienylaziridine led to pyrroline formation under the conditions of radical initiation with AIBN/Ph_3SnH (equation 54).[164] For those vinylaziridines that contain additional unsaturation, the corresponding aza equivalent of a divinylcyclopropane Cope rearrangement is the usual pathway.[220] The subject of heterodivinylcyclopropane Cope rearrangement is covered in detail elsewhere.[177] The

pyrroline–azepine pathways are usually controllable by determining temperature profiles for the reactions. Higher temperatures favor pyrroline formation.

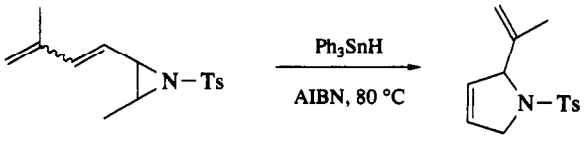
Compared to vinylcyclopropanes, vinylaziridines have not enjoyed wide applicability in synthetic schemes or annulation prior to the discovery and development of [4 + 1] pyrroline annulation (Scheme 39).[41,212,213,221-223] Activation of the dienes with electron-withdrawing groups proved necessary for the formation of vinylaziridines (**173**) and (**176**) (through intermediate triazolines and their thermal decomposition).[223] Noteworthy is the selectivity in bond activation in (**173**) and (**176**). Whereas thermolysis of (**173**) leads to pyrrolizidine (**178**),[212,213,223] through the probable agency of azomethine ylide (**179**), the nucleophilic opening leads exclusively to (**174**) through intermediate allylic iodides (**180**), which are produced as mixtures of (*E*)- and (*Z*)-isomers but are converted to (**174**) through equilibration and recycling of the (*Z*)-isomer (Scheme 40).[221]



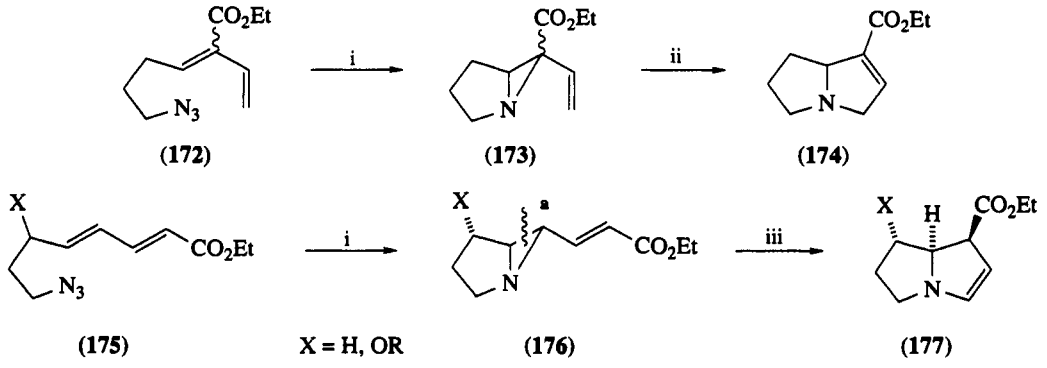
Scheme 38



(53)

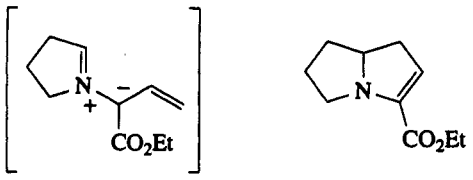


(54)

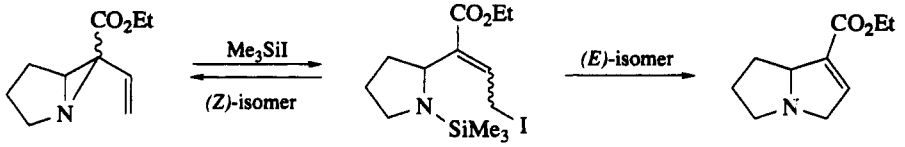


i, toluene, Δ; ii, Me_3SiI, CH_2Cl_2, –50 °C; iii, 485 °C

Scheme 39



(179) (178)

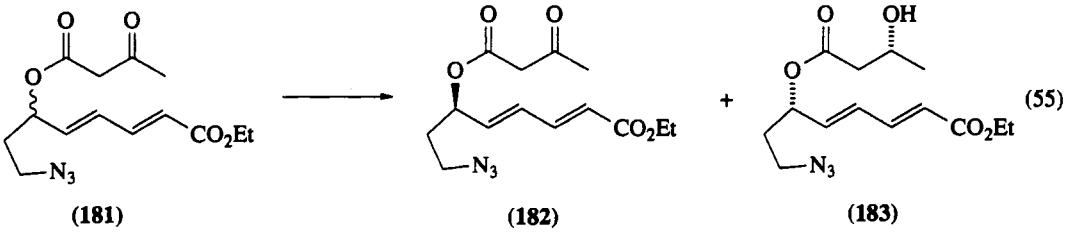


(173) (180) (174)

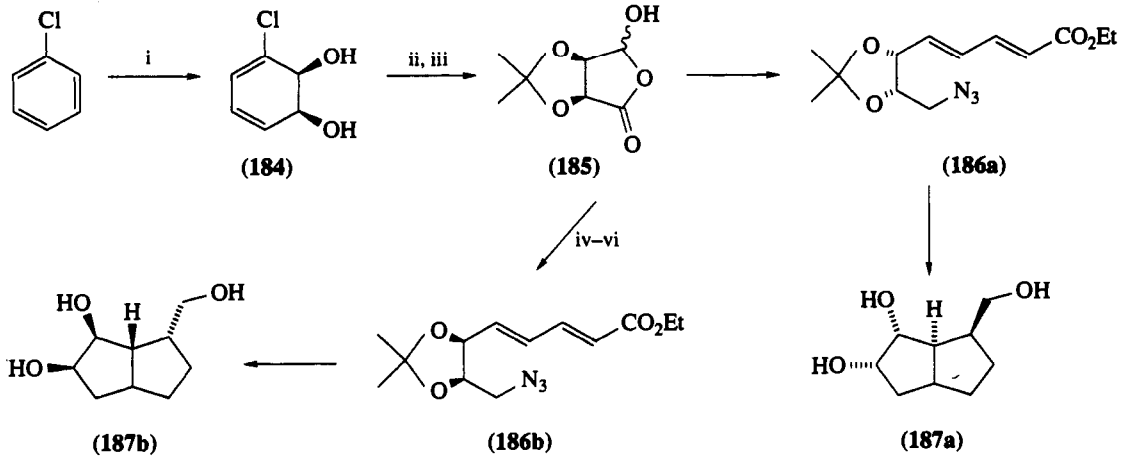
Scheme 40

When oxygenated diene (**175**; X = OR) was utilized, a single isomer of pyrrolizidine (**177**) was formed on thermolysis.[222] (The stereochemistry of the carboxylate was rationalized by the *endo* effect.) Thus a highly selective procedure for the exhaustive synthesis of pyrrolizidine alkaloids was developed (see Sections 8.1.8 and 8.1.9).[41]

Azides (**175**; X = OH) were resolved through microbial reduction of β-keto esters (**181**) with baker's yeast and provided the azido dienes (**182**) and (**183**) in about 70% *ee* in an approach to enantiocontrolled synthesis of pyrrolizidines (equation 55).[224] In this series extensive racemization took place prior to or during the vinylaziridine formation. A conversion of chlorobenzenediol (**184**) to lactone (**185**) and elaboration of this material to either enantiomer of trihydroxyheliotridane (**187**) constituted a fully enantiocontrolled approach to both enantiomeric series of highly oxygenated pyrrolizidine alkaloids (Scheme 41).[225]



(181) (182) (183) (55)

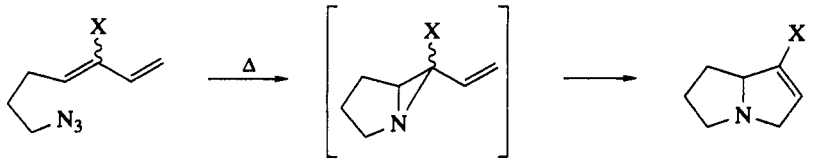


(184) (185) (186a) (186b) (187a) (187b)

i, *Pseudomonas putida* 39D; ii, dimethoxypropane, HCl; iii, O_3, Me_2S; iv, $Ph_3PCH_2CHCHCO_2Et$, Br^-; v, BH_3, THF; vi, MsCl, Et_3N, then NaN_3

Scheme 41

Recently, compounds of type (**188**; Scheme 42) have been found to yield pyrrolines (**190**) through the vinylaziridine–pyrroline rearrangement of (**189**) (not isolated) in refluxing $CHCl_3$ or THF, albeit in moderate yields (31–62%).[226] The heteroatom substitution apparently accelerates the rearrangement.



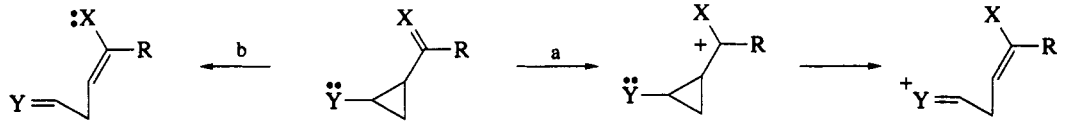
(**188**) (**189**) (**190**)

X = SPh, $OSiMe_2Bu^t$, $O(CH_2)_2OEt$

Scheme 42

8.1.6 CYCLOPROPYL-CARBONYLS AND -IMINES

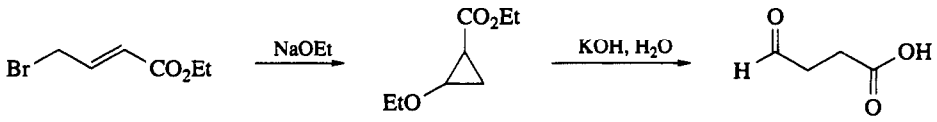
When the vinylcyclopropane system contains a heteroatom within the alkene portion, it is highly susceptible to rearrangements governed by donor–acceptor principles. Under appropriate conditions the ring closure of systems such as (**191**), in addition to the normal diradical pathways, can occur by two additional mechanisms: unravelling of a cyclopropylcarbinyl cation system (path a) or the action of a lone pair of an additional donor atom (or a full anion) resembling the unravelling of a cyclopropylcarbinyl anion (path b; Scheme 43). Ideally, both processes can reinforce one another to lead to a facile rearrangement of systems such as (**192**) to the corresponding 1,4-dicarbonyl compounds, reported as early as 1938 (Scheme 44).[227] Recognition that the cyclopropylcarbinyl cation unravels to provide additional unsaturation led to the methodology of acid- or base-catalyzed unravelling of systems of type (**192a**) to corresponding β,γ-unsaturated carbonyls (equation 56).[228]



(**191**)

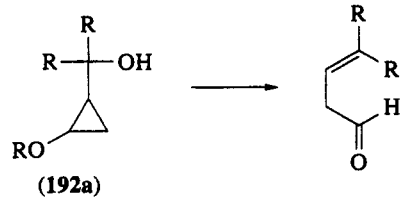
X = O, NR; R = alkyl, aryl, OR

Scheme 43



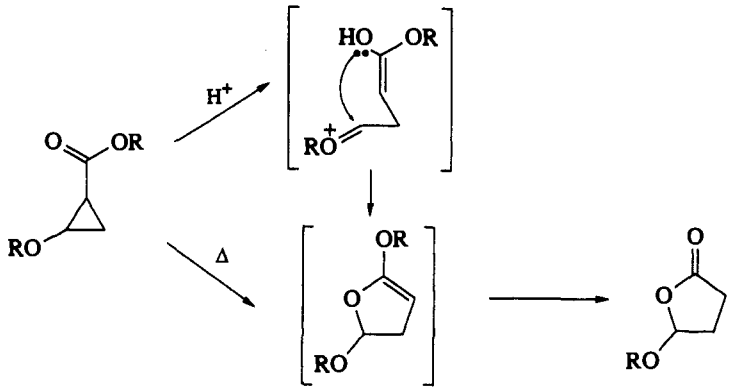
(**192**)

Scheme 44



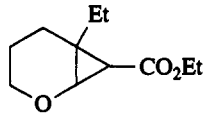
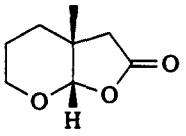
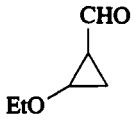
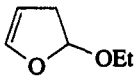
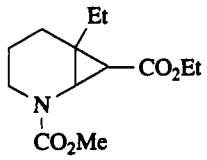
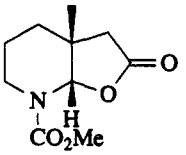
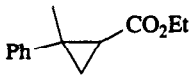
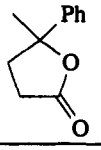
(**192a**) (56)

The above processes constitute the foundation on which Wenkert developed a general synthetic methodology applicable to terpenoid and alkaloid syntheses.[37,38] In some instances, the carbonyl can be viewed as a vinyl moiety participating in the overall heterovinylcyclopropane–cyclopentene rearrangement, as shown in Scheme 45, even though the mechanism involves the cyclopropylcarbinyl rearrangement. Some applications of this reaction are shown in Table 8.

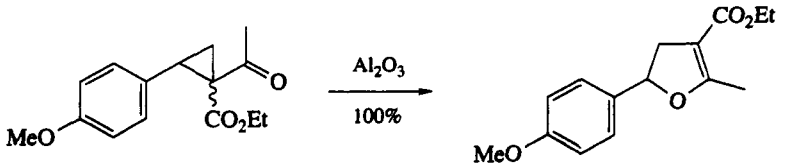


Scheme 45

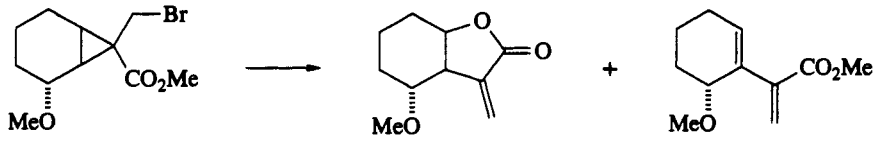
Table 8 Synthesis of Dihydrofurans

Cyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	H^+		93	229
	H^+		70–74	230, 231
	H^+ or OH^-		88	232
	HCl, Δ		80	233

Alumina-catalyzed conversion of either isomer of (**193**) to dihydrofuran (**194**) was reported as an alternative to acid-catalyzed conditions (equation 57).[234] A methodology of α-methylene lactone synthesis relies on the solvolysis of cyclopropyl esters of type (**195**) to give α-methylene lactone (**196**) with Li_2CO_3 in dioxane (equation 58). The formation of the undesired diene (**197**) was diminished by the use of $AgClO_4$.[235]

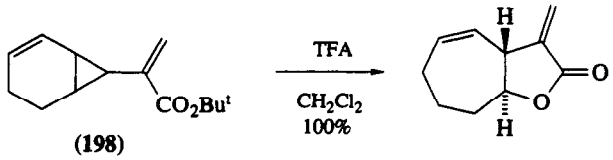


(193) (194) (57)

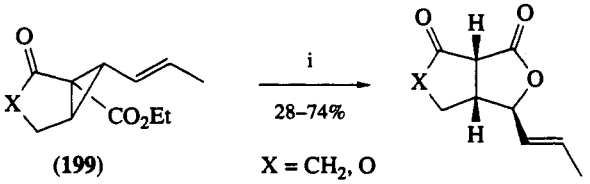


(195) (196) 85% (197) 15% (58)

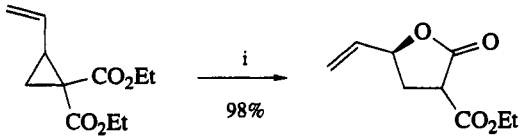
Vinylcyclopropanes containing carboxylates react selectively through the agency of the carbonyl group in acid-catalyzed rearrangements, as shown in equation (59).[236] It is noteworthy that neither of the two alternative pathways, the divinylcyclopropane Cope rearrangement of (**198**) or cyclopentene rearrangement(s), takes place. Further examples of carboxylate over vinyl selectivity are seen in the rearrangements of cyclopropanes (**199**) and (**200**) to the corresponding tetrahydrofuranones (Scheme 46).[237]



(198) (59)



(199) X = CH_2, O

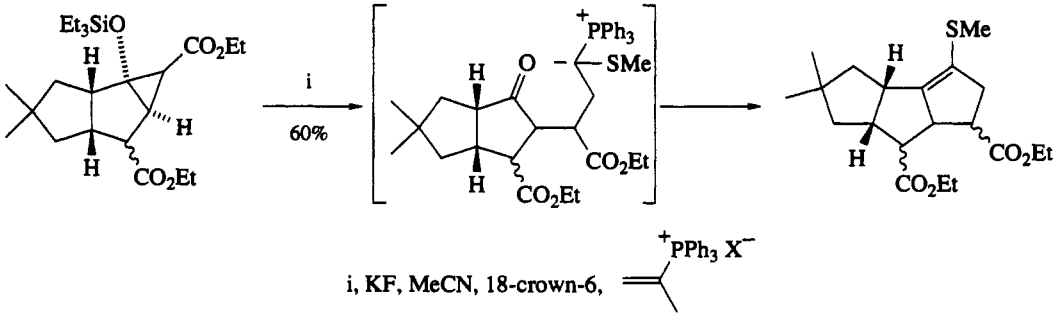


(200)

i, $(Me_3SiO)_2SO_2$, $Cl(CH_2)_2Cl$, reflux, 1 h

Scheme 46

Donor–acceptor-substituted heterovinylcyclopropanes also react by addition or trapping of any intermediates generated during these rearrangements, as the example in Scheme 47 indicates.[238] Further examples of the ring-opening modes and subsequent functionalizations have been exhaustively reviewed.[16,21,45] The examples in Table 9 show the additional modes of reactivity of carbonylcyclopropanes: reduction of cyclopropane, nucleophilic and electrophilic ring opening and thermal reactions. Recent reviews can be consulted for further examples.[12,16,21,251]



Scheme 47

Table 9 Some Reactions of Carbonyl Cyclopropanes

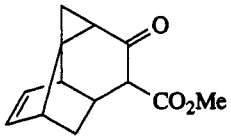
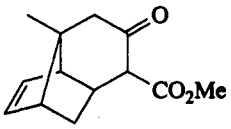
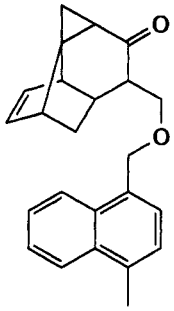
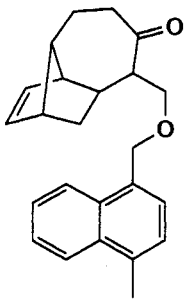
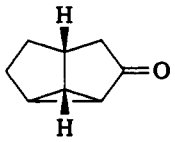
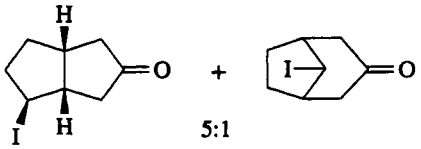
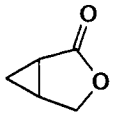
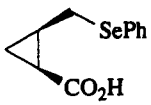
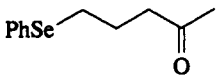
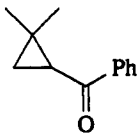
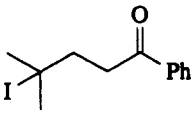
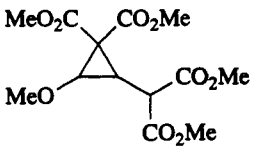
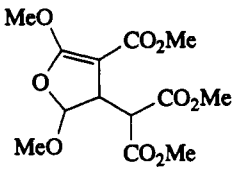
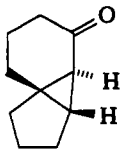
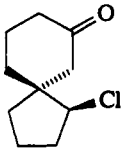
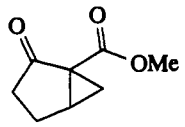
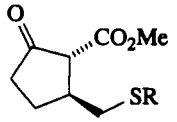
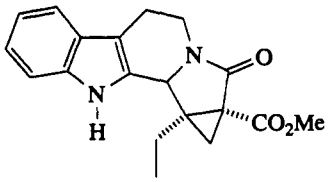
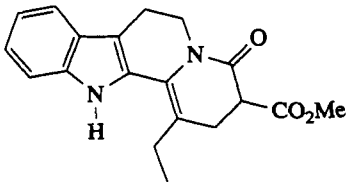
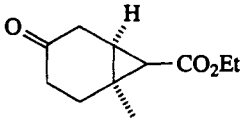
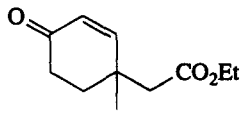
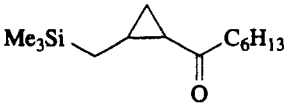
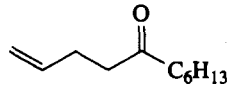
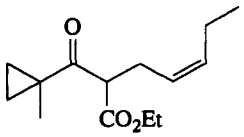
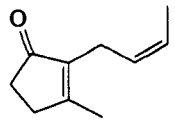
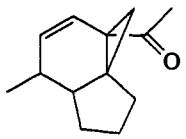
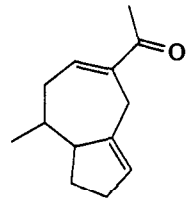
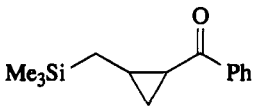
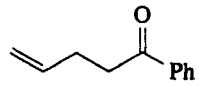
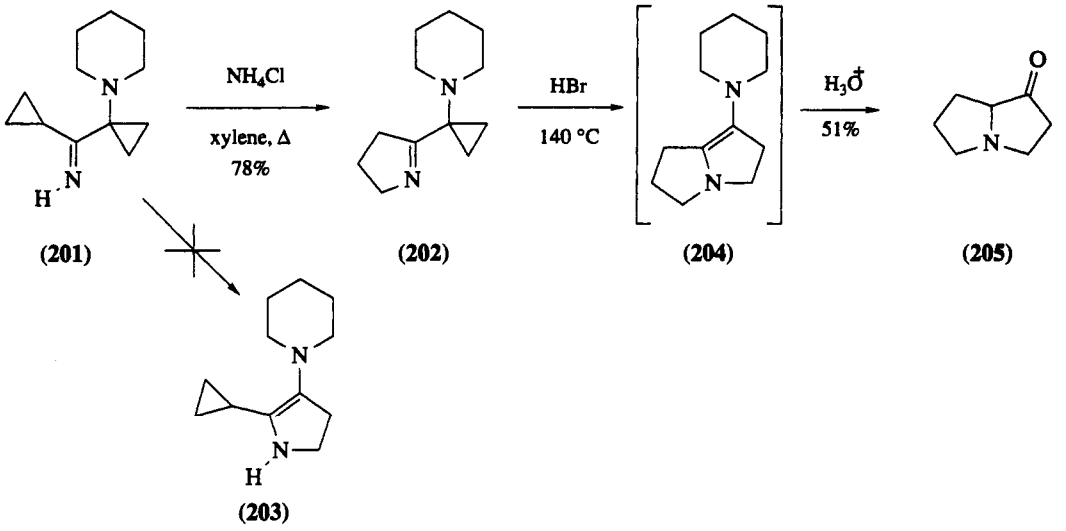
Cyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	H_2, Pd/C, MeOH		95	239
	$CrSO_4$, Zn, DMF/H_2O (2:1)		84	239
	Bu^tMe_2SiI	 5:1	84	240
	PhSeNa, DMF, 120 °C		81	241
	PhSeLi		90	242
	i, Me_3SiI, CCl_4; ii, H_2O		98	243
	DMSO, 25 °C		—	244
	conc. HCl, Et_2O		72	245

Table 9 *(continued)*

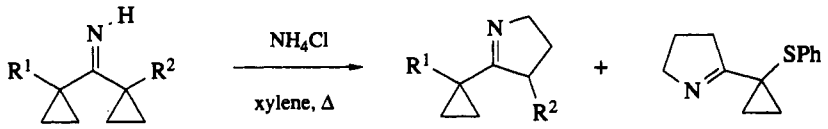
Cyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	RSH (R = Ph, Bn, n-hexyl)		61–93	246
	TFA, CH_2Cl_2, r.t.		80	247
	NaOAc (catalyst), EtOH		87	248
	BF_3, AcOH, CH_2Cl_2, 0 °C		—	249
	515 °C, 1–3 torr, glass wool		—	250
	175 °C		70	75
	BF_3•OEt_2, AcOH		81	249

Rearrangements of cyclopropylimines have been studied in the context of the effects of heteroatom substitution on rearrangements of cyclopropanes quite recently, even though the cyclopropylimine–pyrroline rearrangement (the Cloke rearrangement) has been known since 1929, long before the discovery of the parent vinylcyclopropane system.[252] Dicyclopropylimine (**201**) rearranged to pyrroline (**202**), not to 2-pyrroline (**203**), the product expected from the accelerating effect of the amino substituent (Scheme 48). Further reaction and hydrolysis led to pyrrolizidone (**205**).[253] The effects of substituents (N, S) were investigated on substrates shown in equation (60).[253] Sulfur and nitrogen did not exert an effect of the magnitude expected from similar studies on vinylcyclopropanes, and this may be attributed to the mechanistic duality of this rearrangement, which may involve nucleophilic opening followed by alkylation. The observed preference for the rearrangement of the less-substituted cyclopropane may have its roots in steric effects and the preference for the nucleophilic attack at the less-substituted site. A different result was obtained by Stevens.[254,255] The piperido-substituted cyclopropane in (**206**) rearranged

on thermolysis in the presence of an acid with a non-nucleophilic counterion and gave pyrrole (**207**) upon further, acid-catalyzed elimination (equation 61).[254,255]

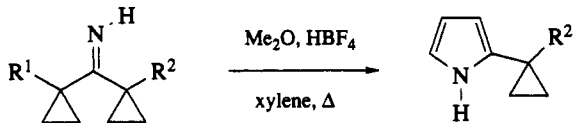


Scheme 48



(60)

(**206a**)	R^1 = piperidinyl, R^2 = H	78%	–
(**206b**)	R^1 = piperidinyl, R^2 = SH	69%	–
(**206c**)	R^1 = H, R^2 = SPh	28%	22%

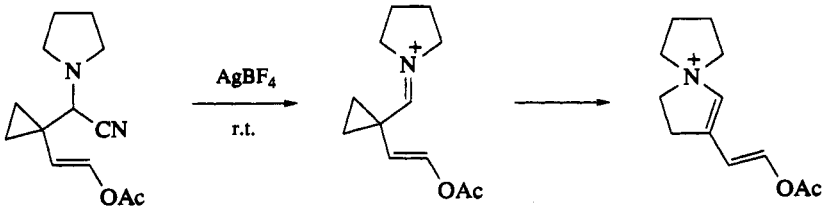


(61)

R^1 = piperidinyl (**207**)

(**206a**)	R^2 = H	32%
(**206b**)	R^2 = SPh	42%

Cyclopropylimines are usually generated by reduction of nitriles or condensation of carbonyl compounds with amines.[255,256] An alternative to this process involves the generation of cyclopropylimmonium salts such as (**209**) at room temperature from cyanohydrin equivalent (**208**; Scheme 49).[257]

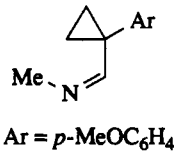
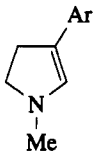
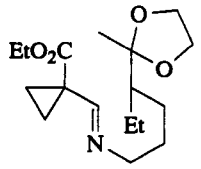
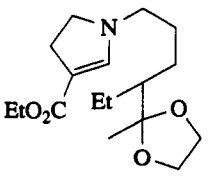
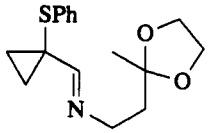
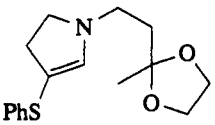


(**208**) (**209**)

Scheme 49

The rearrangement proceeds thermally, under acid catalysis by HBr, NH_4Cl, or *via* nucleophilic opening and reclosure as in the case of vinylaziridines. Some examples of these processes are shown in Table 10. Sulfur substitution has been found effective in accelerating the rearrangement as well as serving as a site of further functionalization. This feature has been especially exhibited in the synthesis of pyrrolizidine and *Amaryllidaceae* alkaloids.[255,256] Section 8.1.9 gives a list of applications.

Table 10 Cyclopropylimine Rearrangement

Cyclopropylimine	*Conditions*	*Product*	*Yield (%)*	*Ref.*
 Ar = *p*-$MeOC_6H_4$	NH_4Cl, 130 °C		100	258, 259
	NH_4Cl, Δ		80	260
	NH_4Cl, Δ		88	261

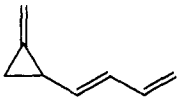
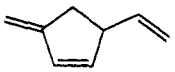
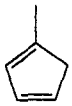
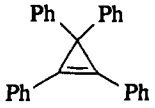
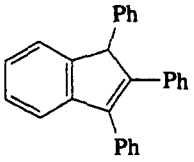
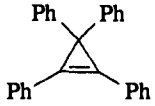
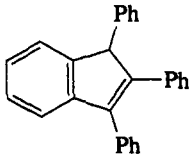
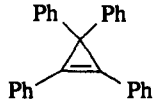
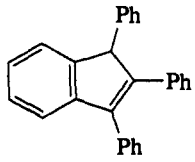
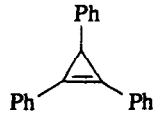
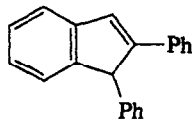
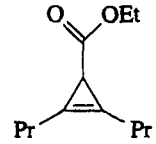
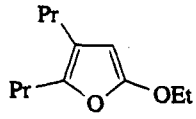
8.1.7 MISCELLANEOUS SYSTEMS

It would be difficult to list all of the cases involving the various combinations of heteroatom substitution in a vinylcyclopropane system. It has been recognized that virtually any heteroatom or any degree of unsaturation can be incorporated into the parent vinylcyclopropane system for almost limitless variability in the type of products that can be expected upon its rearrangements.[42,262] The general transformations depicted in equation (62) have been summarized and reviewed[18,179,263–266] in the context of the synthesis of five-membered heterocycles. Vinylcyclopropenes, methylenevinylcyclopropanes and cyclopropylalkynes all undergo the requisite rearrangements to five-membered rings.[9] The products are the corresponding cyclopentadienes or methylenecyclopentenes and their heteroatom analogs. These topics have been reviewed.[9,13,18,266] The mechanism of these transformations ranges from diradical scission to carbene generation and rearrangement.[18,266,267] Some of the representative transformations are shown in Table 11.

(62)

General discussions and reviews of rearrangements of heterovinylcyclopropane systems with one heteroatom[264] and two or more heteroatoms[263,264,274] not discussed in the previous section are available. Their rearrangements are governed by principles discussed previously, *i.e.* most stable diradical or ylide intermediate or the least-hindered site for nucleophilic attack in the case of nucleophilic openings. The electronegativity of the heteroatom and the conditions of rearrangement determine the regiochemistry of bond cleavage. With systems containing additional unsaturation, the divinylcyclopropane Cope rearrangement remains a viable option.[177] Table 12 lists the rearrangements of various nitrogen-, oxygen-, and sulfur-containing systems. Syntheses of pyrroles,[286] furans[287,288] and thiophenes[289] by the rearrangement of appropriate heterocyclopropanes have been summarized.

Table 11 Rearrangements of Cyclopropenes, Cyclopropylalkynes and Methylenecyclopropanes

Cyclopropane	*Conditions*	*Product(s)*	*Yield (%)*	*Ref.*
	530 °C	1.3:1	67	268
	56 °C		—	269
	$[Pd(DBA)_2]$, 35 °C, 2 h		61	18
	$AgClO_4$, PhH, r.t.		100	270
	200 °C		100	271
	*hν*		46	267
	$[(C_2H_4)PtCl_2]$, $CHCl_3$ r.t., 13 h		—	272
	Cu^I, 100 °C		80	273

The selectivity between five- and seven-membered ring expansions is usually controlled by the parameters discussed for carbocyclic cases; that is, higher temperatures will favor five-membered rings, whereas the Cope-like rearrangements will be reversible at lower temperatures. A regioselectivity between thermal or photochemical rearrangements and metal-mediated rearrangements is illustrated by the examples involving azirines in equation (63)[290] and Scheme 50.[291] In the rearrangements of azirines the stereochemistry of the alkene determines the regiochemistry of the rearrangement and therefore the pathway (formation of five- *versus* seven-membered rings) to products, as shown in equations (64) and (65).[292] No *cis/trans* isomerization was observed, in direct analogy to a similar rearrangement of divinylaziridines of type (**169a**) in Section 8.1.5.[216]

Table 12 Rearrangements of Miscellaneous Systems

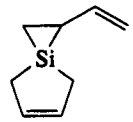
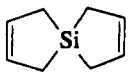
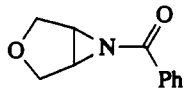
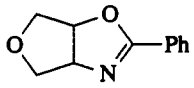
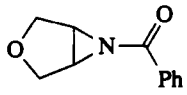
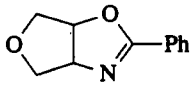
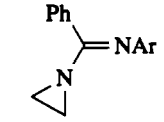
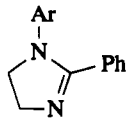
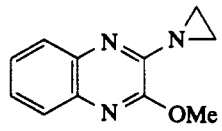
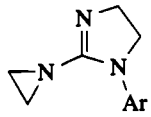
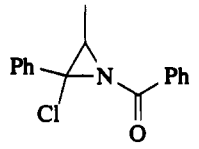
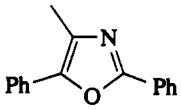
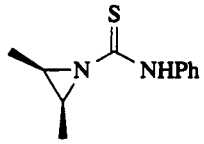
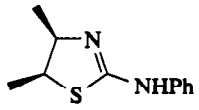
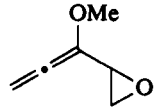
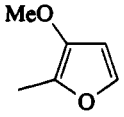
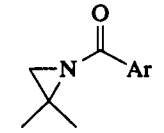
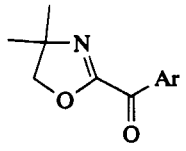
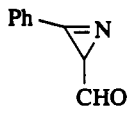
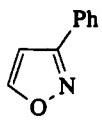
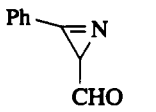
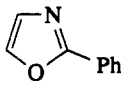
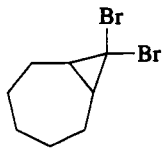
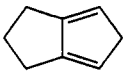
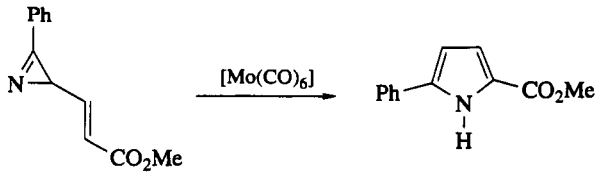
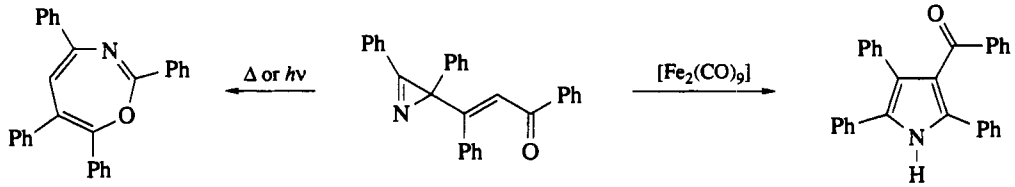
Cyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	*hν*, 254 nm, 310 °C		32	275
	235–250 °C		33	276
	NaI, MeCN, r.t.		79	276
 Ar = *p*-$O_2NC_6H_4$	I^- or SCN^-		90	277
	NaI, acetone, Δ		78	278
	acetone, 5 °C		75	279, 280
	TsOH, PhH		84	281
	KOBu^t, DMSO, r.t.		75	282
 Ar = *p*-$O_2NC_6H_4$	NaI, acetone, Δ		93	283
	200 °C		80	284

Table 12 *(continued)*

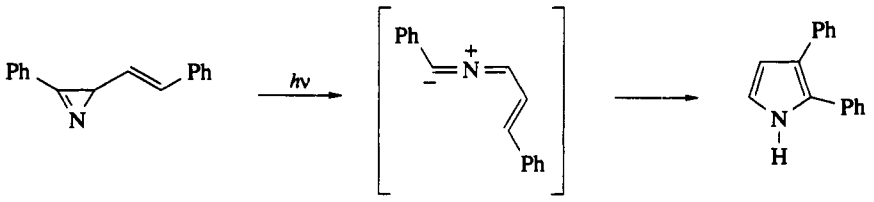
Cyclopropane	*Conditions*	*Product*	*Yield (%)*	*Ref.*
	*hν*		—	284
	MeLi		94	285



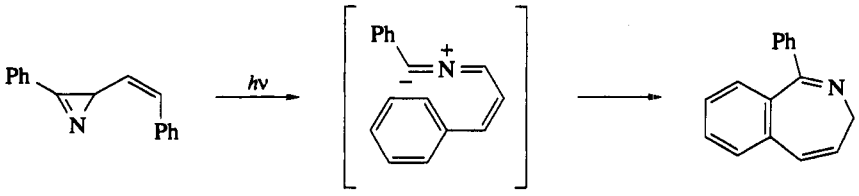
(63)



Scheme 50

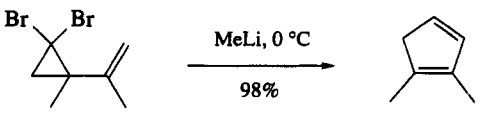


(64)

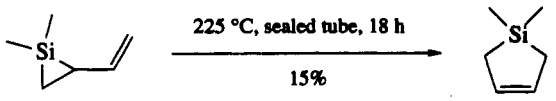


(65)

Other systems that undergo this rearrangement are dibromovinylcyclopropanes (through cyclopropylcarbene) equation (66),[293] and silavinylcyclopropanes in those cases where they can be isolated, as 1,4-addition is the normal mode of addition of silalenes to conjugated dienes (equation 67).[294]



(66)

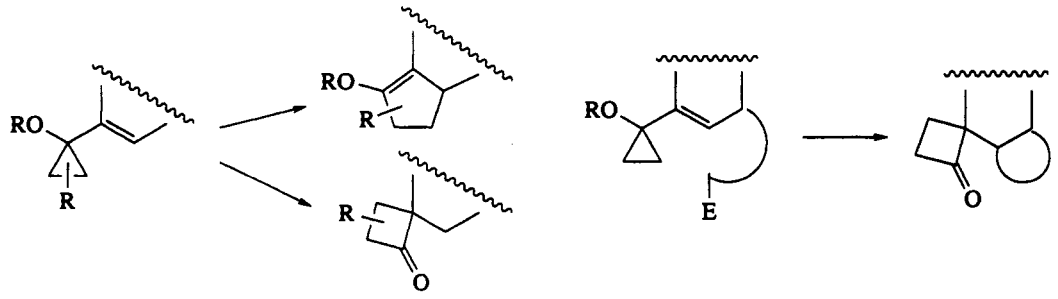


(67)

8.1.8 SURVEY OF GENERAL METHODOLOGIES

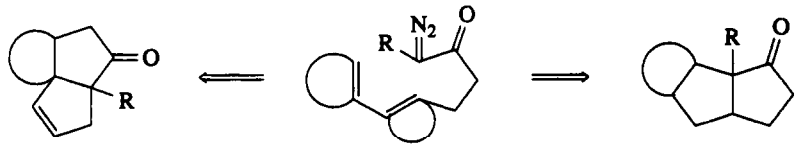
The chemistry discussed in this chapter has been exploited in several important general methods of synthesis. These are summarized in this section with leading references provided. Additional aspects of the rearrangements can be appreciated by analysis of the heterodivinylcyclopropane systems that are reviewed elsewhere.[177] The following survey provides a schematic review of the general methods of synthesis that have surfaced over the years and that are based on the rearrangements of vinylcyclopropanes and their analogs.

Trost developed a general method of synthesis of vinylcyclopropanes (and their sulfur and oxygen analogs) through the application of ylide addition to carbonyl compounds. Three major methods involve the cyclopentene annulation, cyclobutanone synthesis, and ring expansion with concomitant alkylation (Scheme 51).[20]



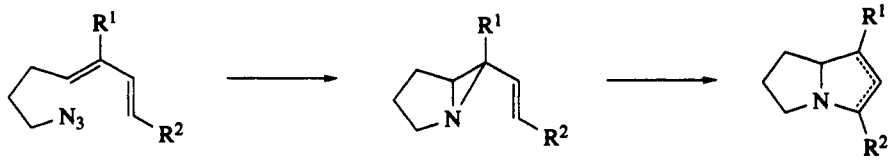
Scheme 51

Hudlicky developed a general method of triquinane synthesis based on a cyclopropanation–rearrangement sequence of dienic diazo ketones (Scheme 52). Topological selectivity of linear *versus* angular triquinane synthesis has been achieved.[41]

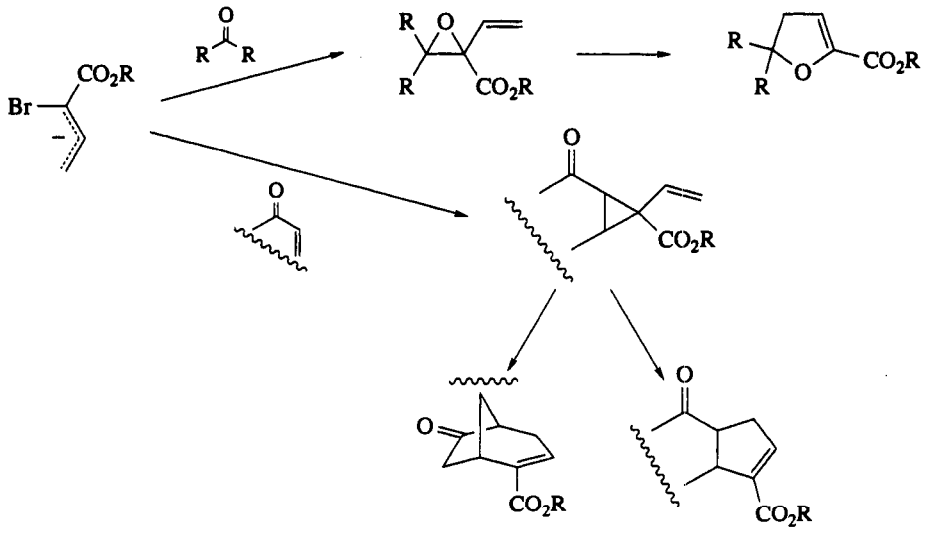


Scheme 52

Extension of this methodology to nitrogenous compounds (Scheme 53) has been implemented *via* azide cycloadditions to dienes as a facile means of synthesis of functionalized pyrrolizidines.[41,223] Recently a [2 + 3] methodology was developed (Scheme 54) that promises to have wide applicability in the synthesis of cyclopentanoids, bridged systems and dihydrofurans.[41]

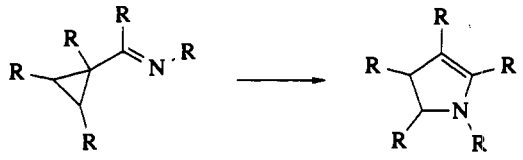


Scheme 53



Scheme 54

The cyclopropylimine–pyrroline rearrangement (equation 68) has been exploited by Stevens in alkaloid syntheses.[255,256] Wenkert's cyclopropylcarbinyl rearrangement (equation 69) served extremely well in the design of 1,4-dicarbonyl synthons or β,γ-unsaturated carbonyl compounds which then were expressed in numerous syntheses of terpenoid and alkaloid natural products.[37,38] Donor–acceptor concepts continue to be expressed in the applicability of these rearrangements to organic synthesis.[16,21]



(68)

(69)

X = OR; Y = RC̄H, O, NR; Z = H, R, OR

8.1.9 SURVEY OF TOTAL SYNTHESES

In this section those rearrangements of vinylcyclopropanes and their analogs that have been used in the synthesis of natural products are featured. The chronological listing of the syntheses provides an additional guide and cross-reference to specific literature dealing with the methodology discussed in this chapter. The presentation of the key steps in the context of the overall targets highlights the variety of structural types accessible *via* the rearrangements. The tabular survey is divided into three sections: Table 13 lists the cases of vinylcyclopropane–cyclopentene rearrangements; Table 14 compiles the rearrangements of vinylaziridines and cyclopropylimines to pyrrolines; and Table 15 shows transformations of vinyloxiranes or cyclopropylcarbonyls to dihydrofuran synthons.

Table 13 Vinylcyclopropane–Cyclopentene Rearrangement

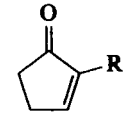
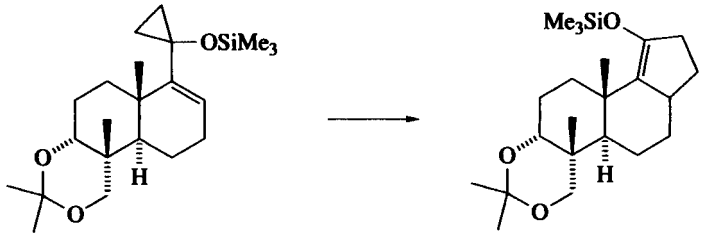
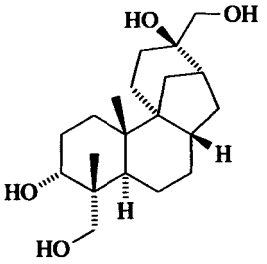
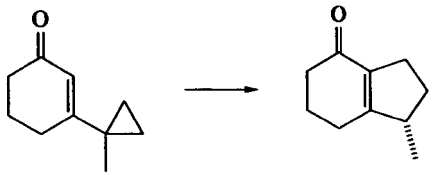
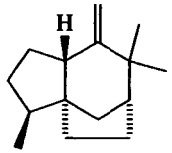
Author (year)	*Key transformation*	*Target*	*Ref.*
Trost (1974)	R = $(CH_2)_6CO_2Bu^t$	 Prostaglandin intermediate	295
Trost (1979)		 Aphidicolin	296
Piers (1979)		 Zizaene	297

Table 13 *(continued)*

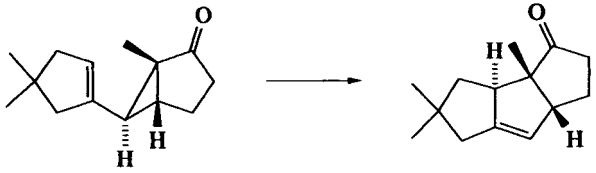
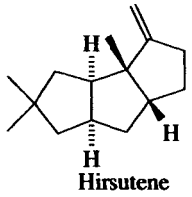
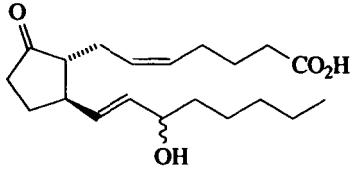
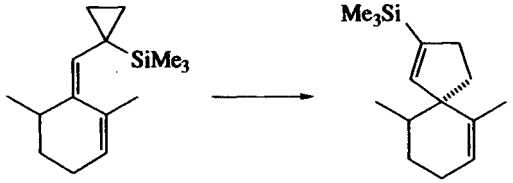
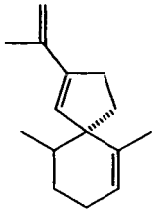
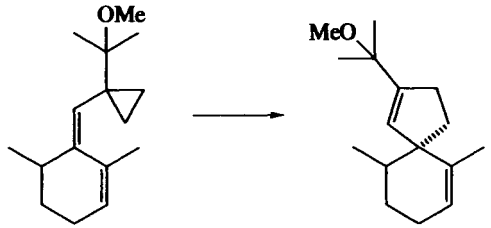
Author (year)	*Key transformation*	*Target*	*Ref.*
Hudlicky (1980)		 Hirsutene	298
Salaun (1981)		 11-Deoxyprostaglandin E_2	90
Paquette (1982, 1984)		 α-Vetispirene	299, 300
			

Table 13 *(continued)*

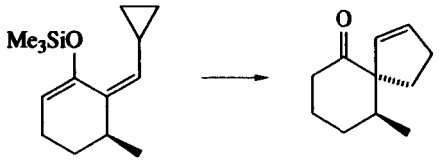
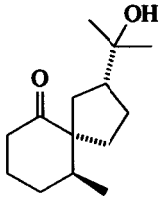
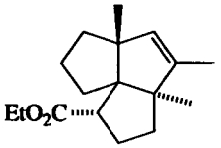
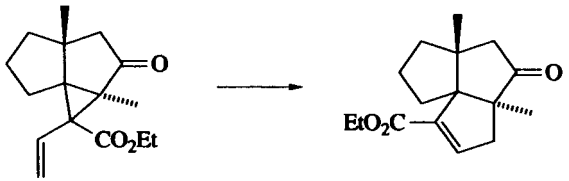
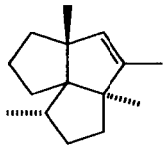
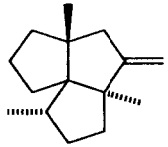
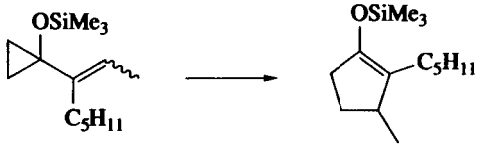
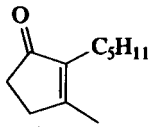
Author (year)	*Key transformation*	*Target*	*Ref.*
Piers (1983)		 Hinesol	301
		 Isocomenic acid (1983)	302
Hudlicky (1983)		 Isocumene	303
		 β-Isocomene (1984)	303
Salaun (1983)		 Dihydrojasmone (and jasmone)	304

Table 13 *(continued)*

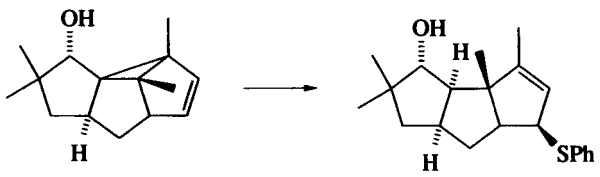
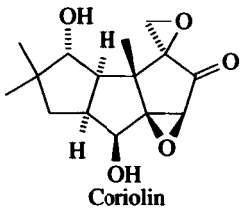
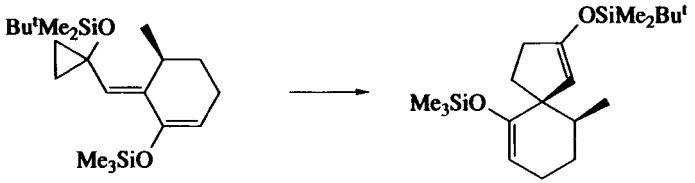
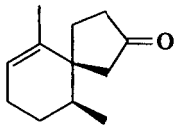
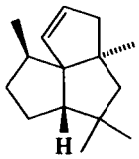
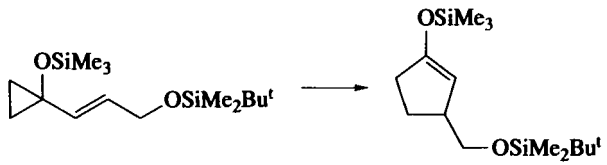
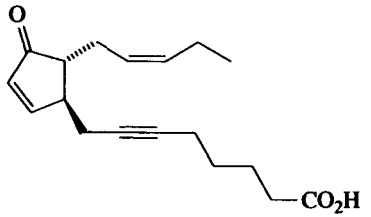
Author (year)	*Key transformation*	*Target*	*Ref.*
Wender (1983)		 Coriolin	117
Salaun (1984)		 Spirovetivane	305
Wender (1985)		 Silphinine	306
Salaun (1985)		 Dicranenone	307

Table 13 *(continued)*

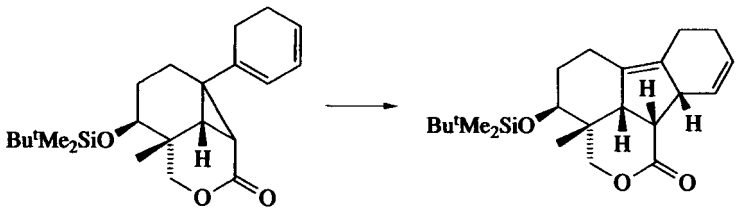
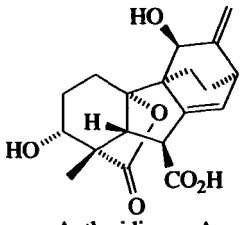
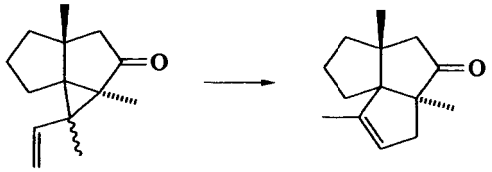
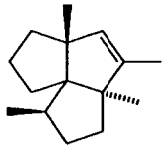
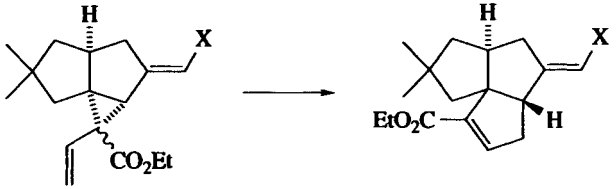
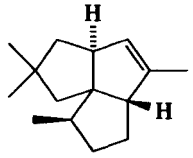
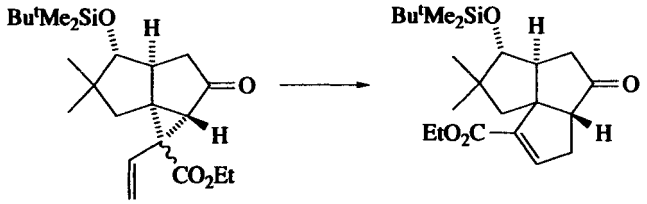
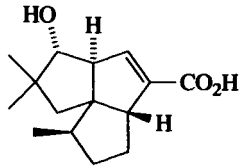
Author (year)	*Key transformation*	*Target*	*Ref.*
Corey (1985)		 Antheridiogen-An	308
Hudlicky (1986)		 Epiisocomene	309
Hudlicky (1987)		 Pentalenene	310, 311
Hudlicky (1987)		 Pentalenic Acid	311

Table 13 *(continued)*

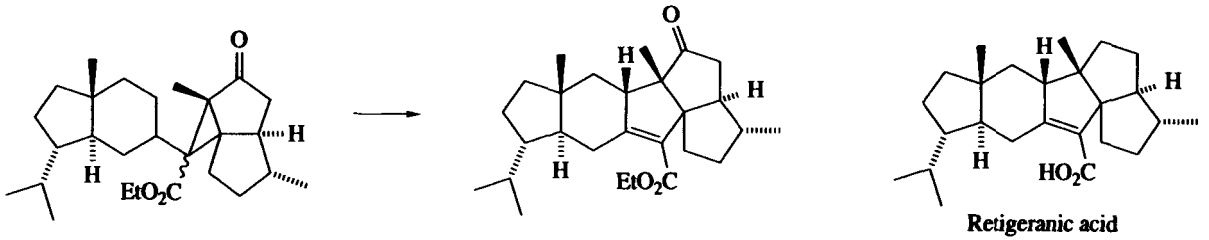
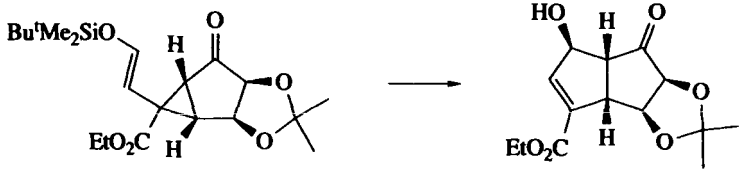
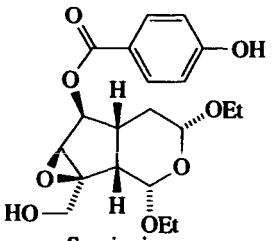
Author (year)	*Key transformation*	*Target*	*Ref.*
Hudlicky (1988)		Retigeranic acid	99, 128
Hudlicky (1989)		 Specionin	103, 128, 312

Table 14 Cyclopropylimine– and Vinylaziridine–Pyrroline Rearrangements

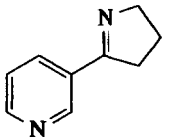
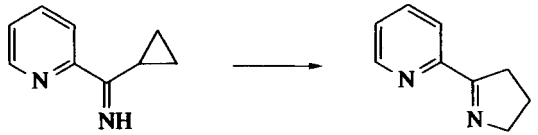
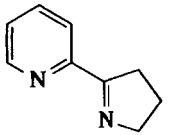
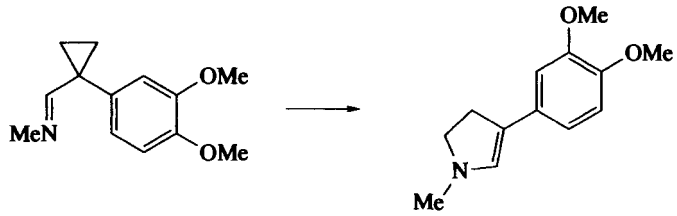
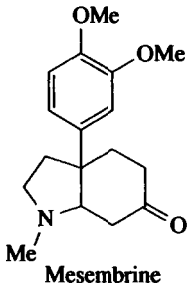
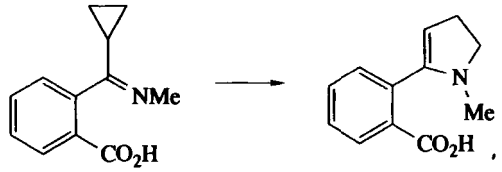
Author (year)	*Key transformation*	*Target*	*Ref.*
Stevens (1967)		 Mysomine	313, 314
Stevens (1967)		 Apoferrosamine	313, 314
Stevens (1968) Keely (1968)		 Mesembrine	315–318
Breuer (1969)		Shihunine	319

Table 14 *(continued)*

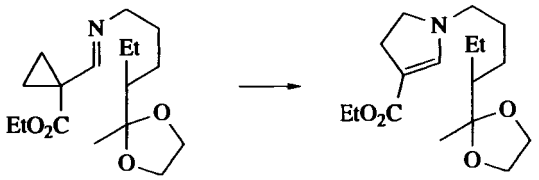
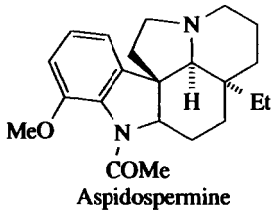
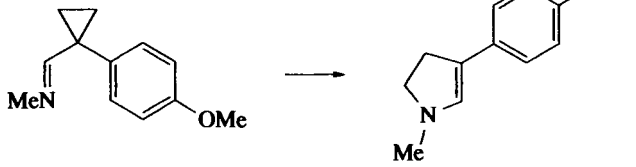
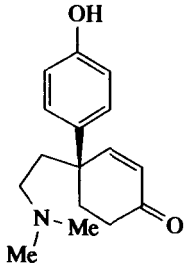
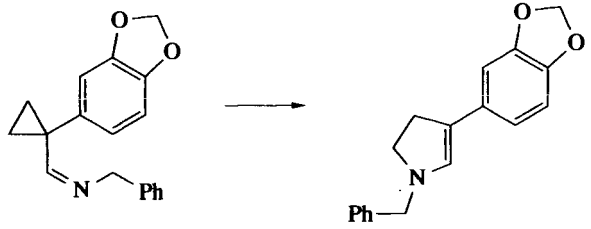
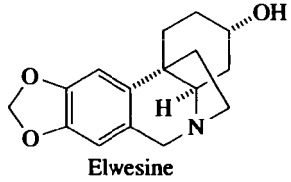
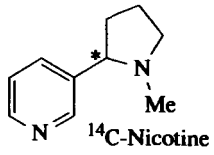
Author (year)	*Key transformation*	*Target*	*Ref.*
Stevens (1971)		 Aspidospermine	260
Stevens (1972)		 Joubertiamine	258
Stevens (1972)		 Elwesine	320
Comes (1973)		 ^{14}C-Nicotine	321

Table 14 *(continued)*

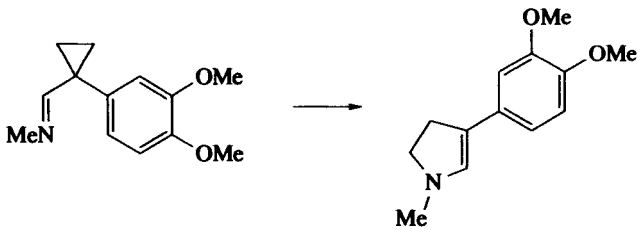
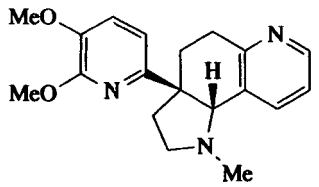
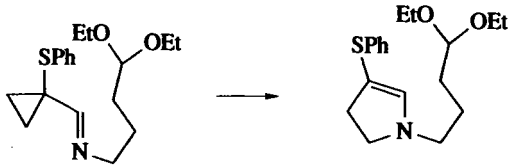
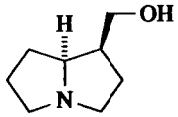
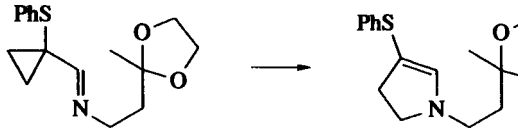
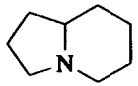
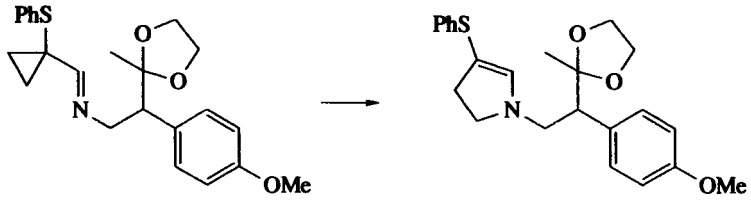
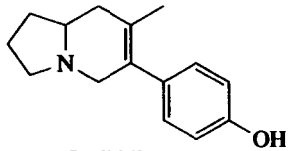
Author (year)	*Key transformation*	*Target*	*Ref.*
Stevens (1975)		 Sceletium alkaloid A-4	317
Stevens (1976)		 Isoretronecanol	261
Stevens (1976)		 δ-Coniceine	261
Stevens (1977)		 Ipalbidine	322

Table 14 *(continued)*

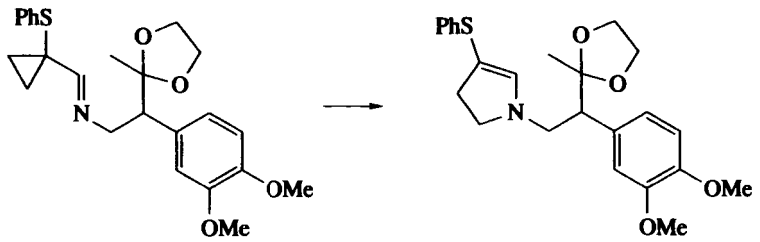
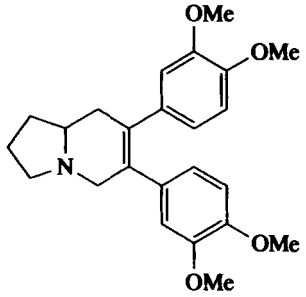
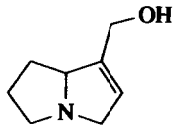
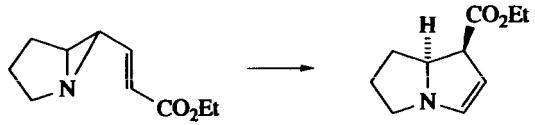
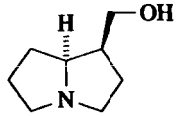
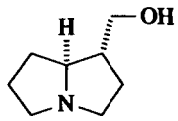
Author (year)	*Key transformation*	*Target*	*Ref.*
Stevens (1977)		 Septicine	322
Hudlicky (1984, 1985 1986, 1987)			212, 221
Pearson (1985)		Supinidine	213
Hudlicky (1986)		 Isoretronecanol  Tracelanthamidine	221, 223

Table 14 *(continued)*

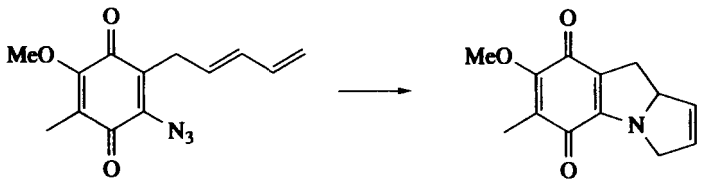
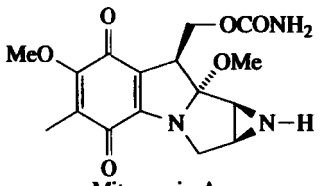
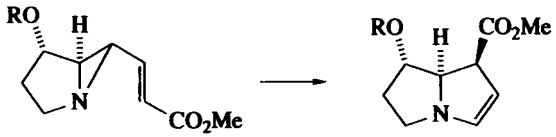
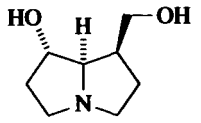
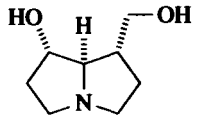
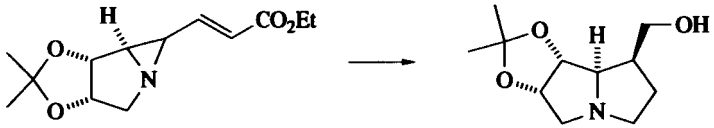
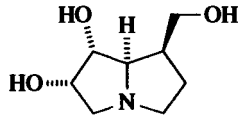
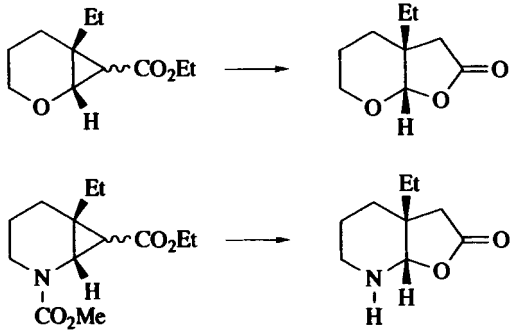
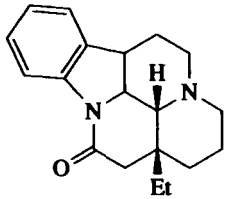
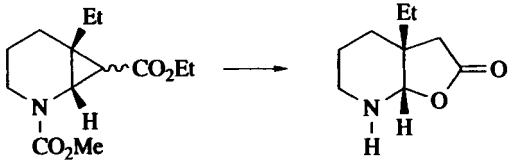
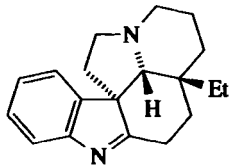
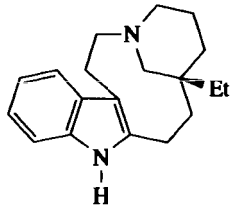
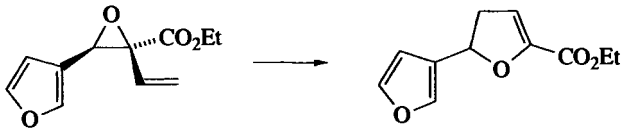
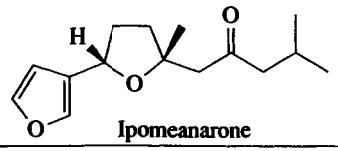
Author (year)	*Key transformation*	*Target*	*Ref.*
Maruyama (1987)		 Mitomycin A	323
Hudlicky (1988)		 Dihydroxyheliotridane  Hastanecine	222, 251
Hudlicky (1989)		 Trihydroxyheliotridane	225, 251

Table 15 Vinyloxirane and Cyclopropyl–Carbonyl–Dihydrofuran Rearrangements

Author (year)	*Key transformation*	*Target*	*Ref.*
Wenkert (1978)		 Eburnamonine	223
Wenkert (1988)		 Dehydroaspidospermidine  Quebrachamine	324
Hudlicky (1989)		 Ipomeanarone	176

8.1.10 CONCLUSION

The chemistry associated with the vinylcyclopropane system and its heteroatom analogs has indeed provided for an incredible variety of transformations. In this chapter an attempt at a survey and a classification has been made in order to place all of the mechanistic pathways over a common denominator. Until now each system has been dealt with separately in the literature except for the vinylcyclopropane–cyclopentene rearrangement, which has been reviewed in the same light as a name reaction. Upon reading this chapter it will become obvious that the immense amount of chemistry done to date bodes well for even better powers of predictability and increased utility of those transformations yet to be applied in organic synthesis. Further development of general synthetic strategies and their application in systematic preparation of complex molecules, as well as the basic understanding of mechanistic details, will indeed continue to be expressed especially in the systematic design of five-membered carbo- and hetero-cyclic compounds. The vinylcyclopropane–cyclopentene rearrangement and all of its variants therefore serve the same function in the domain of five-membered ring compounds as the Diels–Alder reaction occupies in the field of cyclohexane synthesis. It is hoped that through the summary and classification of the chemistry associated with the title systems this comparison has been amply demonstrated.

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8.2
Rearrangements of Divinylcyclopropanes

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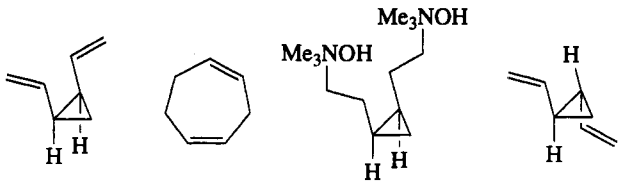
8.2.1 INTRODUCTION

The facile thermal $\sigma^2s + \pi^2s + \pi^2s$ (Cope) rearrangement of *cis*-1,2-divinylcyclopropane (**1**) to 1,4-cycloheptadiene (**2**) was first reported in 1960 by Vogel.[1] In his experiments, Vogel did not isolate (**1**), since, under the conditions of its formation (*e.g.* thermolysis of **3** at 80 °C), (**1**) rearranges rapidly to (**2**). Indeed, it was not until more than a decade later that (**1**) was isolated and shown to rearrange to (**2**) with half-lives of approximately 90 s and 25 min at 35 °C[2] and 11 °C,[2,3] respectively.

Not unexpectedly, *trans*-1,2-divinylcyclopropane (**4**) is much more stable than the *cis* isomer (**1**) and is a readily isolable compound. Nevertheless, at elevated temperatures, *e.g.* 190 °C, (**4**) undergoes smooth bond reorganization to provide 1,4-cycloheptadiene (**2**) in essentially quantitative yield.[1a,1c] Thus, at the time that the Cope rearrangement of 1,2-divinylcyclopropane systems was discovered,[1] it was already clear that both *cis* and *trans* isomers could, in principle, serve as suitable substrates for the reaction. As it turns out, this is an important reaction characteristic, since, in most (but not all) cases, it makes unnecessary the stereoselective preparation of either the *cis* or *trans* starting material.



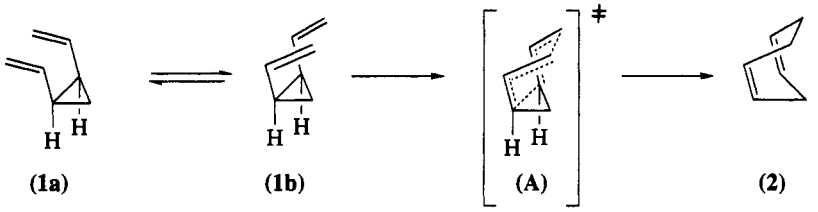
(1) (2) (3) (4)

Since 1960, the thermolysis of 1,2-divinylcyclopropanes has been studied quite extensively from a mechanistic point of view. However, particularly since 1975, synthetic applications of the rearrangement reaction have been explored and these studies have shown that the reaction provides a versatile, effective method for the construction of functionalized mono-, bi- and tri-cyclic substances.[4] In this chapter the mechanistic features of the rearrangement will be outlined briefly. The major portion of the discussion will deal with synthetic aspects of this interesting process.

8.2.2 MECHANISTIC CONSIDERATIONS

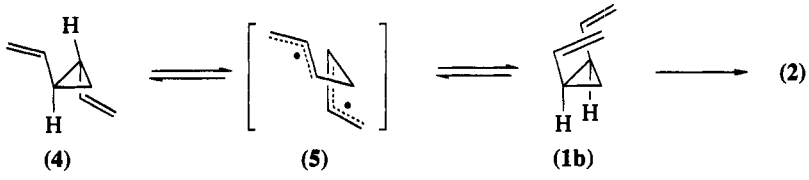
8.2.2.1 Rearrangement Pathways

It appears to be well accepted that the thermal rearrangement of *cis*-1,2-divinylcyclopropane (**1**) proceeds in a concerted fashion *via* a boat-like transition state, in which the vinyl groups lie over the three-membered ring.[5–7] Thus, conformational orientation of (**1**) as shown in (**1b**; equation 1), followed by bond reorganization by way of a transition state represented by (**A**), provides 1,4-cycloheptadiene (**2**), in which both double bonds have *cis* stereochemistry. Concerted rearrangement of (**1**) *via* a chair-like transition state derived directly from conformation (**1a**) would lead to the highly strained *trans,trans*-1,4-cycloheptadiene and it is clear that such a pathway would be of a much higher energy than that involved in the conversion of (**1b**), *via* (**A**), into (**2**).



(1)

The thermolytic transformation of *trans*-1,2-divinylcyclopropane (**4**) into 1,4-cycloheptadiene (**2**) probably proceeds *via* the pathway shown in equation (2). Homolytic cleavage of the cyclopropane ring of (**4**) provides the resonance stabilized diradical (**5**), which, in addition to reverting to (**4**), can undergo bond rotation and subsequent ring closure to give *cis*-1,2-divinylcyclopropane (**1**). The latter substance then rearranges, by way of conformation (**1b**), into (**2**).



(2)

The energy of activation E_a for the overall conversion of (**4**) into (**2**) has been reported[7,8] to be in the range 32.1–34.3 kcal mol^{-1} (1 kcal ≈ 4.2 kJ). In comparison, the data reported by Brown *et al.*[2] and Schneider and Rau[9] show that E_a for the rearrangement of (**1**) to (**2**) is about 19–20 kcal mol^{-1}. Thus, for the conversion of (**4**) into (**2**), the rate-determining step is the isomerization of (**4**) into (**1**), presumably *via* the diradical (**5**). This characteristic is common to most of the known rearrangements of 1,2-divinylcyclopropane systems. That is, for a given pair of isomers, *trans* to *cis* isomerization is generally slower than Cope rearrangement of the *cis* isomer. However, it must be noted that there are exceptions to

this generalization, since thermolysis of certain substituted *cis*-1,2-divinylcyclopropanes results only in *cis–trans* isomerization and not in sigmatropic rearrangement (*vide infra*).

8.2.2.2 Substituent Effects

Substituents attached to the terminal carbons of the vinyl groups can have a profound effect on the rate of Cope rearrangement of *cis*-1,2-divinylcyclopropane systems. For example, Table 1 compares the relative rate of the sigmatropic rearrangement of the parent substance (**1**) with those of the simply substituted substrates (**6**)–(**8**).[9] It can be seen that, although the rate-depressing effects of methyl substituents situated *trans* on the vinyl groups (substrates **6** and **7**) are relatively minor, the effect of a *cis* substituent (substrate **8**) is dramatic. On the basis of the rate data, the destabilizing free energies of activation ($\Delta\Delta G‡$) associated with the steric interactions in transition states (**B**)–(**D**) (Table 1) were calculated.[9] The values (Table 1) show that the methyl–ring interaction in transition state (**D**) produces by far the largest steric effect. Indeed, Schneider and Rau[9] showed that the *cis,cis,cis* substrate (**11**) undergoes reversible *cis–trans* isomerization, (**11**) to (**12**), much faster than it undergoes Cope rearrangement to (**10**; Scheme 1). In a related study, Baldwin and Ullenius[10] reported that, at 165 °C, the (**11**):(**12**) ratio at equilibrium is about 1:4. Furthermore, heating (**12**) at 178 °C for 4.2 h or 75 h gives, in addition to an equilibrium mixture of (**11**) and (**12**), minor (4%) or significant (35%) amounts of the Cope rearrangement product (**10**). Thus, although the sigmatropic bond reorganization of (**11**) is not precluded, the steric interactions present in the transition state (**E**; Scheme 1) make this a higher energy pathway than the isomerization of (**11**) to (**12**).

Other studies have also qualitatively demonstrated the effect of substitution patterns on the ease of *cis*-divinylcyclopropane rearrangements. For example, at temperatures in the range 0–20 °C, the substrates (**13**)–(**15**) are readily transformed into the cycloheptadienes (**16**)–(**18**), respectively (Scheme 2).[11–13] The rearrangement of (**15**) to (**18**) occurs with a half-life of approximately 50 min at 15 °C,[13] and is thus marginally slower than the thermal conversion of the parent *cis*-1,2-divinylcyclopropane (**1**) into 1,4-cycloheptadiene (**2**).[2,3] On the other hand, complete transformation of (**19**) into (**16**) requires heating at 75 °C for 5 h (Scheme 2),[11] again demonstrating the notable rate-retarding effect of a *cis* substituent.

The highly substituted *cis*-divinylcyclopropanes (**20**) and (**21**) do not undergo sigmatropic rearrangement at all.[14] Apparently, the highly sterically congested nature of the transition states (**F**) precludes this possibility. Thermolysis of (**20**) and (**21**) at 170–180 °C produces only equilibrium mixtures of these substances and the corresponding *trans* isomers (**22**) and (**23**), respectively (Scheme 3).[14]

8.2.3 MONOCYCLIC DIVINYLCYCLOPROPANES

8.2.3.1 Stereospecificity

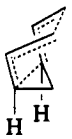
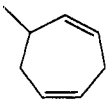
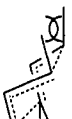
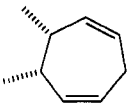
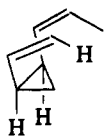
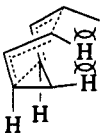
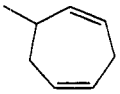
Rearrangement of (**7**) at –10 to 30 °C (Table 1, *vide supra*) provides quantitatively *cis*-6,7-dimethyl-1,4-cycloheptadiene (**10**).[9] Furthermore, prolonged heating of (**11**) at 178 °C produces, in addition to the *trans* isomer (**12**), the same sigmatropic rearrangement product (**10**; Scheme 1).[10] Other studies have shown that thermolyses (178 °C, 4.2 h) of substrates (**24**) and (**25**) give, in quantitative yields, the epimeric cycloheptadienes (**10**) and (**27**), respectively.[10] Presumably, these transformations proceed by way of the corresponding *cis*-1,2-di(1-propenyl)cyclopropanes (**7**) and (**26**).[10]

Collectively, the results summarized above show that, with respect to the stereochemistry of appropriately substituted vinyl groups, the (reversible) *trans* to *cis* isomerization (*e.g.* **12** ⇌ **11**; **24** ⇌ **7**; **25** ⇌ **26**) and the sigmatropic rearrangement of the *cis*-1,2-divinylcyclopropane systems (*e.g.* **7** or **11** → **10**; **26** → **27**) are completely stereospecific. In connection with carrying out stereoselective syntheses, the importance of this reaction characteristic is obvious. Indeed, the stereospecific nature of the Cope rearrangement of 1,2-divinylcyclopropanes has been demonstrated with substrates that are structurally more complex than those discussed above. Specific examples will be presented later in this chapter.

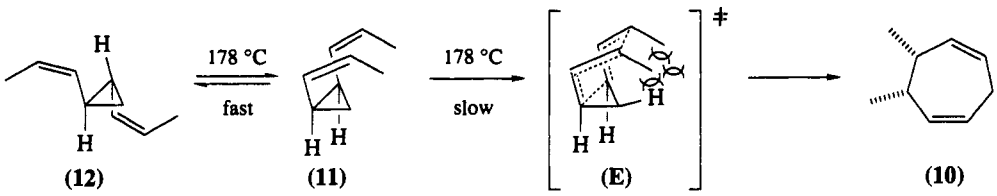
8.2.3.2 Enantiospecificity

Relatively little work has been done in this area. In studies related to the total synthesis of the marine natural product (*R*)-(–)-dictyopterene C′ (**30**), Jaenicke and coworkers[15] have shown that the enantio-

Table 1 Cope Rearrangement of some *cis*-1,2-Divinylcyclopropane Systems[9]

Substrate	*Transition state*	*Steric interaction(s) (destabilizing free energy)*[a]	*Product*	k_{rel} *(40 °C)*[b]
(1)	 (A)	—	(2)	5800
(6)	(B)	Me–H (0.84)	 (9)	1500
(7)	 (C)	Me–Me (1.03)	 (10)	1100
 (8)	 (D)	Me–H (0.84) Me–Ring (4.55)	 (9)	1

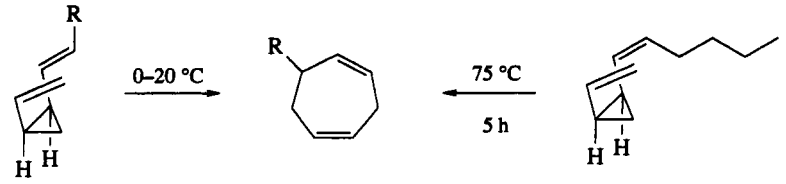
[a] $\Delta\Delta G\dagger$, in kcal mol^{-1}, calculated at 40 °C. [b] By extrapolation of the fast (**1**, **6** and **7**) and slow (**8**) runs. Rate constants were determined as averages of 5 runs at 6 to 8 temperatures over a range of a least 40 °C: (**1**), –20 to 20 °C; (**6**), –10 to 30 °C; (**7**), –10 to 30 °C; (**8**), 50 to 98 °C.



(12) (11) (E) (10)

Scheme 1

merically pure substrates (**28**) and (**29**) rearrange cleanly to the corresponding enantiomerically pure products (**30**) and (**31**), respectively (Scheme 4). Non-natural (*S*)-(+)-dictyopterene C′ (**31**) is also obtained by rearrangement of (1*R*,2*S*)-1-[(*E*)-1-hexenyl]-2-vinylcyclopropane (Scheme 4).[16] These results show, not unexpectedly, that the Cope rearrangements of rather simply substituted *cis*-divinylcyclopropanes are enantiospecific.

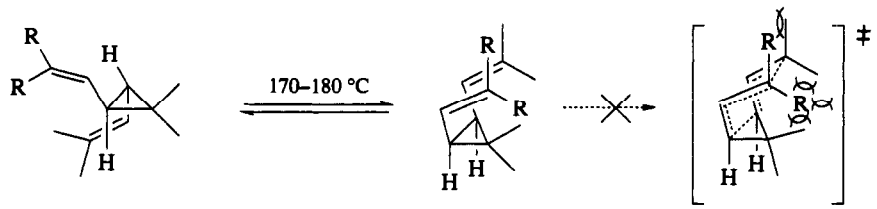


(19)

(13) R = Bu^n
(14) R = *(E)*-1-butenyl
(15) R = *(Z)*-1-butenyl

(16) R = Bu^n
(17) R = *(E)*-1-butenyl
(18) R = *(Z)*-1-butenyl

Scheme 2

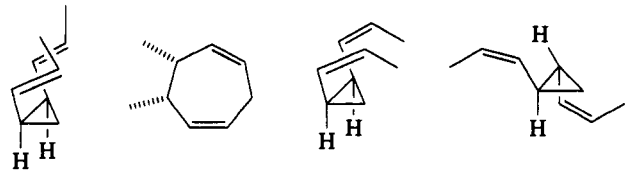


(22) R = H (75%)
(23) R = Me (72%)

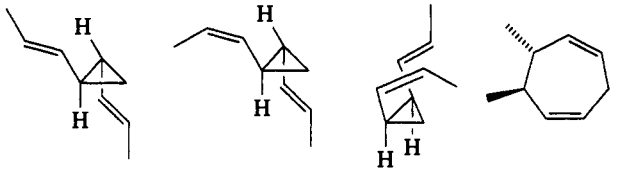
(20) R = H (25%)
(21) R = Me (28%)

(F) R = H or Me

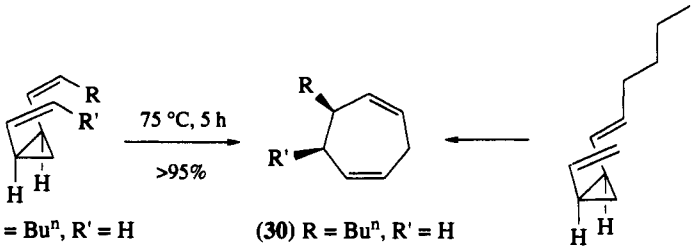
Scheme 3



(7) (10) (11) (12)



(24) (25) (26) (27)



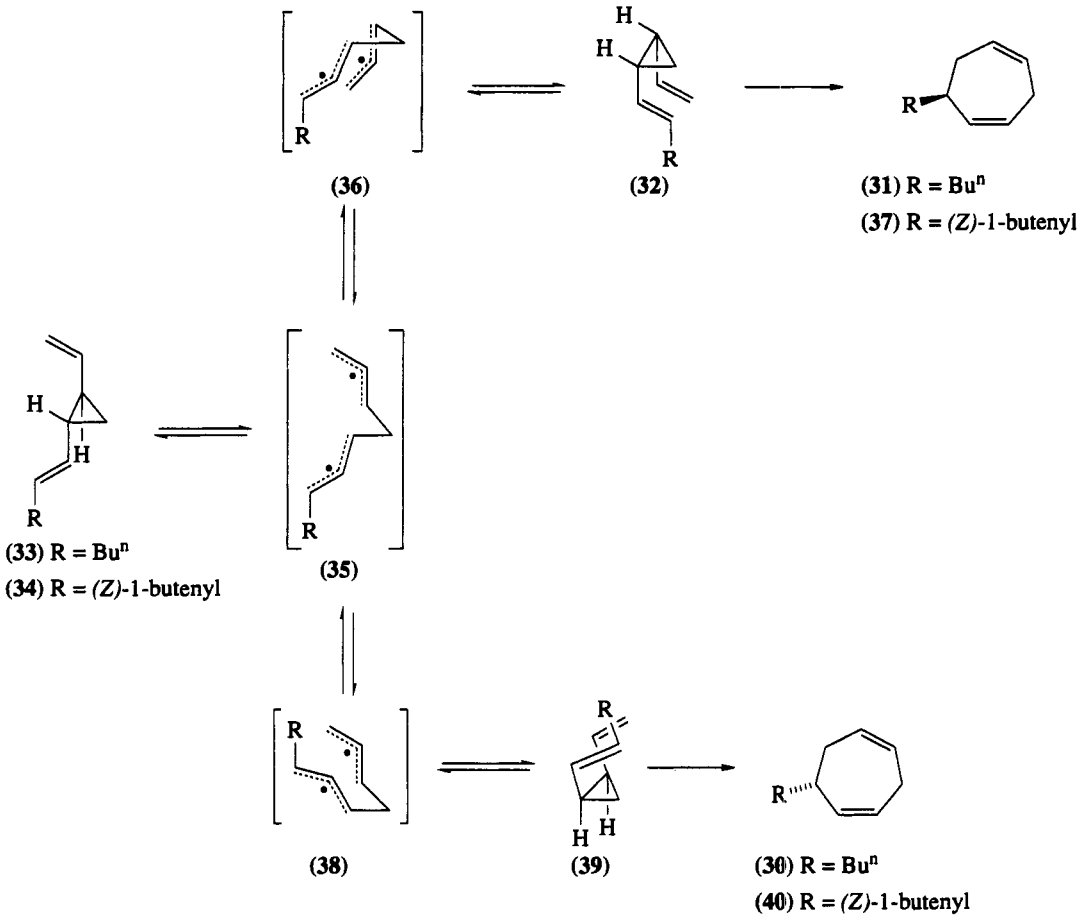
(28) R = Bu^n, R' = H
(29) R = H, R' = Bu^n

(30) R = Bu^n, R' = H
(31) R = H, R' = Bu^n

Scheme 4

With monocyclic *trans*-1,2-divinylcyclopropanes, chirality transfer is, apparently, poor. Thermolysis of (+)-dictyopterene A (**33**) at 165 °C for 48 h and of (–)-dictyopterene B (**34**) at 103–108 °C for 40 h gives, in each case, a mixture of the two enantiomeric Cope rearrangement products, (**30**), (**31**) and (**37**), (**40**), respectively (Scheme 5).[17] Although the uncertainty associated with the optical purities and (or) rotations of the various substances involved[15,17] made a quantitative determination of the product ratios dif-

ficult, it is evident from the results that enantiomers (**31**) and (**37**) predominated marginally over (**30**) and (**40**), respectively. This observation has been rationalized[18] by postulating that, in the intermediate diradical (**35**), the allyl system rotates more rapidly, to give (**36**), than the more bulky heptenyl or heptadienyl groups, to produce (**38**). Ring closure of (**36**) and (**38**), followed by bond reorganization of the (enantiomeric) *cis*-divinylcyclopropanes (**32**) and (**39**), produces the final products.

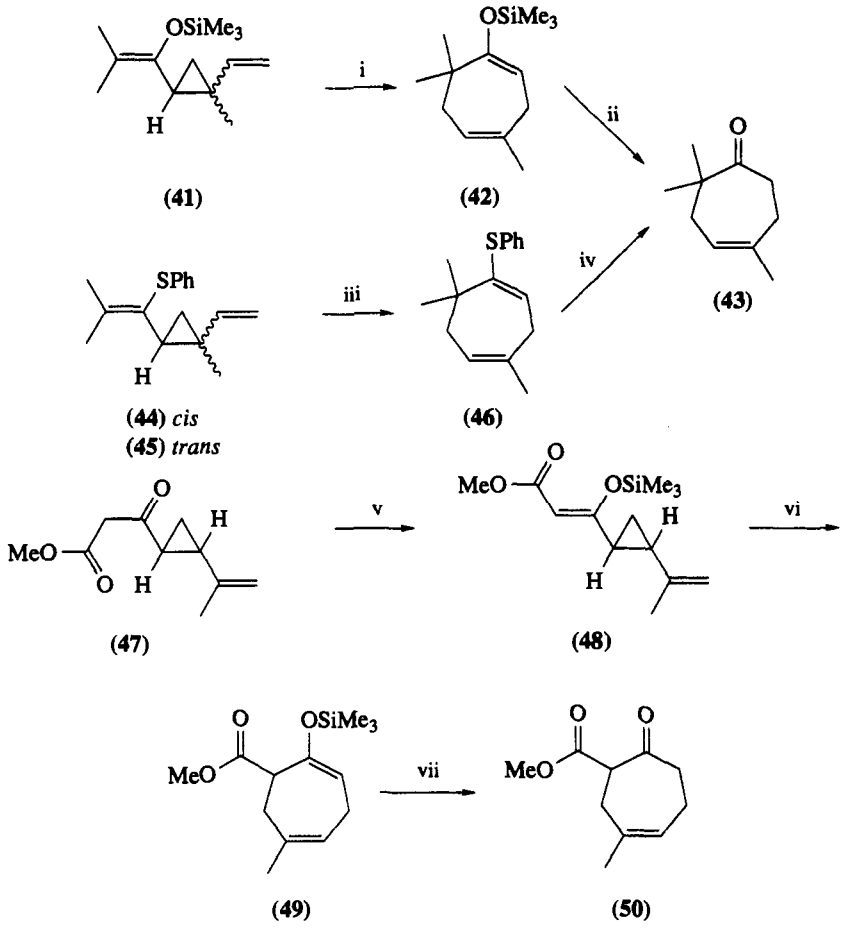


Scheme 5

Although further work in this area is desirable, it appears that in the Cope rearrangement of simple *trans*-divinylcyclopropanes, such as (**33**) and (**34**), enantioselectivity is poor.

8.2.3.3 Synthesis of Functionalized Cycloheptanes

The use of the Cope rearrangement of 1,2-divinylcyclopropanes for the synthesis of functionalized seven-membered rings has been illustrated in a number of studies. For example, thermolysis of (**41**) (mixture of *cis* and *trans* isomers), followed by cleavage of the enol silyl ether function in the resultant product (**42**), provides the natural product karahanaenone (**43**; Scheme 6).[19] In this case, as in many others, the fact that (**41**) was not stereochemically homogeneous was of no consequence, since both isomers of (**41**) cleanly afford the same rearrangement product. Similarly, sigmatropic rearrangement of the isomers (**44**) and (**45**) and subsequent hydrolysis of the resultant vinyl sulfide (**46**) also produces karahanaenone (**43**).[20] The efficient conversion of substrate (**47**) into the keto ester (**50**) *via* a route in which the Cope rearrangement of (**48**) played a key role has been reported.[21]

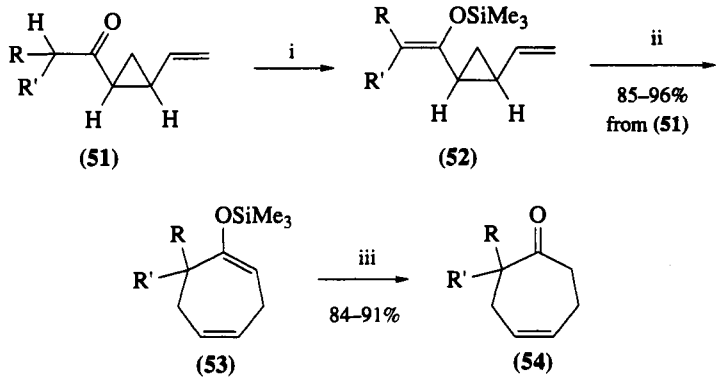


i, 165–175 °C, PhH; ii, Bu^nLi, THF; iii, *cis*, 25 °C; *trans*, 160 °C (70%); iv, $HgCl_2$, H_2O–MeCN (45%); v, Me_3SiCl, Et_3N, Et_2O (100%); vi, 210 °C, PhH (96%); vii, KF, MeOH (95%)

Scheme 6

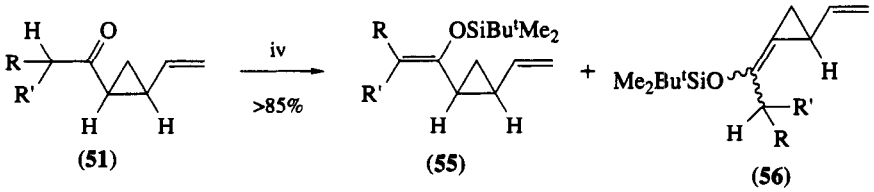
In an investigation related to the synthesis of substituted 4-cyclohepten-1-ones,[22] the stereochemically homogeneous *cis*-2-vinylcyclopropyl ketones (**51a–51d**) were converted cleanly to the enol silyl ethers (**52**; Scheme 7). Thermolysis of the latter substances, followed by acid hydrolysis of the resultant products (**53**), gives excellent yields of the ketones (**54a–54d**). Interestingly, however, kinetic deprotonation of each of the *cis*-ketones (**51e–51h**) is not chemoselective. Treatment of these substrates with LDA–TBDMS-Cl provides mixtures of the enol silyl ethers (**55**) and (**56**), in ratios varying from 4:1 (substrate **51g**) to 1:9 (substrate **51f**). Fortunately, the *trans*-ketones (**57e–57h**) give synthetically more satisfactory results, since these substances can be converted chemoselectively into the *trans*-divinylcyclopropanes (**58**). As expected, Cope rearrangements of compounds (**58**) require temperatures considerably higher than those employed for the conversion of (**52**) into (**53**). However, the reactions are clean and the products (**59**), obtained in good to excellent yields, are readily hydrolyzed to the ketones (**54e–54h**).

In a recent study of the chemistry of the cyclopropenone acetal (**60**), the very interesting transformation shown in equation (3) was achieved.[23] Although this conversion was the only reported example of this novel process, it seems likely that the use of other functionalized and (or) stereochemically modified reagents would provide efficient syntheses of a wide variety of interestingly substituted seven-membered rings.

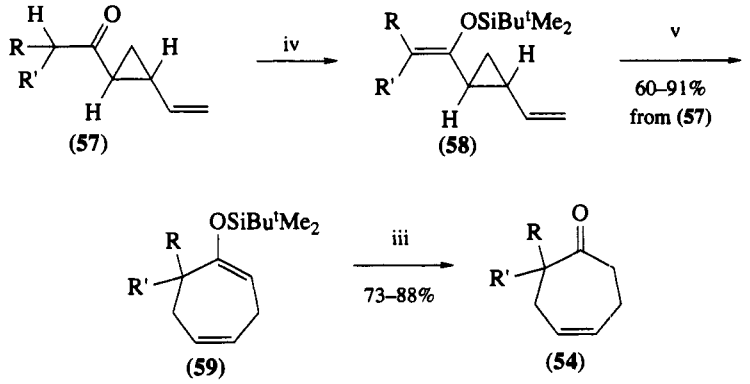


(51) (52) (53) (54)

a: R = Bu^n, R' = H; **b**: R = Ph, R' = H; **c**: R, R' = $(CH_2)_3$; **d**: R, R' = $(CH_2)_4$



(51) (55) (56)

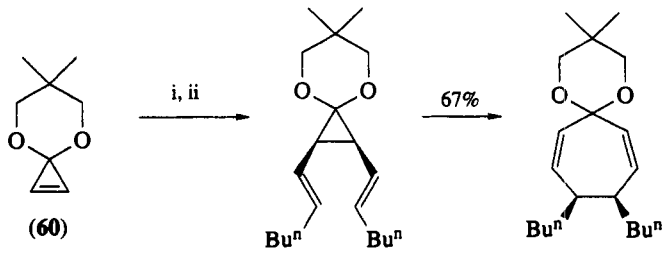


(57) (58) (59) (54)

e: R, R' = $(CH_2)_5$; **f**: R, R' = $CH_2CMe_2(CH_2)_3$; **g**: R, R' = $(CH_2)_6$; **h**: R = Bu^t, R' = H

i, LDA, THF; Me_3SiCl, Et_3N; ii, 100–110 °C, 30 min; iii, HCl, H_2O, MeOH; iv, LDA, THF; Bu^tMe_2SiCl, HMPA; v, 230 °C, 30–60 min

Scheme 7



(60) (3)

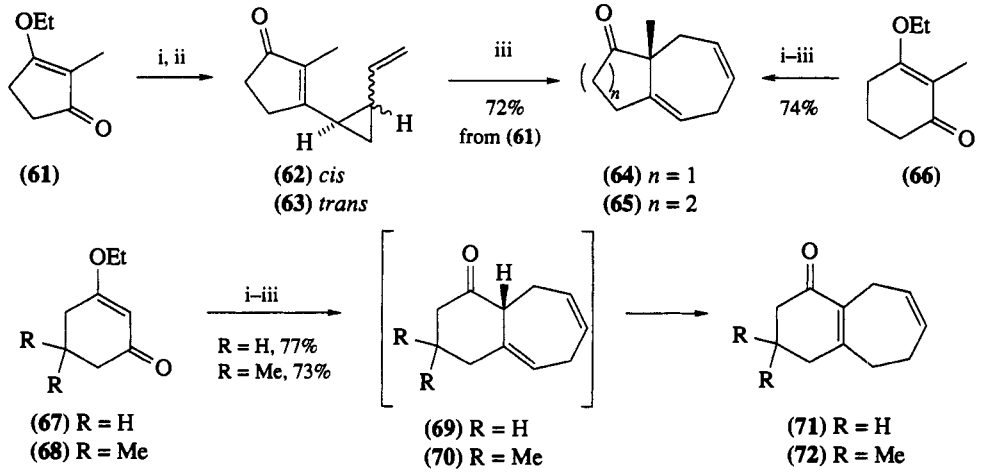
i, $(Bu^n\text{-}\!\!\nearrow)_2CuLi$, THF–$Et_2O$, –70 °C; ii, $Bu^n\text{-}\!\!\nearrow\!\!\text{-}I$, $(Ph_3P)_4Pd$, –70 °C to r.t.

8.2.4 β-(2-VINYLCYCLOPROPYL)-α,β-UNSATURATED KETONES

8.2.4.1 Synthesis of Functionalized Bicyclo[5.*n*.0]alkanes and Related Substances

The Cope rearrangement of 1,2-divinylcyclopropane systems in which one of the vinyl groups is part of an α,β-unsaturated ketone moiety has found considerable use in synthesis. A significant number of substrates have been prepared and subjected to thermal rearrangement and some of the products have been employed effectively for natural product syntheses.

The reaction of 2-vinylcyclopropyllithium reagents with β-alkoxy enones has served well as a method for preparing β-(2-vinylcyclopropyl) enones.[19,24] For example, treatment of (**61**) with a mixture of *cis*- and *trans*-2-vinylcyclopropyllithium, followed by mild acid hydrolysis of the resultant products, provides the epimeric divinylcyclopropanes (**62**) and (**63**) (Scheme 8).[19] Although (**62**) rearranges slowly at room temperature, the *trans* substrate (**63**) requires, as expected, elevated temperatures for rearrangement. Indeed, heating of the mixture of (**62**) and (**63**) at 170–180 °C provides (**64**) cleanly and efficiently.[19] Thus, not unexpectedly, the stereoselective preparation of the requisite divinylcyclopropane substrates is unnecessary, since both (**62**) and (**63**) are readily converted into the same product (**64**). In similar fashion, the enones (**66**)–(**68**) are smoothly transformed into the rearrangement products (**65**), (**71**) and (**72**), respectively.[19] Under the rearrangement reaction conditions, the primary products (**69**) and (**70**), derived from (**67**) and (**68**), undergo isomerization to the more stable enones (**71**) and (**72**), respectively.

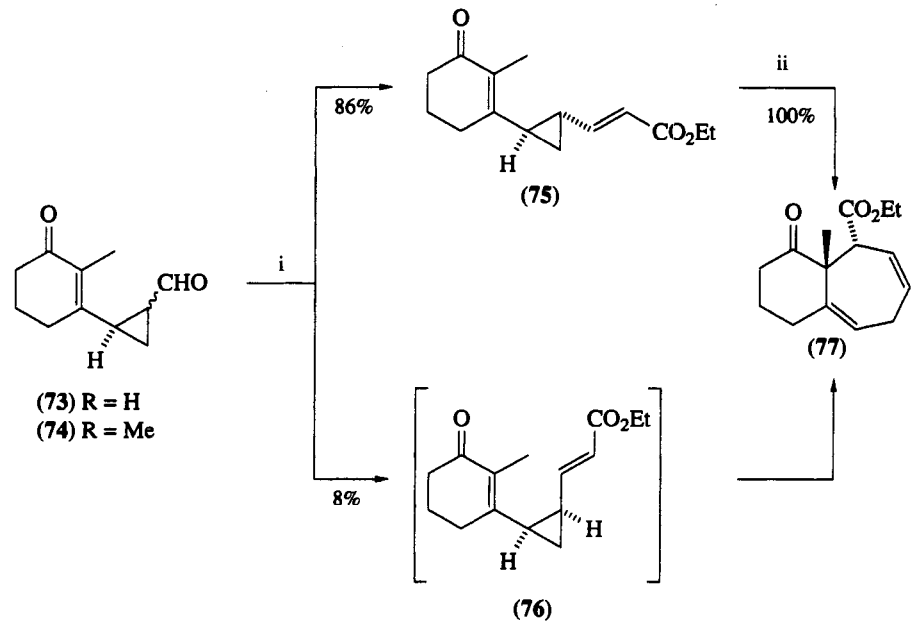


i, 7:3 mixture of *cis*- and *trans*-2-vinylcyclopropyllithium, Et_2O; ii, HCl, H_2O; iii, 170–180 °C, PhH

Scheme 8

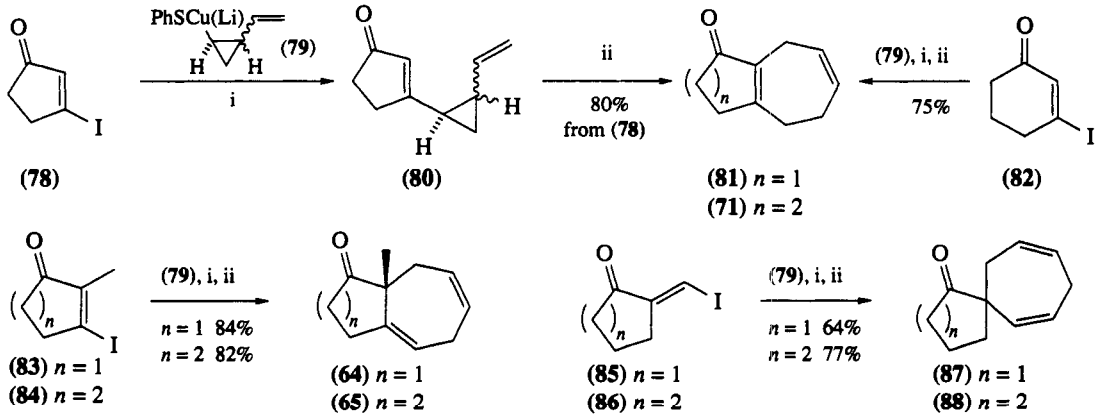
Chemoselective Wittig reactions on keto aldehydes, such as (**73**) and (**74**), also provide substrates suitable for sigmatropic rearrangement.[25,26] For example, treatment of (**74**) (mixture of epimers) with $Ph_3P{=}CHCO_2Et$ provides the *trans*-divinylcyclopropane (**75**; 86%) and the keto ester (**77**; 8%), the latter being derived from room temperature Cope rearrangement of the initially formed intermediate (**76**; Scheme 9).[26] Thermolysis of (**75**) produces (**77**) quantitatively. The efficient conversions of (**75**) and (**76**) into the stereochemically homogeneous keto ester (**77**) again illustrates the highly stereoselective nature of the sigmatropic rearrangement of *cis*- and *trans*-1,2-divinylcyclopropane systems.

The reaction of cyclopropylcuprate reagents with β-iodo enones has proven to be a useful method for preparing β-(2-vinylcyclopropyl) enones. For example, reaction of (**78**) with the cuprate reagent (**79**) (7:3 mixture of *cis* and *trans* isomers, readily prepared from the corresponding mixture of 1-bromo-2-vinylcyclopropanes), followed by thermal rearrangement of the resultant product (**80**), gives the ketone (**81**; Scheme 10).[27] Similarly, the substrates (**82**)–(**84**) are smoothly transformed into the bicyclic ketones (**71**), (**64**) and (**65**), while subjection of the (*E*)-2-(iodomethylene)cycloalkanones (**85**) and (**86**) to the same reaction sequence affords the corresponding spirodienones (**87**) and (**88**). Since the iodo enones are readily prepared from 1,3-dicarbonyl compounds[28] and the cuprate reagent (**79**) is obtained *via* a separate synthetic route, the overall annulation sequences are convergent, short, and efficient.



i, $Ph_3P{=}CHCO_2Et$, THF, 20 °C; ii, 140 °C, xylene, 6 h

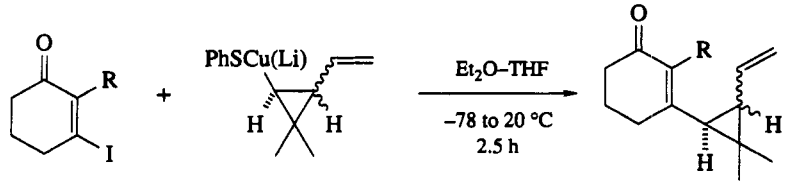
Scheme 9



i, THF, –78 °C, 1 h; –20 °C, 1 h; 0 °C, 1–2 h; ii, neat, 180 °C, 30–45 min

Scheme 10

Cuprate methodology can also be used to prepare more highly substituted substrates. Thus, treatment of the 3-iodo-2-cyclohexen-1-ones (**82**) and (**84**) with the epimeric, stereochemically homogeneous cuprates (**89**) and (**90**) produces the divinylcyclopropanes (**91**)–(**94**) in excellent yields (equation (4)).[27]



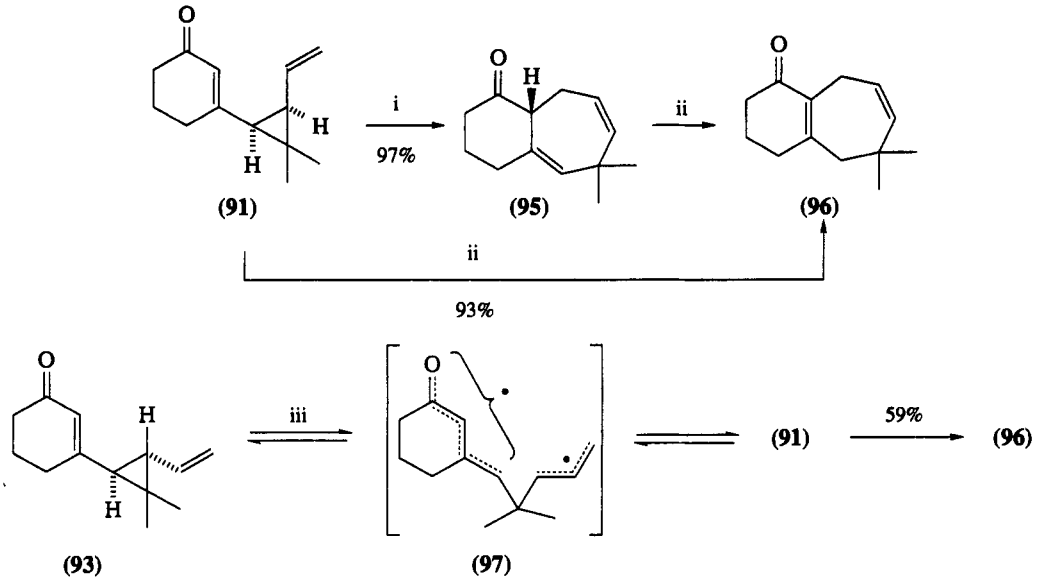
(4)

(**82**) R = H
(**84**) R = Me

(**89**) *cis*
(**90**) *trans*

(**91**) R = H, *cis* (88%)
(**92**) R = Me, *cis* (76%)
(**93**) R = H, *trans* (95%)
(**94**) R = Me, *trans* (82%)

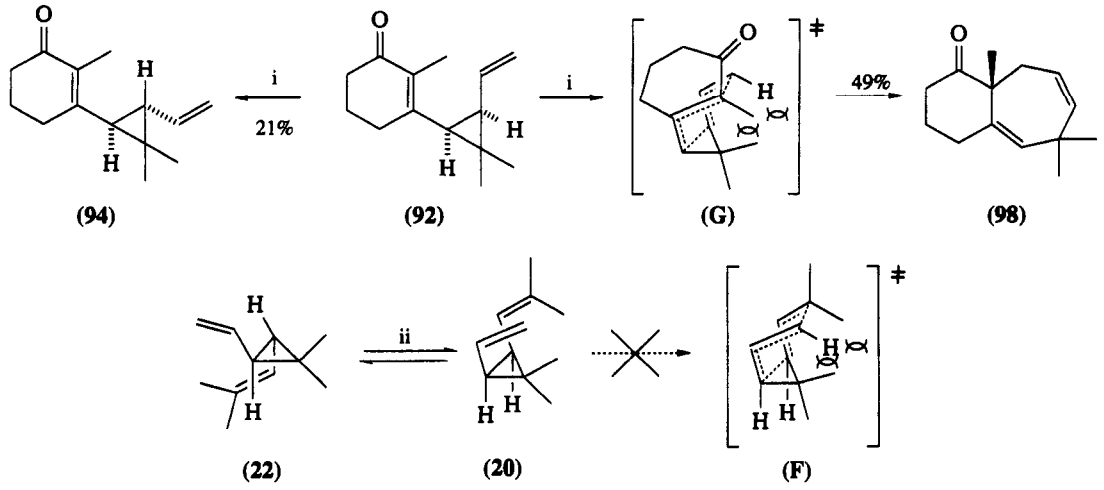
Rearrangement of the epimers (**91**) and (**93**) is, in each case, unexceptional (Scheme 11).[27] Thermolysis of (**91**) in hexane provides the dienone (**95**), while heating either (**91**) or (**95**) at 110 °C (neat) affords the conjugated ketone (**96**). Although, as expected, rearrangement of (**93**) requires much higher temperatures, the same product (**96**) is formed in good yield. Presumably, this conversion proceeds by way of the stabilized diradical (**97**) and the *cis*-divinylcyclopropane (**91**).



i, hexane, reflux, 4 h; ii, neat, 110 °C, 10 min; iii, *o*-dichlorobenzene, 220 °C, 14 h

Scheme 11

The *cis* substrate (**92**) represents an interesting case. Thermolysis of this material under a variety of conditions produces mixtures of (**94**) and (**98**), in which the latter substance nearly invariably predominates (Scheme 12).[27] For example, heating of (**92**) in collidine at 140–150 °C gives (**94**) and (**98**) in a ratio of about 1:2. Under these and other thermolysis conditions, the *trans*-divinylcyclopropane (**94**) is stable.



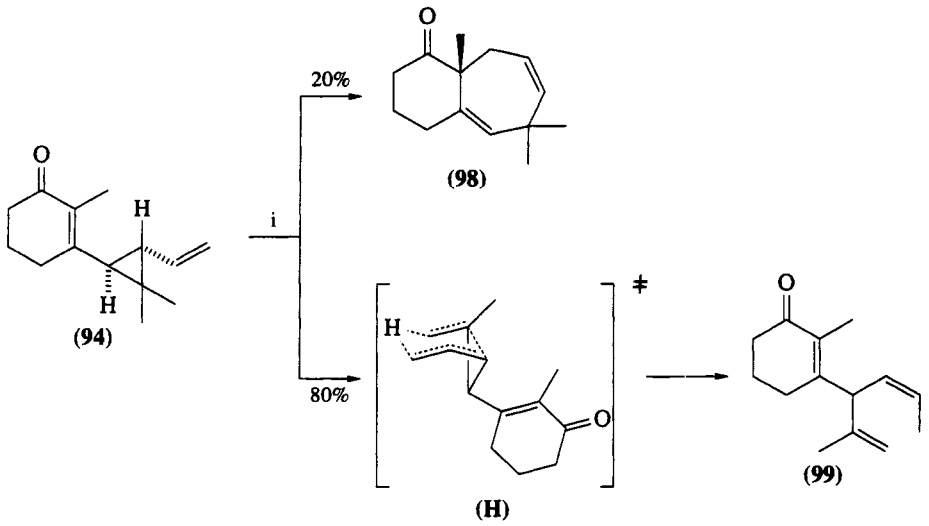
i, collidine, 140–150 °C, 43.5 h; ii, 180 °C, 3 h

Scheme 12

As mentioned previously, thermolysis of (**20**) at 180 °C does not result in Cope rearrangement but provides an equilibrium mixture of (**20**) and its epimer (**22**).[14] Interestingly, in terms of steric congestion, the

transition states for Cope rearrangement of (**20**) and (**92**), (**F**) and (**G**), respectively, are similar (Scheme 12). Therefore, it is noteworthy that (**92**) does undergo sigmatropic rearrangement (albeit in competition with isomerization to **94**), while (**20**) does not. In (**92**), of course, one of the substituted vinyl groups is part of an α,β-unsaturated ketone function and, apparently, this structural feature lowers the activation energy of the Cope rearrangement process.

The *trans* substrate (**94**) is quite resistant to thermal rearrangement. However, thermolysis of this substance at 220 °C (Scheme 13)[27] provides the Cope rearrangement product (**98**) and the trienone (**99**), in a ratio of 1:4. Product (**99**) results from a [1,5] sigmatropic hydrogen migration, presumably *via* a transition state that can be represented by (**H**).[6,29] Interestingly, in the thermolysis of (**94**), the latter process is energetically more favorable than the alternative Cope rearrangement pathway.



i, *o*-dichlorobenzene, 220 °C, 16 h

Scheme 13

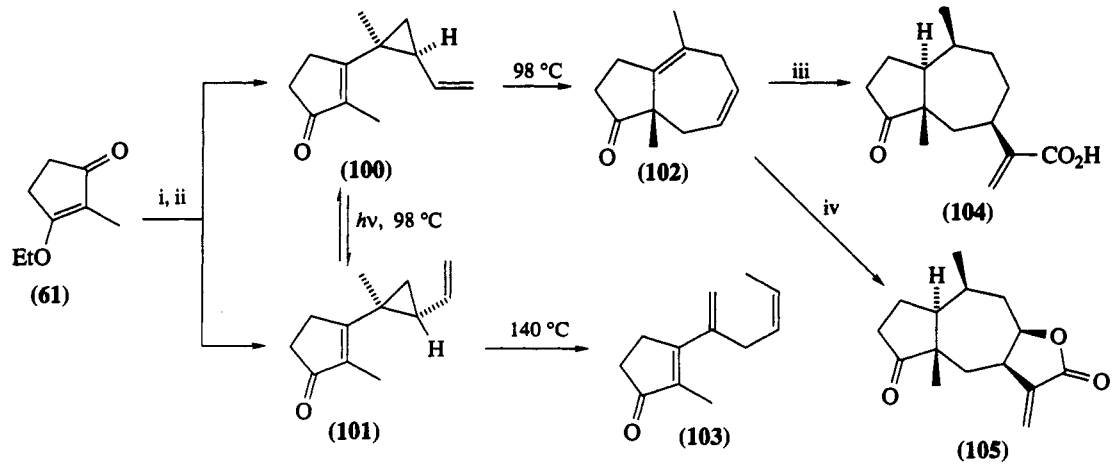
From a synthetic viewpoint, a comparison of the thermolyses of the epimers (**92**) and (**94**) (Schemes 12 and 13) illustrates the point, previously mentioned, that, in certain cases in which alternative modes of rearrangement are possible, the stereoselective formation of the *cis*-divinylcyclopropane substrate is important. Thus, while thermal rearrangement of the *cis* substrate (**92**) provides the Cope rearrangement product (**98**) in reasonable yield, thermolysis of the *trans* isomer (**94**) does not.

8.2.4.2 Natural Product Syntheses

Naturally occurring compounds that possess as part of their structures bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane skeletons are very common in the terpenoid family of natural products. Since both of these carbon frameworks are readily prepared by sigmatropic rearrangement of β-(2-vinylcyclopropyl) enones, it is not surprising that this method has been applied to the total synthesis of terpenoids.

Wender *et al.* have reported interesting syntheses of the pseudoguaiane sesquiterpenoids (±)-damsinic acid (**104**) and (±)-confertin (**105**) (Scheme 14).[30] Using methodology similar to that described earlier (see Scheme 8) the enone (**61**) is converted into a 1:4 mixture of the epimeric divinylcyclopropanes (**100**) and (**101**), respectively. Interestingly, thermolysis of this mixture at temperatures ≥ 140 °C gives a mixture of the desired dienone (**102**) and the trienone (**103**), also in a ratio of 1:4, respectively. Clearly, while the *cis* substrate (**100**) is readily transformed into (**102**), the thermal isomerization of the *trans* isomer (**101**) into (**100**) is precluded by the more facile rearrangement of (**101**) to (**103**) *via* a [1,5] sigmatropic hydrogen shift.[6,29] Thus, it appeared initially that an efficient preparation of (**102**) would require the stereoselective preparation of the *cis* substrate (**100**).

Not unexpectedly, it is found that, although the *cis* substrate (**100**) rearranges readily at 98 °C, the *trans* isomer (**101**) is stable under these conditions. More important, however, was the finding that the two isomers (**100**) and (**101**) can be equilibrated by photolysis. Consequently, the problem of preparing

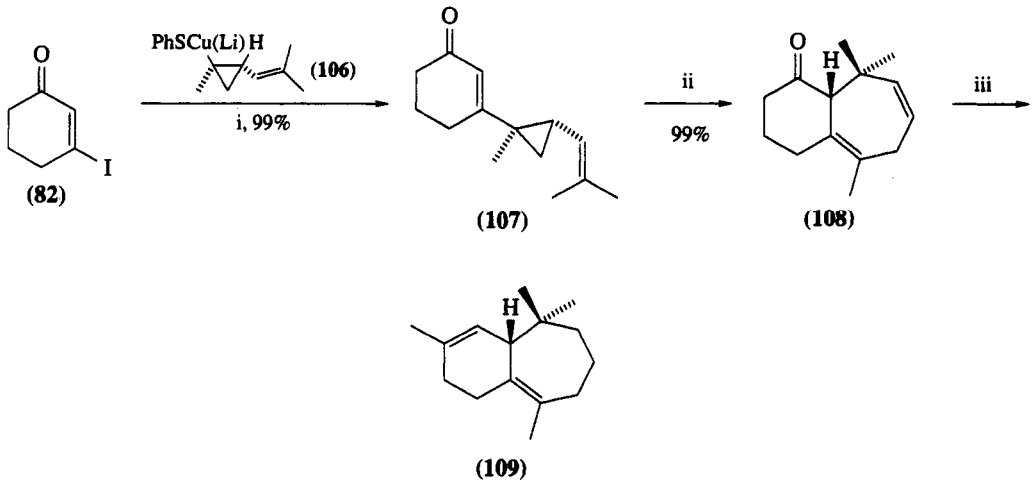


i, 1:4 mixture of *cis*- and *trans*-1-methyl-2-vinylcyclopropyllithium; ii, H_3O^+; iii, 9 steps; iv, 10 steps

Scheme 14

(**100**) stereoselectively was elegantly circumvented by subjecting the mixture of (**100**) and (**101**) to simultaneous irradiation (>290 nm) and thermolysis (98 °C). In this manner, both (**100**) and (**101**) are converted into (**102**) and the latter material is obtained in excellent yield (80–90%). The dienone (**102**) serves as a useful intermediate for the synthesis of (±)-damsinic acid (**104**) and (±)-confertin (**105**).[30]

The bicyclo[5.4.0]undecane sesquiterpenoid (±)-β-himachalene (**109**) was prepared *via* a route in which thermolysis of a β-(2-vinylcyclopropyl) enone played a key role (Scheme 15).[31] Reaction of the β-iodo enone (**82**) with the stereochemically homogeneous cyclopropylcuprate (**106**) provides the functionalized *trans*-divinylcyclopropane (**107**). Thermolysis of (**107**) gives exclusively the Cope rearrangement product (**108**), which is converted into (±)-β-himachalene (**109**). Notably, in contrast to structurally related systems (*vide supra*), the β,γ-unsaturated ketone function in (**108**) shows no inclination to rearrange to the corresponding α,β-unsaturated (conjugated) ketone.

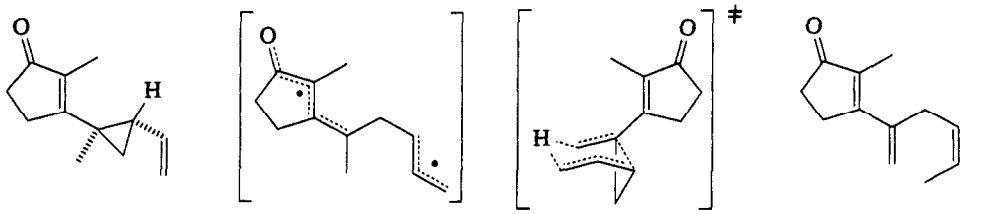


i, THF–Et_2O, –78 °C, 10 min; –20 °C, 15 min; r.t., 2 h; ii, xylene, reflux, 3 h; iii, 4 steps

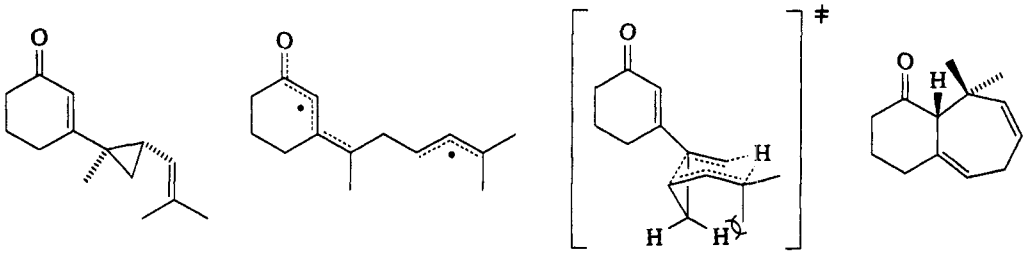
Scheme 15

It is interesting to compare the thermal behavior of compounds (**101**; Scheme 14) and (**107**; Scheme 15). Although, in each case, the substrate reacts chemoselectively, (**101**) undergoes solely [1,5] sigmatropic hydrogen migration to give (**103**), while thermolysis of (**107**) proceeds exclusively by way of Cope rearrangement to provide (**108**). This remarkable difference between structurally rather similar sub-

strates may be rationalized as follows. The rate-limiting steps of the Cope rearrangement of (**101**) and (**107**) would be (are) the isomerization of these substances into the corresponding *cis* isomers, presumably *via* the diradicals (**110**) and (**111**), respectively. Due to the difference in substitution patterns (methyl groups), it seems likely that (**111**) would be more stable than (**110**). Therefore, assuming little energy difference between (**101**) and (**107**), one might expect that the energy of activation for the Cope rearrangement process involving (**107**) would be marginally lower than that involving (**101**). More importantly, however, the (supposed) transition state for [1,5] sigmatropic hydrogen migration[6,29] in substrate (**107**) would be destabilized by a notable steric interaction, as shown in (**J**). The corresponding transition state (**I**) derived from (**101**) is devoid of any major steric repulsions and, therefore, one would expect that the energy barrier for (**101**) → (**I**) would be considerably lower than that for (**107**) → (**J**). Energetically, the two effects outlined above reinforce each other and, therefore, it is possible to rationalize, at least qualitatively, why the thermal rearrangements of (**101**) and (**107**) proceed *via* distinctly different pathways.

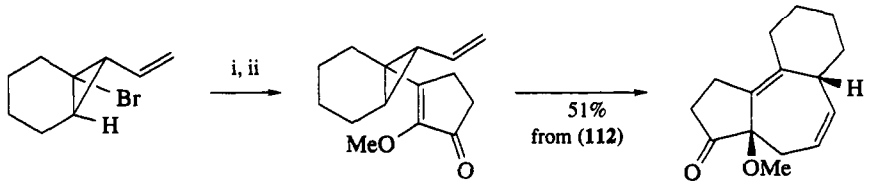


(**101**) (**110**) (**I**) (**103**)



(**107**) (**111**) (**J**) (**108**)

In connection with developing a synthetic approach to tigliane-, daphnane- and ingenane-type diterpenoids, Wender *et al.* have reported the reaction sequence shown in Scheme 16.[32] Interestingly, the functionalized *cis*-divinylcyclopropane (**112**) rearranges readily at room temperature, thus providing, in highly stereoselective fashion, the structurally rather complex product (**113**) from relatively simple starting materials.



(**112**) (**113**)

i, Bu^{t}Li, Et_2O; 2,3-dimethoxy-2-cyclopenten-1-one; ii, H_3O^+, r.t.

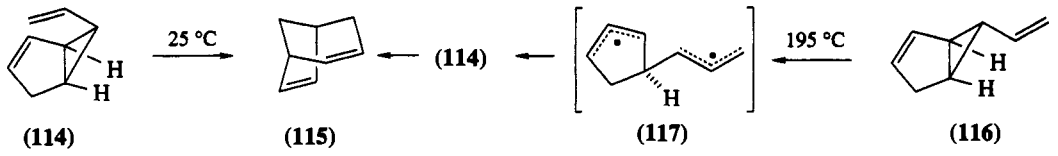
Scheme 16

8.2.5 6-(1-ALKENYL)BICYCLO[3.1.0]HEX-2-ENES

8.2.5.1 Background

The Cope rearrangement of 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene (**114**) to bicyclo[3.2.1]octa-2,6-diene (**115**)[33] has been shown[34] to take place with a half-life of approximately 1 d at 25 °C (E_a = 22.9 kcal

mol^{-1}) (Scheme 17). As expected, the *exo* isomer (**116**), although stable at ambient temperatures, rearranges at elevated temperatures (*e.g.* 195 °C)[35] to provide the bicyclic diene (**115**) cleanly and efficiently. By means of an elegant study using optically active substrates, Baldwin and Gilbert[35] have shown that rearrangement of (**116**) to (**115**) proceeds entirely *via* a one-center epimerization at C-6 and not by way of inversion at both bridgehead carbons. Thus, thermolyses of optically active (**114**) and (**116**) (identical optical purities, absolute configurations as shown in Scheme 17) at 60 °C and 195 °C, respectively, give the same product (**115**). Importantly, the two samples of the latter substance exhibit essentially identical optical rotations. Presumably, the conversion of (**116**) into (**115**) involves the intermediacy of the diradical (**117**). The latter species, upon suitable bond rotation and ring closure, would give (**114**), which would rapidly rearrange to (**115**).



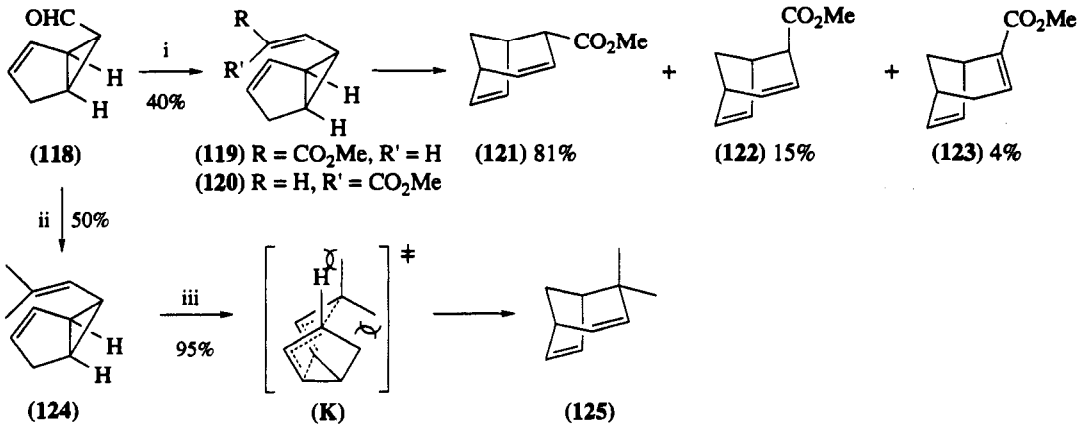
(**114**) (**115**) (**117**) (**116**)

Scheme 17

The Cope rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes would appear to be a (potentially) excellent method for the preparation of functionalized, substituted bicyclo[3.2.1]octanes. Therefore, particularly since the latter carbon skeleton is a common structural feature of many terpenoid natural products, it is surprising that during the period 1965–1980 this type of transformation received relatively little attention from the community of synthetic organic chemists. The 1980s, however, have seen considerable activity in this area and the results of some of this work is summarized in the next two subsections of this chapter.

8.2.5.2 Synthesis of Substituted Bicyclo[3.2.1]octa-2,6-dienes

The readily available aldehyde (**118**) has served as a suitable precursor for a number of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes. For example, treatment of (**118**) with $Ph_3P{=}CHCO_2Me$ gives a mixture of the bicyclic diene esters (**121**)–(**123**) (Scheme 18).[36] In view of the stereospecific nature of the Cope rearrangement process (*vide supra*), it is highly likely that (**121**) and (**122**) are derived by bond reorganization of the initially formed Wittig products (**119**) and (**120**), respectively. The ratio of (**121**):(**122**) is, therefore, a reflection of the (expected) fact that the Wittig reaction produces primarily the *trans*-α,β-unsaturated ester (**119**). The diene ester (**123**) is, presumably, formed by partial isomerization of (**121**) and (or) (**122**).



(**118**) (**119**) R = CO_2Me, R' = H (**121**) 81% (**122**) 15% (**123**) 4%
(**120**) R = H, R' = CO_2Me

(**124**) (**K**) (**125**)

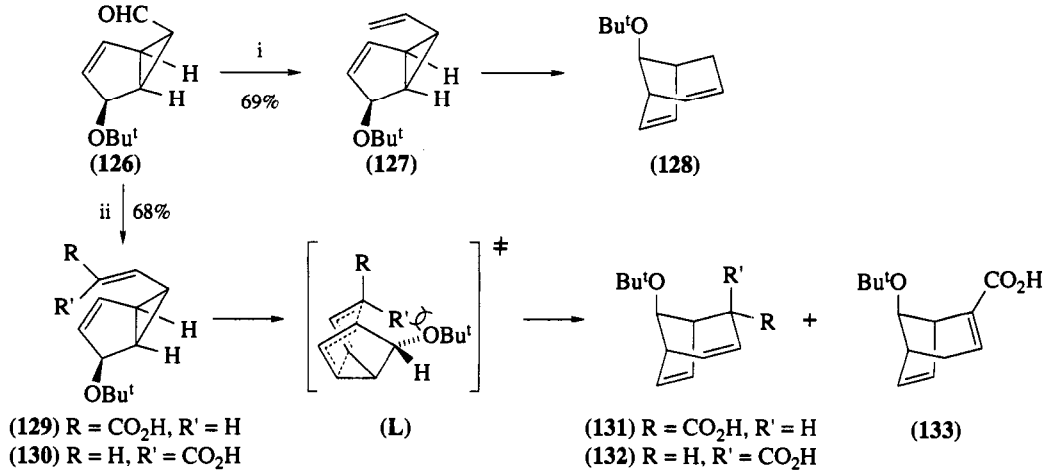
i, $Ph_3P{=}CHCO_2Me$, PhH, reflux, 18 h; ii, $Ph_3P{=}CMe_2$, THF, reflux, 1 h; iii, 350 °C, 15 Torr (1995 Pa)

Scheme 18

Substitution of the 6-*endo*-(1-alkenyl) moiety with alkyl groups notably retards the rate of rearrangement. For example, in contrast to the 'parent' substrate (**114**), the diene (**124**) (readily obtained from the

aldehyde **118**) is stable under the conditions of its preparation and, at room temperature, can be stored without change for months (Scheme 18).[37] Presumably, steric crowding in the transition state (**K**) for the Cope rearrangement is primarily responsible for this stability. Nevertheless, flash vacuum thermolysis of (**124**) provides (**125**) quantitatively.[37]

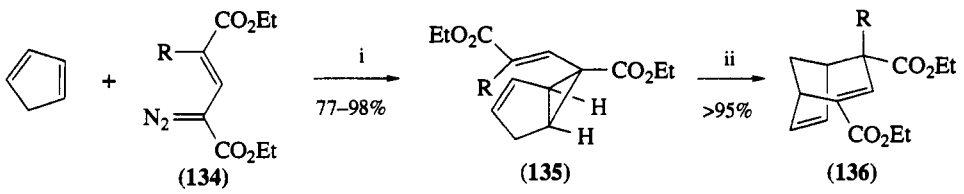
Reaction of the ether aldehyde (**126**) with $Ph_3P{=}CH_2$ provides the diene (**128**; Scheme 19).[38] Furthermore, subjection of (**126**) to a Knoevenagel condensation using malonic acid gives a mixture of the acids (**131**)–(**133**). These conversions demonstrate the feasibility of effecting stereoselective functionalization at C-8 of bicyclo[3.2.1]octa-2,6-diene systems (*e.g.* **128**, **131** and **132**) by starting with the corresponding C(4)-substituted 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes (*e.g.* **127**, **129** and **130**). It is also pertinent to mention explicitly the formation of the acid (**132**). The transition state for the Cope rearrangement of (**130**), the presumed precursor of (**132**), is destabilized by a severe steric interaction between a CO_2H group and the *endo*-Bu^{t}O function (see **L**, R = H, R′ = CO_2H). Consequently, if this conversion is indeed a 'normal' Cope rearrangement, the facility with which it proceeds is surprising.



i, $Ph_3P{=}CH_2$, THF, reflux, 3 h; ii, $CH_2(CO_2H)_2$, piperidine, pyridine, 100 °C, 2 h

Scheme 19

Interesting recent studies have shown that bicyclo[3.1.0]hex-2-enes suitable for Cope rearrangement may be prepared directly from cyclopentadiene.[39,40] For example, carbenoid addition of the diazo diester (**134a**) to cyclopentadiene, followed by distillation of the product, gives the bicyclic diene (**136a**) in 98% yield (Scheme 20).[39] When the alkoxy-substituted diazo esters (**134b–134e**) are employed, the *endo*-divinylcyclopropanes (**135b–135e**) can be isolated in excellent yields and are found to be stable for days at room temperature. However, in refluxing toluene, these substances rearrange cleanly to the stereochemically homogeneous alkoxy diesters (**136b–136e**). The remarkable feature of these transformations is the highly stereoselective nature of the carbenoid addition reactions, which provide only the *endo*-divinylcyclopropanes (**135**). Also, as expected, the Cope rearrangements of (**135b–135e**) are completely stereoselective, with the *cis*-R and *trans*-CO_2Et substituents on the 6-(1-alkenyl) group of (**135**) ending up *exo* and *endo*, respectively, in the diene products (**136**).

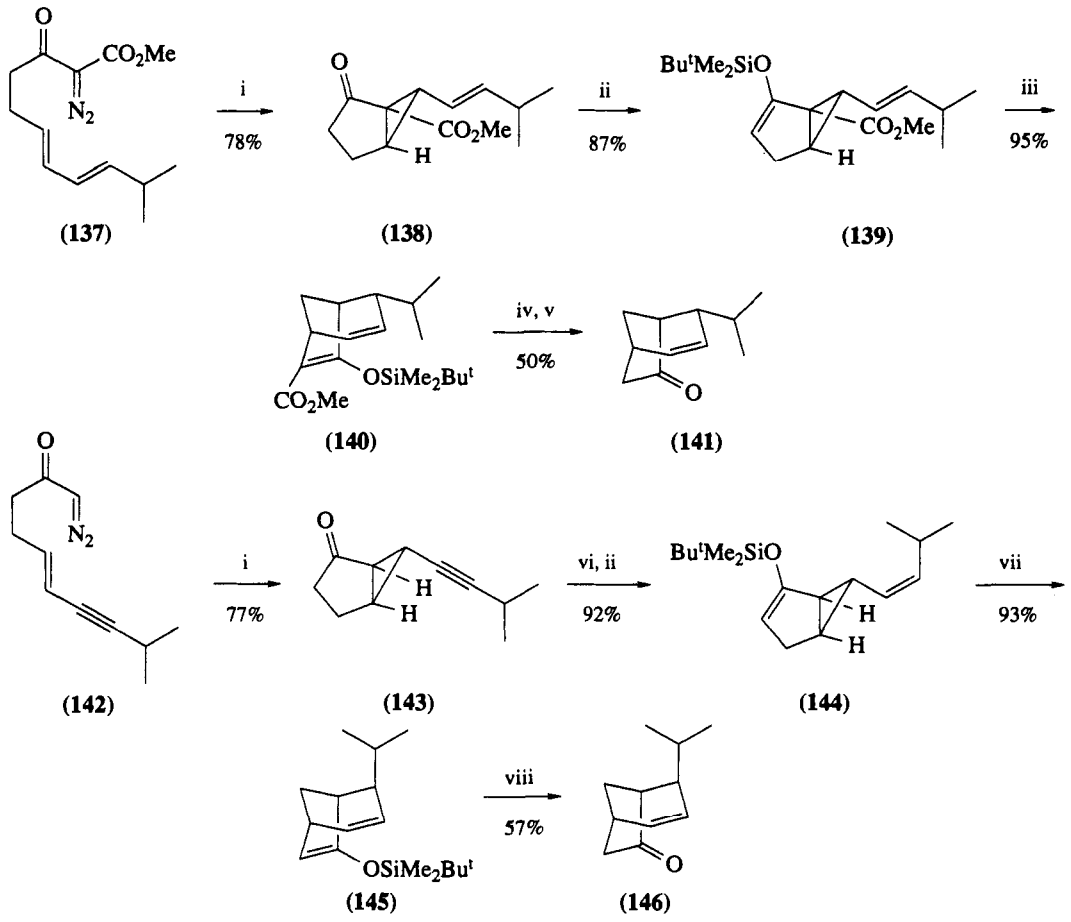


a, R = H; **b**, R = OMe; **c**, R = OEt; **d**, R = OPr^i; **e**, R = OBu^t

i, $Rh_2(OAc)_4$; ii, distillation (**135a**) or PhMe, reflux, 12 h (**135b–e**)

Scheme 20

Recent investigations have demonstrated that 6-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones are excellent precursors of Cope rearrangement substrates. The efficacy of this methodology may be illustrated initially by the synthesis of the diastereomeric ketones (**141**) and (**146**; Scheme 21).[41] Carbenoid cyclization of the diazo compounds (**137**) and (**142**) provides the bicyclic ketones (**138**) and (**143**). Since ring closures of this type are well known to be stereospecific with respect to the stereochemistry of the double bond involved, only the expected 6-*exo* substituted products are formed. Thermolytic sigmatropic rearrangement of the enol silyl ethers (**139**) and (**144**) (readily derived from **138** and **143**) proceeds in stereospecific fashion to afford the bicyclic dienes (**140**) and (**145**). The latter substances are readily converted into the epimeric keto alkenes (**141**) and (**146**). These syntheses illustrate clearly the stereochemical control that can be achieved *via* Cope rearrangement of bicyclo[3.1.0]hex-2-ene substrates possessing geometrically isomeric 6-(1-alkenyl) groups.

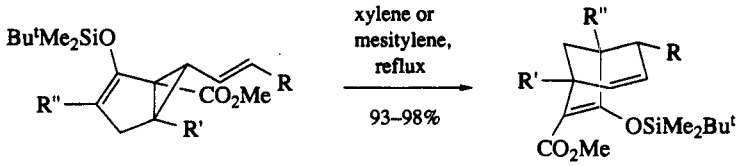


i, $Cu(acac)_2$, PhH, reflux; ii, LDA, THF, −78 °C; Bu^tMe_2SiCl, HMPA, −78 °C to r.t.; iii, 200 °C, 2 h, PhH (sealed tube); iv, Bu^n_4NF, THF; v, HCl, H_2O, THF, reflux; vi, H_2, $Pd/CaCO_3$, quinoline, pentane; vii, 240 °C, 4.5 h, PhH, (sealed tube); viii, HCl, H_2O, THF, r.t.

Scheme 21

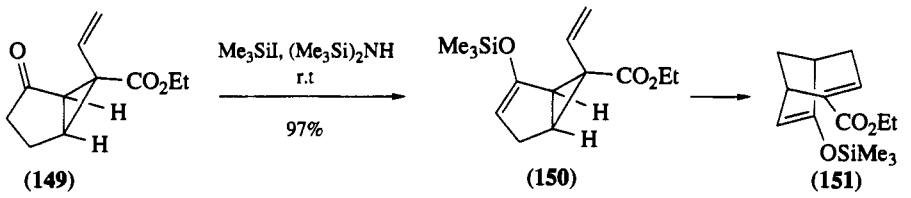
Thermolysis of the enol silyl ethers (**147a–147c**) (readily prepared *via* the methods outlined in Scheme 21, see **137** → **139**) provides high yields of the bicyclic dienes (**148a–148c**), as shown in equation (5).[41] Furthermore, the keto ester (**149**), when subjected to the reaction conditions shown in equation (6), is smoothly converted into the diene ester (**151**), presumably *via* the *cis*-divinylcyclopropane (**150**).[42]

The conversions summarized in Scheme 21 and equations (5) and (6) show clearly the synthetic versatility of using bicyclo[3.1.0]hexan-2-ones as precursors of divinylcyclopropanes. Indeed, bicyclo[3.2.1]octa-2,6-dienes possessing alkyl substituents at either bridgehead position (**148a**,**148c**) or at C-4 with *endo* (**141**,**148b**) or *exo* orientation (**146**) are readily prepared. Furthermore, the rearrangement



(147) (148) (5)

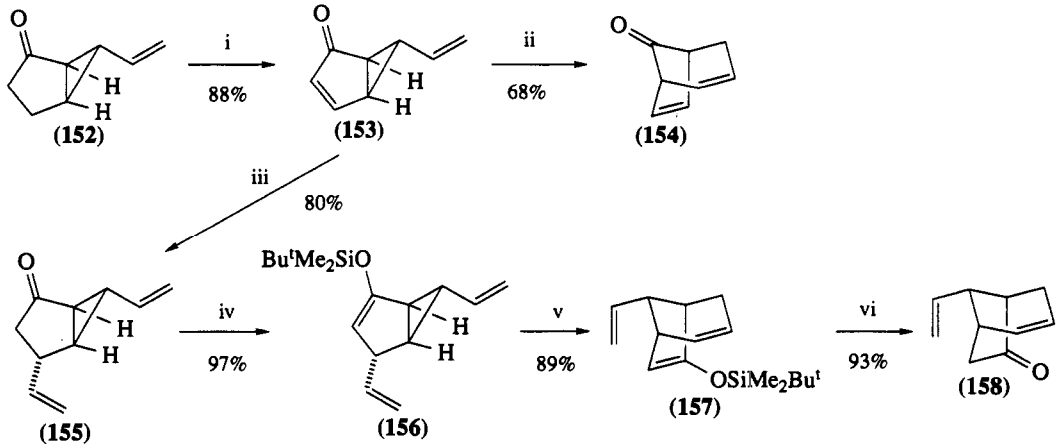
a, R = R" = H, R' = Me; **b**, R = R' = Me, R" = H; **c**, R = R' = H, R" = Me



(149) (150) (151) (6)

products contain, on the three carbon and two carbon bridges of the bicyclic system, functional groups that are readily amenable to further synthetic manipulations.

Bicyclo[3.1.0]hexan-2-ones are also suitable precursors for the synthesis of C(8)-functionalized bicyclo[3.2.1]octa-2,6-dienes. For example, the bicyclic enone (**153**), readily prepared from the ketone (**152**), contains a *trans*-divinylcyclopropane system in which one of the 'vinyl' groups consists of the enone carbon–carbon double bond. Indeed, thermolysis of (**153**) provides the Cope rearrangement product (**154**), which possesses at C-8 a synthetically versatile carbonyl group (Scheme 22).[41] Alternatively, copper(I)-catalyzed conjugate addition of vinylmagnesium bromide to the enone (**153**) provides a single product (**155**). The stereoselectivity of this process may be attributed to steric factors, with the reagent approaching the enone system from the less-hindered convex face. Thermolytic sigmatropic rearrangement of the enol silyl ether (**156**), readily obtained from (**155**), provides the triene (**157**), which can be hydrolyzed to the keto diene (**158**).[41] Thus, bicyclo[3.2.1]octane systems possessing at C-8 a useful functional group (*e.g.* **154**) or an *exo* substituent (*e.g.* **157** and **158**) are readily prepared.



(152) (153) (154) (155) (156) (157) (158)

i, LDA, THF, –78 °C; PhSeCl, –78 to 0 °C; HOAc, H_2O, H_2O_2, 0 °C; ii, 160 °C, 4 h, PhH (sealed tube); iii, H_2C=CHMgBr, CuBr•Me_2S, THF, –30 to 0 °C; iv, LDA, THF, –78 °C; Bu^tMe_2SiCl, HMPA, –78 °C to r.t.; v, 200 °C, 5 h, PhH (sealed tube); vi, HCl, H_2O, THF, r.t.

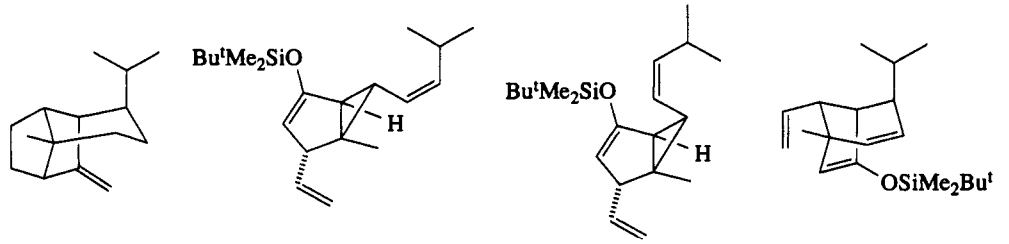
Scheme 22

8.2.5.3 Natural Product Syntheses

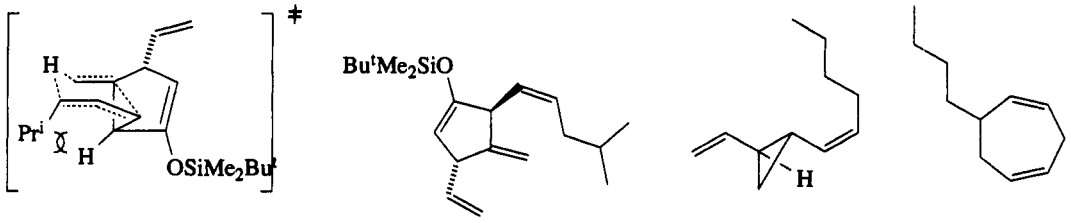
On the basis of the work summarized above, it would appear that the Cope rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes should be usefully applicable to the synthesis of natural products that possess, as part of their structures, the bicyclo[3.2.1]octane carbon skeleton. Recent work in this area,

involving total syntheses of the sesquiterpenoids (±)-sinularene, (±)-prezizanol and (±)-prezizaene, is discussed below.

The key intermediate for the synthesis of (±)-sinularene (**159**),[43] a structurally unusual marine natural product, was the bicyclic divinylcyclopropane (**160**). Successful Cope rearrangement of this substance would be expected to proceed *via* the *endo* isomer (**161**) to produce the bicyclo[3.2.1]octa-2,6-diene (**162**), possessing the correct stereochemistry at C-4 (*exo*-isopropyl group) and functionality (*exo*-vinyl group at C-8, enol ether associated with C-6 and C-7) that would allow the straightforward preparation of the tricyclic ring system of (±)-(**159**).



(**159**) (**160**) (**161**) (**162**)

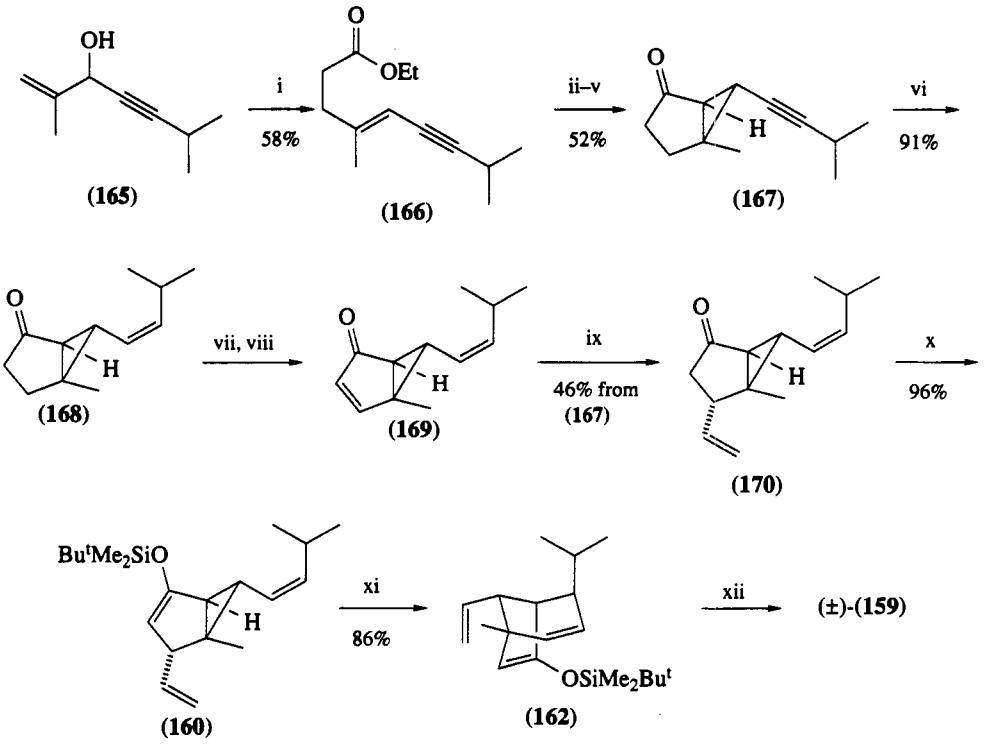


(**M**) (**163**) (**164**) (**16**)

In theory, thermolysis of (**160**) could also result in a [1,5] sigmatropic hydrogen migration,[6,29] involving the C-5 methyl group, to produce the unusually substituted cyclopentene (**163**). However, the expected transition state for this process[6,29] would be destabilized by a severe steric repulsion, as shown in (**M**), and, therefore, the energy of activation (E_a) for (**160**) → (**163**) would probably be considerably higher than 31.2 kcal mol^{-1}, the value associated with the conversion of the 'parent' *cis*-1-methyl-2-vinylcyclopropane into *cis*-1,4-hexadiene.[44] On the other hand, lack of appropriate literature data makes it difficult to predict the value of E_a associated with the isomerization of (**160**) to (**161**), the rate-determining step for the conversion (**160**) → (**162**). Nevertheless, since the energy of activation for the transformation of (**164**, racemate) into (**16**) has been shown[8] to be 32.8 ± 0.8 kcal mol^{-1}, one might expect E_a for (**160**) → (**161**) to be in the range 31–33 kcal mol^{-1}. Consequently, of the two alternative rearrangement pathways (**160** → **162** or **163**), it appeared that the Cope rearrangement would be energetically favored. This expectation turned out to be correct.

The stereochemically controlled synthesis of the key substrate (**160**) is outlined in Scheme 23.[43] A stereoselective ortho ester based Claisen rearrangement is employed to convert the alcohol (**165**) into the ester (**166**), which is transformed *via* a standard sequence of reactions into the bicyclic ketone (**167**). Chemo- and stereo-selective hydrogenation of the latter material provides the bicyclo[3.1.0]hexan-2-one (**168**), possessing the required (*Z*)-3-methyl-1-butenyl group at C-6. To set the stage for introduction of the necessary C-4 vinyl group, the ketone (**168**) is converted into the enone (**169**) by $Pd(OAc)_2$ oxidation of the corresponding enol trimethylsilyl ether. Treatment of (**169**) with lithium divinylcuprate gives a mixture of (**170**) and the corresponding C-4 epimer, in a ratio of about 9:1, respectively. Although this conjugate addition was not entirely stereoselective, the major product, resulting from approach of the cuprate reagent to the less-hindered side of the enone (**169**), possesses the required *exo* stereochemistry at C-4.

Routine conversion of the ketone (**170**) into the enol silyl ether (**160**) set the stage for investigating the key Cope rearrangement reaction. In the event, thermolysis of (**160**) provides a single product (**162**) in high yield. This result not only confirmed the expectation that the Cope rearrangement of (**160**) would be energetically favored over the alternative [1,5] sigmatropic hydrogen migration, but also demonstrated the efficacy of the Cope process for the stereoselective synthesis of a highly functionalized bicyclo[3.2.1]octa-2,6-diene. The diene (**162**) was readily converted into (±)-sinularene (**159**).[43]

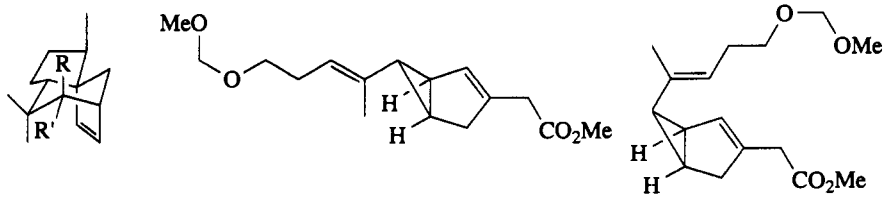


i, $(EtO)_3CMe$, $EtCO_2H$, 130 °C, 20 h; ii, KOH, H_2O–MeOH; iii, $(COCl)_2$, PhH, reflux; iv, CH_2N_2, Et_2O; v, $Cu(acac)_2$, PhH, reflux; vi, H_2, $Pd/CaCO_3$, n-C_5H_{12}; vii, Me_3SiI, Et_3N, CH_2Cl_2, –78 °C; viii, $Pd(OAc)_2$, MeCN, r.t.; ix, $(CH_2{=}CH)_2CuLi$, Et_2O, –30 °C to r.t.; x, LDA, THF, –78 °C; Bu^{t}Me$_2$SiCl, THF–HMPA, –78 °C to r.t.; xi, 220 °C, 4.5 h, PhH (sealed tube); xii, 4 steps

Scheme 23

The key step of the total syntheses of (±)-prezizanol (**171**) and (±)-prezizaene (**172**) was initially envisaged to be the Cope rearrangement of the 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene (**173**).[45] The stereoselective synthesis of this material was readily achieved,[45] but, unfortunately, thermolysis of (**173**) in benzene at temperatures in the range 155–220 °C produces a plethora of products from which the desired material (**175**) can be isolated in only poor yields (25% at best).[45,46] In contrast, thermolysis (PhH, 190 °C, 9 h) of substrate (**176**) proceeds cleanly to give (**177**).[45] Therefore, it is evident that the unsatisfactory nature of the rearrangement of (**173**) is due to the presence of the β,γ-unsaturated ester function, which, perhaps not surprisingly, is unstable at the high temperatures necessary to effect isomerization of (**173**) into the *endo* isomer (**174**). Therefore, since the [3,3] sigmatropic rearrangement of (**174**) would be expected to occur at relatively low temperatures, it appeared that the efficient production of (**175**) would have to involve the intermediacy of (**174**) rather than (**173**).

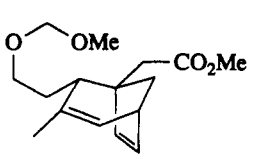
The stereoselective preparation of the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene (**174**) was achieved *via* the route summarized in Scheme 24.[46] Slow addition of a THF solution of the dichlorocyclopropane

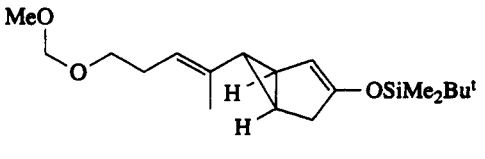


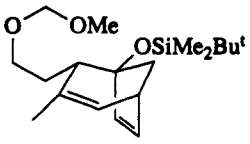
(**171**) R = Me, R' = OH
(**172**) R, R' = CH_2

(**173**)

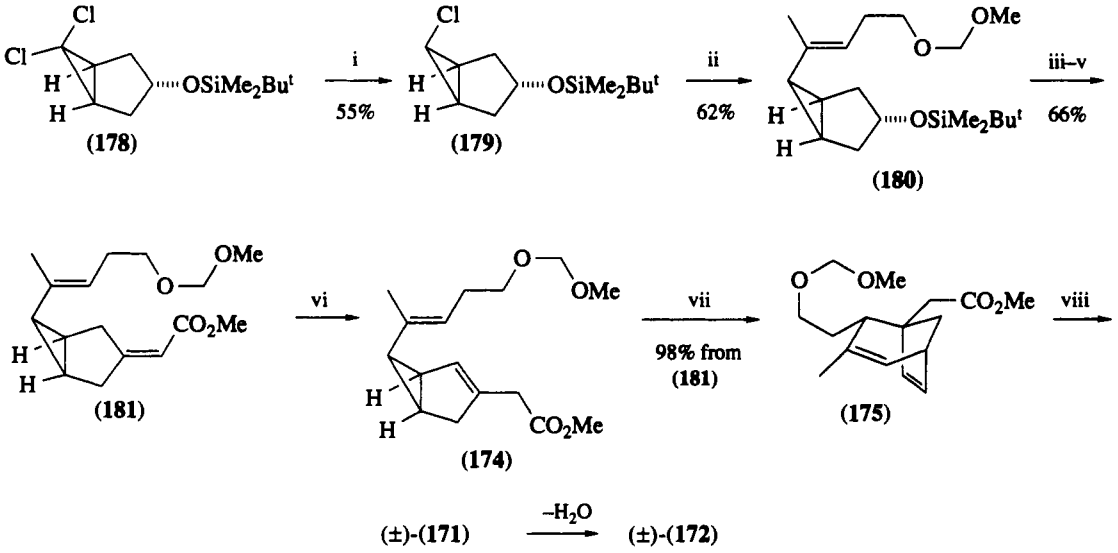
(**174**)


(175)


(176)


(177)

(**178**) to an excess of *t*-butyllithium at −107 °C, followed by protonation of the resultant intermediate, gives a mixture of (**179**) and the corresponding *exo*-chloride (4:1, respectively), from which (**179**) is obtained in 55% yield by chromatography. Treatment of (**179**) with lithium 4,4′-di-*t*-butylbiphenylide, conversion of the resultant cyclopropyllithium reagent into the corresponding organozinc chloride and palladium(0)-catalyzed coupling of the latter species with (*E*)-2-iodo-5-methoxymethoxy-2-pentene affords the bicyclic alkene (**180**). A standard sequence of reactions transforms the latter material into the α,β-unsaturated ester (**181**), which, upon deconjugation *via* the corresponding enolate anion, is converted into the key intermediate (**174**). At room temperature, the *cis*-divinylcyclopropane (**174**) rearranges slowly to (**175**) and, upon distillation at 110 °C under reduced pressure, is converted into (**175**) in essentially quantitative yield. Thus, a comparison of the thermolytic behavior of the epimers (**173**) and (**174**) shows clearly that, for the preparation of the bicyclic diene (**175**) *via* a Cope rearrangement process, the *endo* isomer (**174**) is a much more effective precursor than the *exo* isomer (**173**). Compound (**175**) serves as a suitable intermediate for the total synthesis of (±)-prezizanol (**171**), which, upon dehydration, gives (±)-prezizaene (**172**).[46]



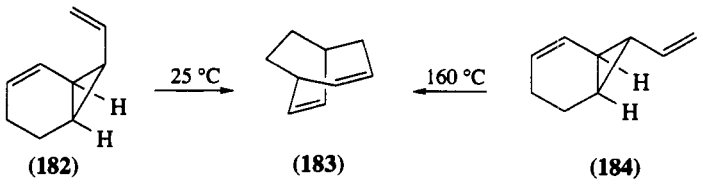
i, Bu^tLi, THF–Et_2O–pentane, −107 °C; AcOH, Et_2O, −107 °C; ii, (4,4′-di-*t*-butylbiphenyl)$^-$ Li^+, THF, −78 °C; $ZnCl_2$, THF, −78 to 0 °C; $(Ph_3P)_4Pd$, (*E*)-2-iodo-5-methoxymethoxy-2-pentene, THF, reflux, 1 h; iii, TBAF, THF; iv, PCC, NaOAc, CH_2Cl_2; v, $[(MeO)_2POCHCO_2Me]Li$, THF; vi, LDA, THF, −78 °C; HOAc, Et_2O, −78 °C; vii, 110 °C, 0.1 Torr (13.3 Pa); viii, 11 steps

Scheme 24

8.2.6 7-(1-ALKENYL)BICYCLO[4.1.0]HEPT-2-ENES

Although relatively little work has been done in this area, Schneider and Csacsko[47] have shown that 7-*endo*-vinylbicyclo[4.1.0]hept-2-ene (**182**) rearranges to bicyclo[3.2.2]nona-2,6-diene (**183**) under conditions (≤ 25 °C) similar to those required for bond reorganization of *cis*-1,2-divinylcyclopropane or

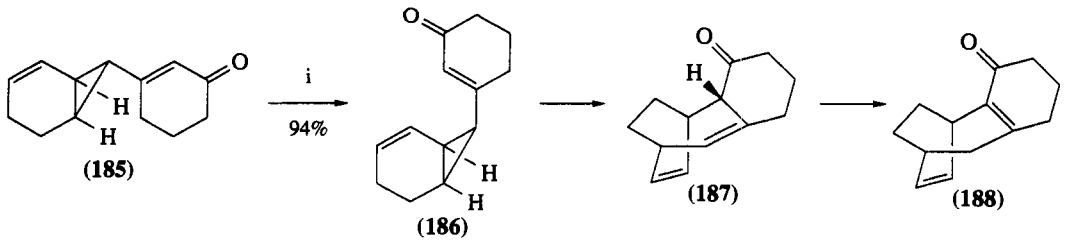
6-*endo*-vinylbicyclo[3.1.0]hex-2-ene. Furthermore, the corresponding *exo* isomer (**184**), upon thermolysis at 160 °C, also provides the bicyclic diene (**183**) in essentially quantitative yield (Scheme 25).[47]



(**182**) (**183**) (**184**)

Scheme 25

Thermolysis of the enone (**185**) produces the tricyclic ketone (**188**) in high yield (Scheme 26).[48] Supposedly, this transformation involves initial isomerization, *via* a diradical intermediate, of (**185**) into the *endo* isomer (**186**). Cope rearrangement of the latter substance gives the β,γ-unsaturated ketone (**187**), which, under the reaction conditions, isomerizes to the more stable conjugated isomer (**188**).

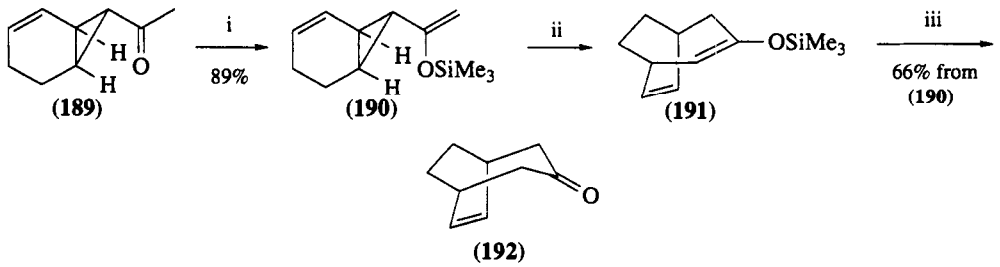


(**185**) (**186**) (**187**) (**188**)

i, *o*-dichlorobenzene, reflux, 40 h

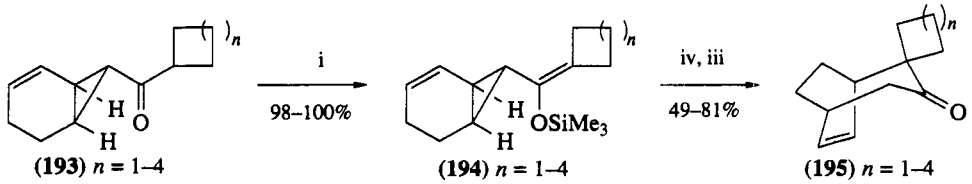
Scheme 26

The synthesis of bicyclo[3.2.2]non-6-en-3-one (**192**) and the spiro-substituted derivatives (**195**) can be achieved *via* similar methodology. Thus, thermolysis of the enol silyl ether (**190**), which is readily derived from the ketone (**189**), gives the bicyclic substance (**191**). Mild acid hydrolysis of (**191**) affords (**192**; Scheme 27).[49] In a similar fashion the *exo*-ketones (**193**) have been converted, *via* the enol silyl ethers (**194**), into the tricyclic keto alkenes (**195**).[49]



(**189**) (**190**) (**191**)

(**192**)



(**193**) n = 1–4 (**194**) n = 1–4 (**195**) n = 1–4

i, LDA, THF, –78 to 0 °C; Me_3SiCl, –78 °C to r.t.; ii, 240 °C, neat, 6 h; iii, HCl, H_2O, THF; iv, 240 °C, neat, 12 h

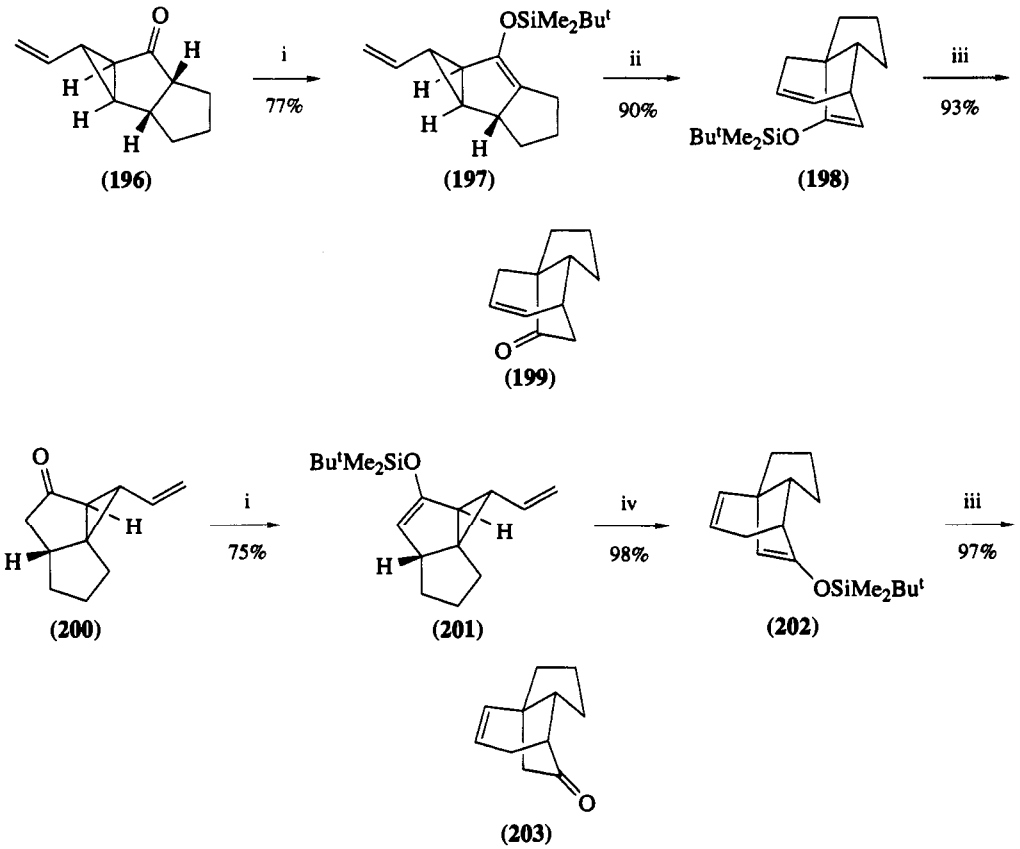
Scheme 27

Although small in number, the investigations summarized above show that the Cope rearrangement of 7-(1-alkenyl)bicyclo[4.1.0]hept-2-enes is an effective method for the synthesis of usefully functionalized bicyclo[3.2.2]nona-2,6-dienes.

8.2.7 TRICYCLIC 1,2-DIVINYLCYCLOPROPANE SYSTEMS

8.2.7.1 Synthesis of Tricyclic Substances Containing the Bicyclo[3.2.1]octane Carbon Skeleton

Recent studies, directed primarily toward the development of synthetic approaches to tricyclic and tetracyclic natural products, have demonstrated the viability of Cope rearrangements of substrates possessing a 1,2-divinylcyclopropane moiety as part of a tricyclic ring system. In these investigations, as in related studies described earlier (*vide supra*), one of the 'vinyl' groups is introduced by conversion of a ketone function into an enol silyl ether. For example, transformation of the tricyclic ketone (**196**) into the *trans*-divinylcyclopropane (**197**), followed by thermolysis of the latter substance, affords the tricyclic diene (**198**) cleanly and efficiently (Scheme 28).[50] Cleavage of the enol silyl ether function of (**198**) provides the ketone (**199**). In a similar fashion, the ketone (**200**), an isomer of (**196**), is transformed smoothly into the bridged tricyclic ketone (**203**) *via* the isolable intermediates (**201**) and (**202**) (Scheme 28).[51] It is worthwhile to note explicitly that, although the products (**199**) and (**203**) possess the same carbon skeleton, the functional groups are located at different positions.

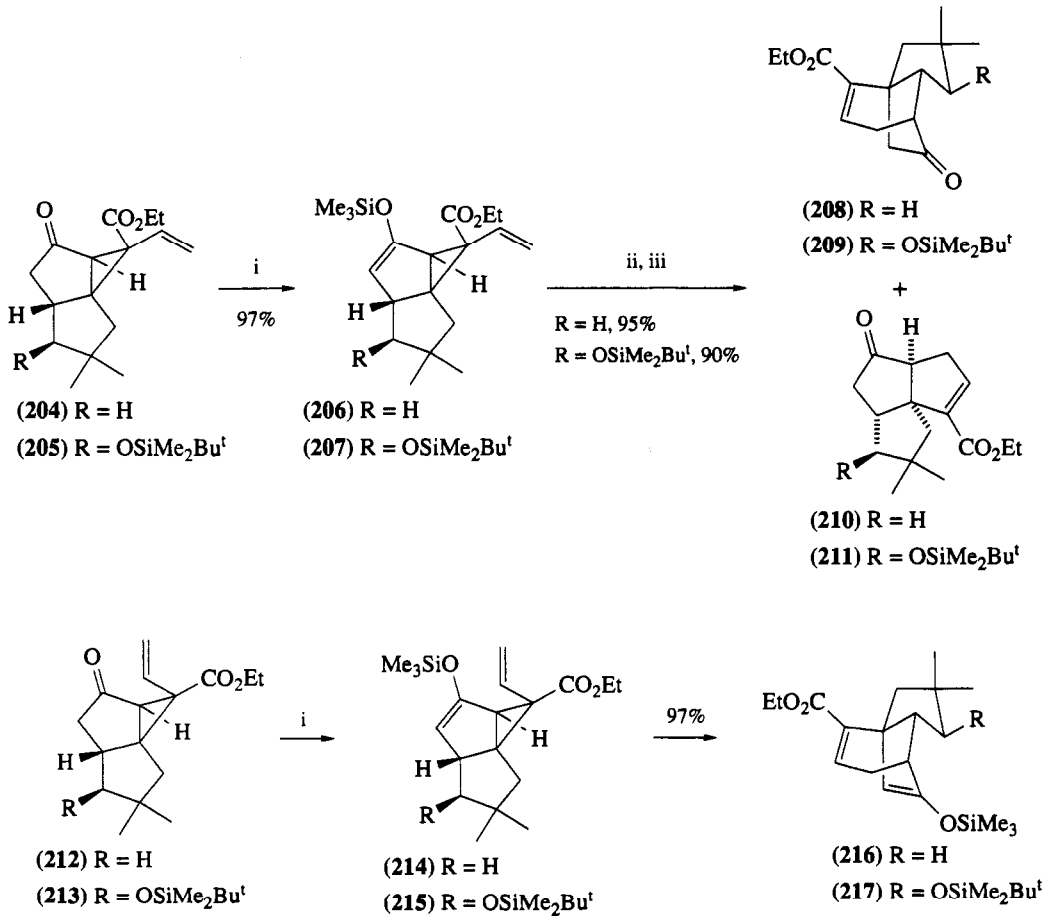


i, LDA, THF, –78 °C; Bu^tMe_2SiCl, THF–HMPA, –78 °C to r.t.; ii, 155 °C, 5 h, PhH (sealed tube); iii, TBAF, THF, –78 °C; iv, 170 °C, 5 h, PhH (sealed tube)

Scheme 28

Hudlicky and coworkers[42,52] have reported recently the Cope rearrangement of similar, but more highly functionalized substrates. For example, the keto esters (**204**) and (**205**) are readily converted into the

corresponding enol ethers (**206**) and (**207**) (Scheme 29).[42,52] Thermolysis of the latter substances at high temperatures, followed by acid hydrolysis of the enol ether functions in the resultant products, affords primarily the products (**208**) and (**209**) derived from Cope rearrangements, accompanied by lesser amounts of the angularly fused triquinanes (**210**) and (**211**), respectively. Interestingly, when the substrates (**212**) and (**213**), containing *endo*-vinyl substituents, are treated with TMS-I in the presence of $(TMS)_2NH$, the tricyclic substances (**216**) and (**217**) are obtained directly (Scheme 29).[42,52] Not unexpectedly, the intermediate *cis*-divinylcyclopropanes (**214**) and (**215**) undergo sigmatropic rearrangement at relatively low temperatures.



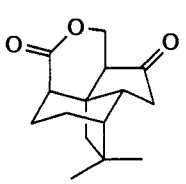
i, Me_3SiI, $(Me_3Si)_2NH$, pentane, –20 °C; ii, 585 °C, $PbCO_3$-conditioned Vycor tube; iii, HCl, H_2O, CH_2Cl_2

Scheme 29

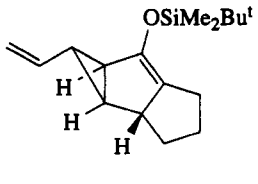
8.2.7.2 Natural Product Synthesis

The cytotoxic sesquiterpenoid (–)-quadrone, isolated from the fungus *Aspergillus terreus*, possesses the constitution and absolute stereochemistry shown in (**218**). The tricyclic carbon skeleton of this interesting natural product is the same as that found in compound (**198**), which, as described above (Scheme 28), is readily prepared by thermolysis of the tricyclic diene (**197**).[50] Thus, it appeared that the Cope rearrangement of a suitably substituted and functionalized derivative of (**197**) might serve effectively as a key intermediate in a total synthesis of (±)-quadrone (**218**); that is, successful Cope rearrangement of a substrate, such as (**219**), would provide, stereoselectively, the tricyclic substance (**220**). Presumably, the intermediate (**220**) could then be converted into the keto aldehyde (**221**), which had already been transformed into (±)-quadrone (**218**).[53]

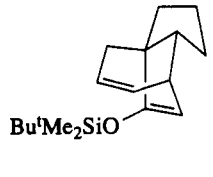
Treatment of the ketone (**222**) as shown in Scheme 30[51] gives a mixture of products from which the required divinylcyclopropane (**219**) may be isolated (chromatography) in 47% yield. Unfortunately, sub-



(218)



(197)



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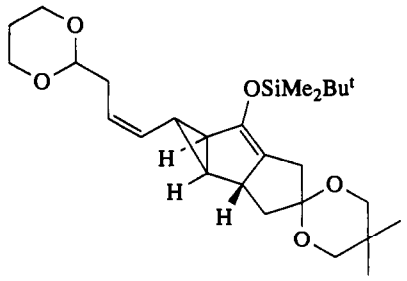
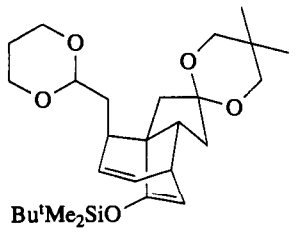
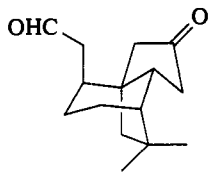


(219)

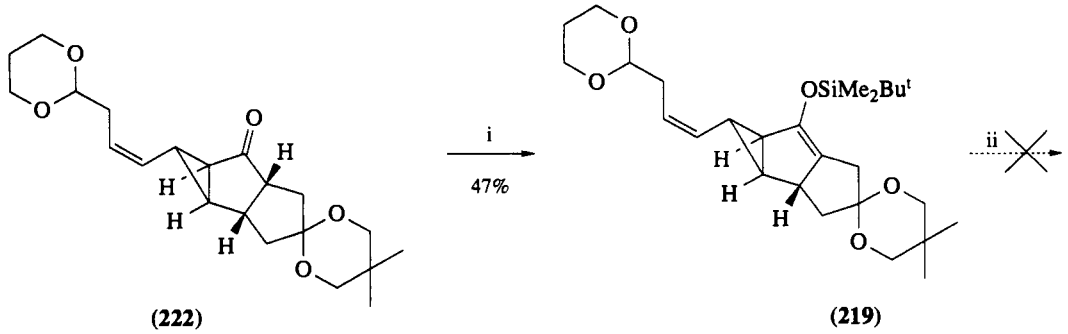


(220)



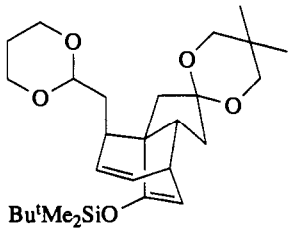
(221)

strate (**219**) does not undergo Cope rearrangement. Thermolysis of this material provides a mixture of products that does not contain any of the diene (**220**).[51]

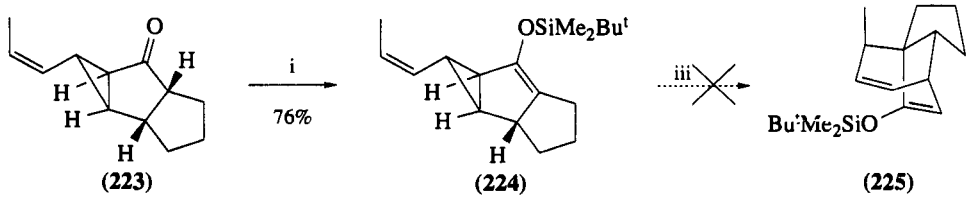


(222)

(219)



(220)



(223)

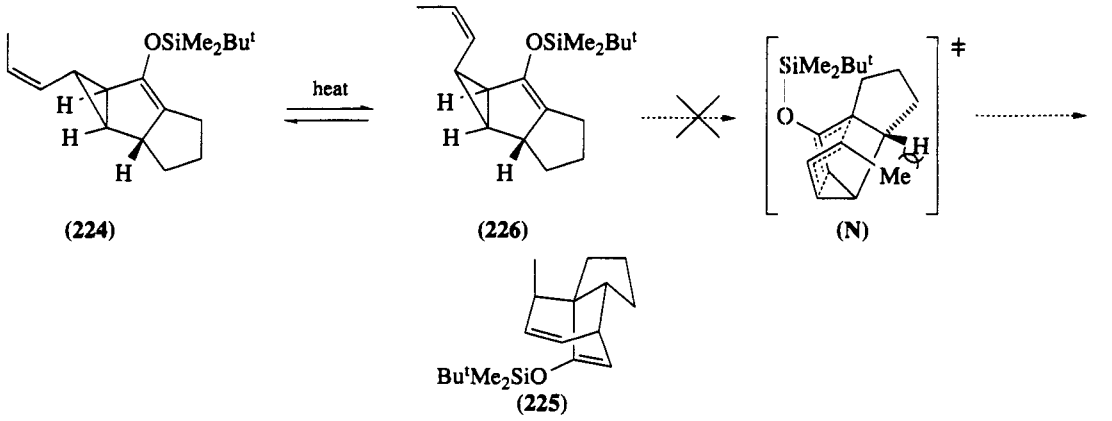
(224)

(225)

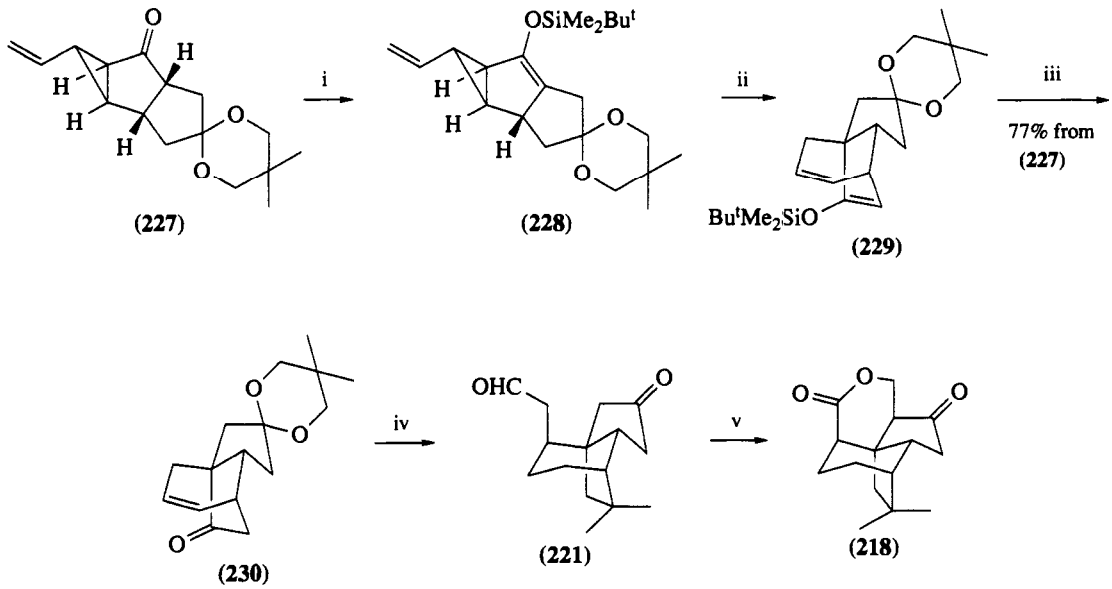
i, LDA, THF, –78 °C; $Bu^tMe_2SiOSO_2CF_3$, THF–HMPA, –78 °C to r.t.; ii, 170 °C, 5 h, PhH (sealed tube); iii, 170–175 °C, 4 h, PhH (sealed tube)

Scheme 30

In an effort to probe the reason(s) underlying the failure of the attempted thermolytic conversion of (**219**) into (**220**), the structurally simpler substrate (**224**) was prepared from the ketone (**223**; Scheme 30).[51] Interestingly, thermolysis of (**224**) also provides a mixture of products, a careful spectral examination of which shows clearly that the Cope rearrangement product (**225**) is not present. A comparison of this result with that obtained from thermolysis of (**197**), which proceeds smoothly to give (**198**) in 93% yield, shows once again that *cis* substituents on the 'vinyl' groups can have a profound effect on the efficacy of the Cope rearrangement of 1,2-divinylcyclopropane systems. Furthermore, since one would expect isomerization of (**224**) to the corresponding *endo* isomer (**226**) to be a facile process (Scheme 31), the failure of the conversion (**224**) → (**225**) must be related to the second step, involving sigmatropic rearrangement of (**226**) to (**225**). Indeed, an examination of molecular models indicates that, due to the inflexible nature of the tricyclic ring system of (**226**), the (proposed) transition state for the conversion (**226**) → (**225**) possesses a severe steric interaction between the angular proton and the methyl group of the *cis*-1-propenyl moiety (see N; Scheme 31). Apparently, due primarily to this destabilizing feature, the transition state (N) is disfavored relative to those related to other modes of bond reorganization and, therefore, none of the Cope rearrangement product (**225**) is produced. A similar line of reasoning may be invoked to rationalize the failure of (**219**) to undergo sigmatropic rearrangement to (**220**).



Scheme 31



i, LDA, THF, –78 °C; $Bu^tMe_2SiOSO_2CF_3$, THF–HMPA, –78 °C to r.t.; ii, 170-175 °C, 5 h, PhH (sealed tube); iii, TBAF, THF, –78 °C; iv, 10 steps; v, see ref. 53

Scheme 32

A successful formal total synthesis of (±)-quadrone (**218**) *via* a route in which a divinylcyclopropane rearrangement played a key role was achieved by employing the substrate (**228**; Scheme 32).[54] This material is readily prepared from the ketone (**227**) and, in contrast to compounds (**219**) and (**224**), undergoes smooth Cope rearrangement to the tricyclic diene acetal (**229**), which is easily transformed into the keto acetal (**230**). A rather lengthy sequence of reactions effects conversion of (**230**) into the keto aldehyde (**221**), which, as mentioned previously, has served as an intermediate in a total synthesis of (±)-quadrone (**218**).[53]

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8.3
Charge-accelerated Rearrangements

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8.3.1 CHARGE-ACCELERATED REARRANGEMENTS: BACKGROUND

8.3.1.1 Introduction

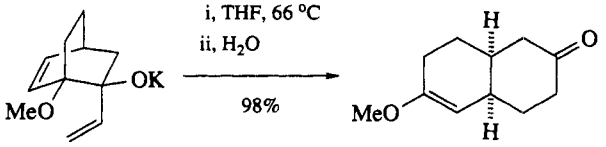
The strain intrinsic to small-ring compounds creates a potential for facile rearrangement which is not present in more conventional molecules. This characteristic of three- and four-membered rings has been extensively exploited in synthesis, particularly in such well-established ring expansion strategies as the vinylcyclopropane and divinylcyclobutane rearrangements. Although these reactions have proven utility as synthetic methods, they often suffer from serious limitations. Many of these rearrangements only proceed under relatively harsh reaction conditions (*e.g.* at high temperatures), and frequently require the ap-

plication of special techniques such as flash vacuum pyrolysis. Side reactions complicate the course of some small-ring rearrangements, compromising the efficiency of the reactions, and leading to mixtures of isomeric products which can be difficult to separate. Often these rearrangements also proceed with disappointingly low stereoselectivity.

It is now established that many of these limitations can be overcome by exploiting the accelerated rearrangements of small-ring compounds bearing charged substituents. The subject of this chapter is an overview of the progress recorded in this area to date. To place this chemistry in proper perspective, this background section summarizes the general features of charge-accelerated pericyclic reactions which have emerged during the past 20 years from studies of compounds which do not incorporate small rings. It should be noted that this subject is treated in greater detail in the chapters specifically concerned with sigmatropic processes (Chapters 7.1–7.3, this volume).

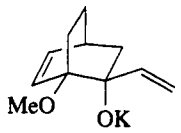
8.3.1.2 Azaanion- and Oxyanion-accelerated Rearrangements

The thermal rearrangement of 3-hydroxy-substituted 1,5-hexadiene derivatives (the 'oxy-Cope' rearrangement) is regarded as a useful synthetic route to δ,ε-unsaturated carbonyl compounds.[1] This 3,3-sigmatropic process is generally carried out at 200–400 °C, and is frequently accompanied by side reactions such as fragmentation initiated by 1,5-hydrogen shifts. In 1975, Evans and Golob[2] reported the remarkable observation that the potassium salts derived from 3-hydroxy-1,5-hexadienes undergo dramatically accelerated oxy-Cope rearrangement, in some cases exhibiting rate enhancements of 10^{17} compared to the corresponding alcohols. For example, the half-life for the rearrangement of (**1**; equation 1) at 66 °C was calculated to be only 1.4 min. The isomeric alkoxide (**3**), however, remained unchanged even after heating for 24 h. This and later observations by Evans and coworkers provided strong evidence that these rearrangements follow concerted pathways.[3,4] Since its discovery in 1975, the anionic variant of the oxy-Cope rearrangement has been widely exploited, particularly in the area of natural product synthesis.[5,6]



(1)

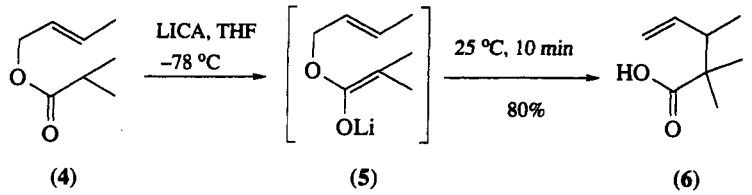
(1) (2)



(3)

Providing a rationale for the extraordinary rate acceleration observed in these reactions has been the aim of several theoretical and mechanistic studies. For example, Evans has shown from estimates of bond dissociation energies[7] as well as by *ab initio* calculations[8] that the effect of an oxyanion substituent is to weaken the adjacent carbon–carbon bond, thus facilitating the dissociation of this bond which is undergoing cleavage in the transition state for rearrangement. The experiments of Evans and coworkers stimulated Carpenter to develop a simple but operationally useful model for predicting the effect of substituents on a wide variety of pericyclic reactions.[9] According to this model, the activation energy for rearrangement of the anionic species is reduced because of the increased charge delocalization possible in the pericyclic transition state which, by definition, involves a completely conjugated array of orbitals. This stabilizing interaction is not present in the reactant, and consequently the net result is a reduction in $\Delta^{\ddagger}$. Carpenter's model predicts that this stabilizing effect should be observed for 'anionic, radical, or cationic substituents, provided that the skeletal atoms form an even-membered, uncharged ring in the transition state'.[10]

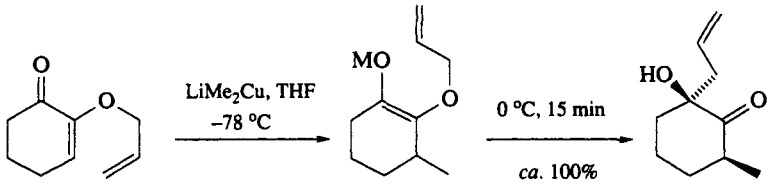
The ability of charged substituents to accelerate the 3,3-sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) has also been documented. The effect of oxyanion substituents on the rate and course of aliphatic Claisen rearrangements has been the subject of particular attention.[5,11] In 1972, Ireland and Mueller reported that the lithium enolate derivatives of allyl esters undergo rapid and effi-



(4) (5) (6) (2)

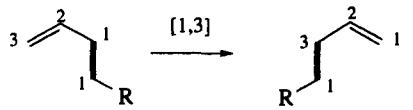
cient rearrangement at ambient temperature (*e.g.* equation 2).[12–14] By contrast, the thermal aliphatic Claisen rearrangement of allyl vinyl ethers generally requires temperatures in excess of 150 °C.

Oxyanion substituents at the terminal vinyl carbon of allyl vinyl ethers can also impart a considerable rate acceleration to the Claisen rearrangement. For example, enolate derivatives of α-allyloxy ketones rearrange to α-hydroxy-γ,δ-unsaturated ketones at temperatures as low as −42 °C; this reaction has been employed in an elegant tandem conjugate addition–Claisen rearrangement strategy (equation 3).[15] In some cases, however, the reactions of enolates derived from α-allyloxy carbonyl compounds have been found to follow alternative 2,3-sigmatropic (Wittig-type) rearrangement pathways.[16]

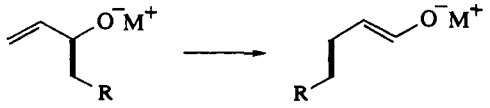


(7) (8) (9) (3)

The familiar Cope and Claisen rearrangements are classified as 3,3-sigmatropic rearrangements; by comparison, thermal 1,3-sigmatropic migrations of carbon atoms (equation 4) have received relatively little attention. Carpenter's model[9] predicts that an oxyanion substituent positioned at either terminus of the migrating σ-bond should facilitate these rearrangements, and in fact, recent studies have demonstrated that 1,3-sigmatropic shifts of alkali metal salts of both allylic (equation 5) and homoallylic (equation 6) alcohols can exhibit dramatic rate accelerations.



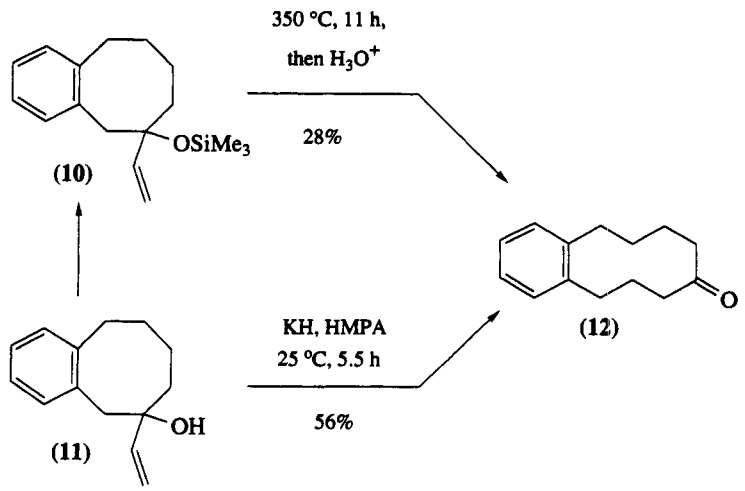
(4)



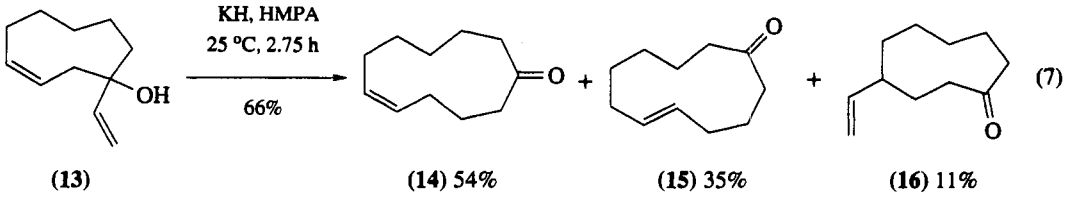
(5)

(6)

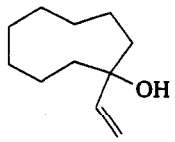
Early examples of accelerated 1,3-sigmatropic rearrangements involving allylic alcohol derivatives were reported by Thies and Seitz.[17] Thies and coworkers had previously employed thermal rearrangements of medium-ring 1-trimethylsilyloxy-1-vinyl-3-cycloalkene derivatives as a useful method for two-carbon ring expansion. These reactions require relatively high temperatures (280–350 °C), however, and in some cases, *e.g.* (**10**) → (**12**), proceed in rather poor yield (Scheme 1). Thies and Seitz found that the ring expansion of the corresponding potassium alkoxides in highly dissociating media such as HMPA occurs rapidly at room temperature, and is often considerably cleaner than the analogous thermal rearrangements. This two-carbon ring expansion strategy has also been successfully applied to several medium-ring 1-vinyl-3-cycloalkenols (equation 7), although in some cases oxy-Cope rearrangement, *e.g.* (**13**) → (**16**), is observed as a competing process. In the case of larger ring systems, *e.g.* cyclotridecenol, 3,3-sigmatropic rearrangement in fact becomes the predominant mode of reaction.



Scheme 1

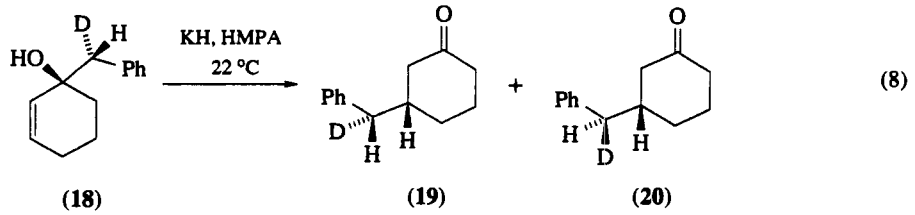


A noteworthy feature of these 1,3-rearrangements is the requirement that the migrating carbon be activated by a vinyl or aryl π-bond; that is, in equation (5), R must be a vinyl or aryl group. Saturated 1-vinylcycloalkanols such as (**17**) show no tendency to rearrange when treated with KH in HMPA at room temperature.[17b] These results are consistent with a concerted 1,3-shift mechanism, but also raise the possibility that these reactions can follow a stepwise pathway involving fragmentation to an allylic (or benzylic) carbanion, followed by intramolecular Michael addition. Related 1,3-rearrangements in which the migrating carbon is even more activated (*e.g.* as a dithiane derivative) appear to proceed *via* such retro-aldol/conjugate addition mechanisms.[18]



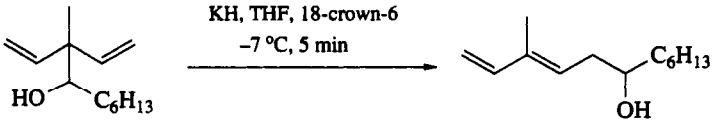
(**17**)

Zoeckler and Carpenter have also studied oxyanion-accelerated 1,3-sigmatropic rearrangements of allylic alcohols, focusing particular attention on the stereochemical course of the reaction.[10] An interesting feature of Carpenter's model for accelerated pericyclic reactions is that it predicts that charged substituents should accelerate orbital symmetry forbidden[19] pathways more than the corresponding allowed ones. This principle is a consequence of the ability of charged substituents to more effectively stabilize antiaromatic forbidden transition states by interacting with the low-lying LUMO or high-lying HOMOs which they possess. In accord with these predictions, the 1,3-sigmatropic rearrangement of (**18**; equation 8) was found to proceed predominantly (≥65%) by the suprafacial-retention pathway to afford (**19**), even

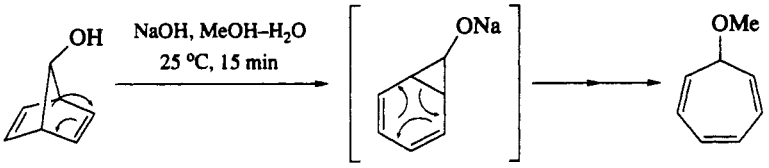


though the Woodward–Hoffmann rules suggest that inversion of configuration at the migrating carbon should be favored.

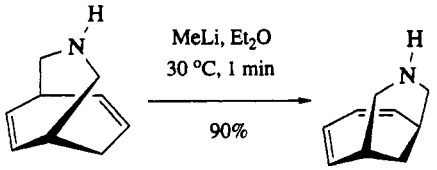
Several examples of anion-accelerated 1,3-sigmatropic rearrangements involving homoallylic alcohols (equation 6) have also been reported. In fact, reactions of this type involving lithium, magnesium, and zinc alkoxides have been known for many years.[20] However, whereas the rearrangements of magnesium and zinc salts of alcohols such as (**21**; equation 9) require several days of heating at 65 °C, the reactions of the corresponding potassium salts are complete within minutes at 0 °C.[21] The sodium salt of 7-norbornadienol (**23**) is subject to a similar 1,3-sigmatropic shift which takes place at room temperature. In this reaction the norcaradiene derivative which is generated then undergoes a further disrotatory 6π-electrocyclic rearrangement to eventually furnish methyl tropyl ether (equation 10).[22] Krow and Reilly have reported a very similar 1,3-shift, accelerated by an azaanion substituent (equation 11).[23] Deuterium-labeling studies indicated that this rearrangement occurs *via* suprafacial migration with predominant retention of configuration at the migrating carbon, an outcome which is in accord with Carpenter's model.



(21) (22) (9)

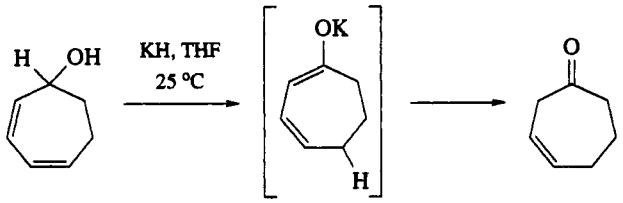


(23) (24) (25) (10)

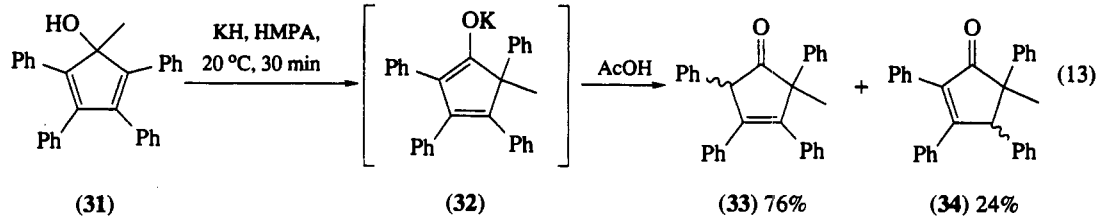


(26) (27) (11)

The ability of an oxyanion substituent to facilitate 1,5-hydrogen sigmatropy was demonstrated by Paquette *et al.* in 1980. For example, rearrangement of the potassium salt of 2,4-cycloheptadienol occurs more than 10^5 times faster than the rearrangement of the corresponding alcohol (equation 12).[24] Accelerated 1,5-shifts of alkyl, vinyl, aryl and cyclopropyl groups in cyclopentadiene derivatives (*e.g.* equation 13) have also been reported.[25]



(28) (29) (30) (12)

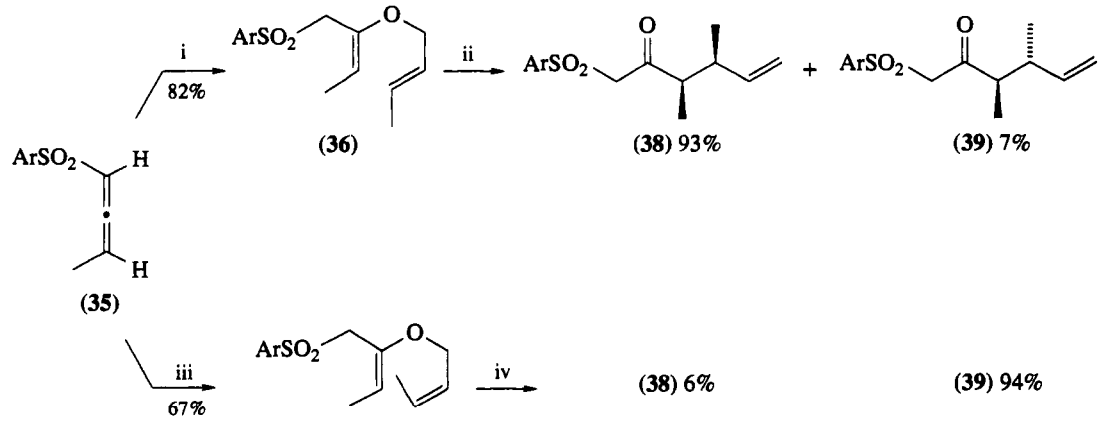


(31) (32) (33) 76% (34) 24%

8.3.1.3 Carbanion-accelerated Rearrangements

The ability of certain carbanion substituents to accelerate the aliphatic Claisen rearrangement has been documented in several laboratories. These reactions bear close analogy to the Ireland ester enolate rearrangement and related oxyanion-accelerated processes discussed in the previous section. Denmark reported the first examples of the carbanion-accelerated Claisen rearrangement in 1982.[26] Subsequent studies have established that this reaction has broad scope and provides a valuable synthetic route to γ,δ-unsaturated ketones.[27] Arylsulfonyl-stabilized carbanions appear to be particularly effective in promoting these reactions. Analogous carbanions stabilized by other sulfur-based functional groups tend to decompose *via* elimination pathways, and nitrile and ester derivatives also fail to undergo rearrangement, presumably due to the extensive delocalization of charge in these anions.

The arylsulfonyl carbanion accelerated Claisen rearrangement is completely regioselective and has also been found to be highly diastereoselective (Scheme 2).[27a] The stereochemical course of the reaction conforms to the familiar chair-like transition state model usually invoked for the classic thermal process. Recently, high degrees of asymmetric induction have been observed in the rearrangements of chiral cyclic phosphoramidate stabilized carbanion derivatives.[27c]

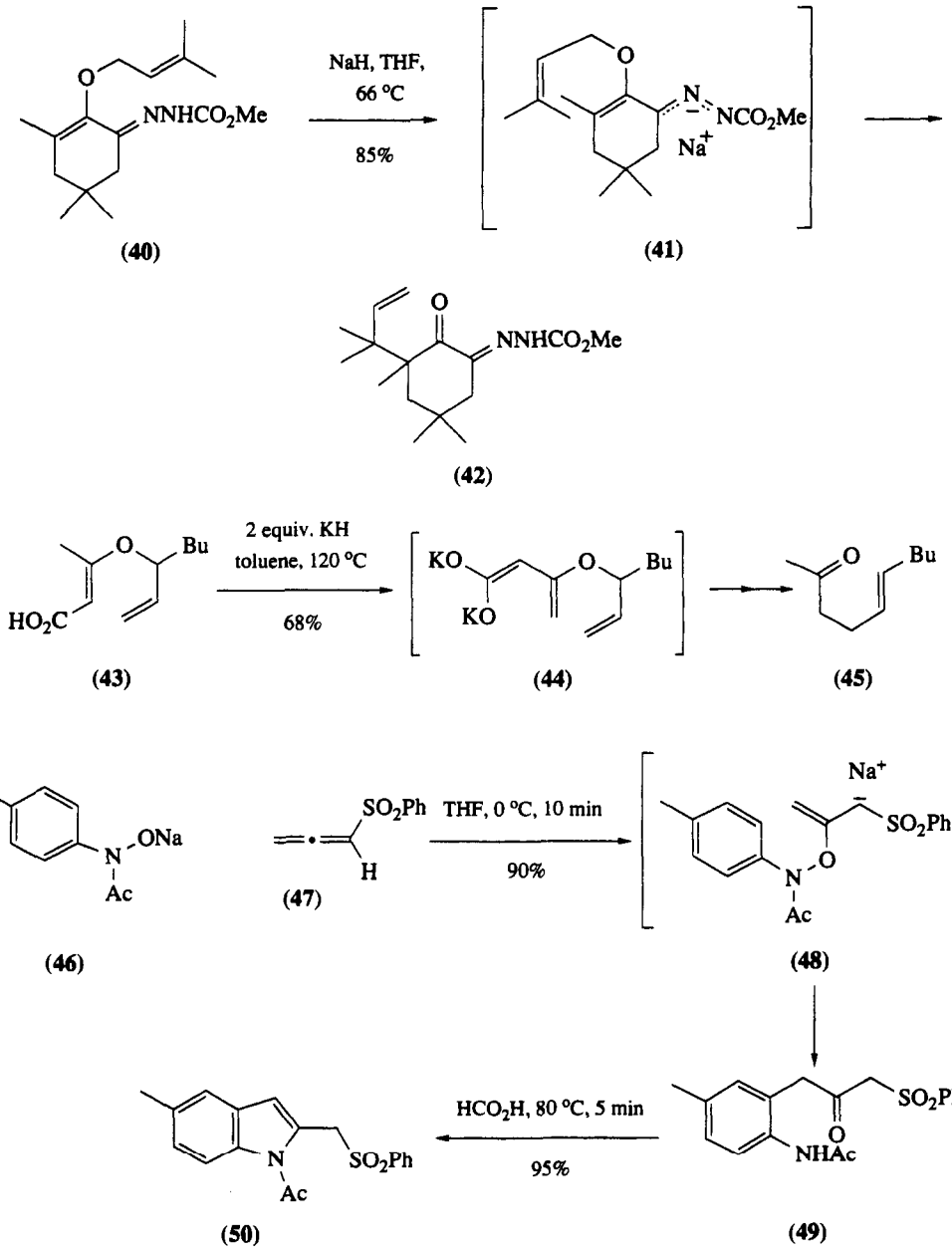


i, *(E)*-$HOCH_2CH{=}CHMe$, NaH, THF; ii, KCH_2SOMe, DMSO, 20 °C, 4 h;
iii, *(Z)*-$HOCH_2CH{=}CHMe$, NaH, THF; iv, $LiCH_2SOMe$, DMSO, 50 °C, 1.5 h

Scheme 2

Other carbanionic substituents are equally effective in promoting unusually facile rearrangements of allyl vinyl ethers. Ponaras has reported that the rearrangement of the hydrazone sodium salt (**41**; equation 14) occurs with $t_{1/2}$ = 15 h at 66 °C; note that this reaction creates a sterically congested product with two adjacent quaternary centers.[28] Büchi and Vogel have described Claisen rearrangements accelerated by carboxylic acid dianions (equation 15).[29] No rearrangement was observed at 120 °C with the corresponding simple carboxylate salt.

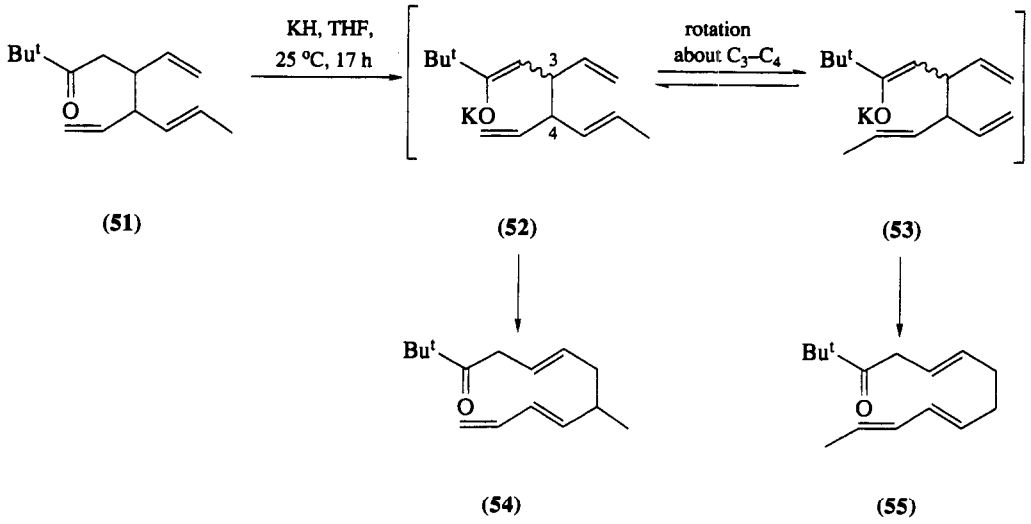
Blechert has developed an interesting synthesis of 2-substituted indoles which involves the conjugate addition of *N*-phenylhydroxylamine salts (or *N*-phenylnitrones) to electron-deficient allenes, followed by carbanion-accelerated hetero-Cope rearrangement of the Michael adduct.[30] For example, addition of the hydroxylamine salt (**46**) to the allenyl sulfone (**47**) produces the anion (**48**), which undergoes rapid 3,3-sigmatropic rearrangement to afford the β-keto sulfone (**49**). Cyclization to the indole proceeds smoothly upon exposure to formic acid (Scheme 3).



Scheme 3

Wender and coworkers reported the first example of an enolate-accelerated Cope rearrangement in 1985.[31] Exposure of the trienone (**51**; Scheme 4) to potassium hydride in THF at room temperature for 17 h led to the formation of a 1.2:1 mixture of (**55**) and (**54**); each rearranged trienone was produced as a mixture of alkene isomers. The facility with which the rearrangement of the ketone enolates takes place is underscored by the observation that the corresponding silyl enol ethers remain unchanged under identical conditions, and require temperatures in excess of 100 °C for efficient rearrangement.

Finally, no examples of carbanion-accelerated 1,3-sigmatropic rearrangements appear to have been observed to date, although Okamura and coworkers have reported a transformation which may involve a sulfinyl carbanion accelerated 1,5-hydrogen shift.[32]



Scheme 4

8.3.2 CHARGE-ACCELERATED REARRANGEMENTS OF CYCLOPROPANES

8.3.2.1 Introduction

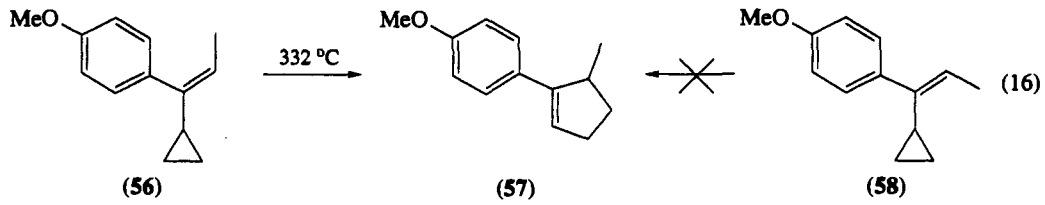
The rearrangement of a cyclopropane ring is the pivotal step in a large number of important synthetic strategies.[33] Cyclopropane ring expansion and ring fission reactions have been effected using a very wide range of reaction conditions. Thus, rearrangements have been induced by both thermal and photochemical activation of cyclopropane derivatives, by treatment with nucleophilic, electrophilic, and radical species, and also with the aid of various main-group and transition metal reagents. Many of these rearrangements involve charged cyclopropane derivatives as either starting materials or reactive intermediates. The subject of this chapter is charge-accelerated small-ring rearrangements; this area is defined as including only those reactions which, although accelerated by charged substituents, nonetheless can also take place in the absence of such substituents. Among cyclopropane rearrangements, the most important process of this type is the vinylcyclopropane to cyclopentene rearrangement.

The vinylcyclopropane (VCP) rearrangement is the subject of several excellent reviews,[34] including Chapter 8.1, this volume. As detailed in these references, the VCP rearrangement has seen extensive application as a strategy for the synthesis of a variety of substituted and functionalized five-membered carbocycles. In spite of these successful applications, several features of the conventional, thermal process compromise its utility as a general synthetic method. As will be seen in the next section, these limitations can to a large extent be overcome through recourse to charge-accelerated variants of the reaction. The most serious limitations associated with the thermal version of the VCP rearrangement include those mentioned below.

(i) *Extreme reaction conditions.* The vinylcyclopropane to cyclopentene rearrangement proceeds with activation energies in the range of 30 to 65 kcal mol^{-1} (1 cal = 4.18 J).[34b] Consequently, high temperatures (frequently over 500 °C) are required to effect the reaction, particularly in sterically congested systems. In some cases these harsh conditions are not compatible with highly functionalized synthetic intermediates.

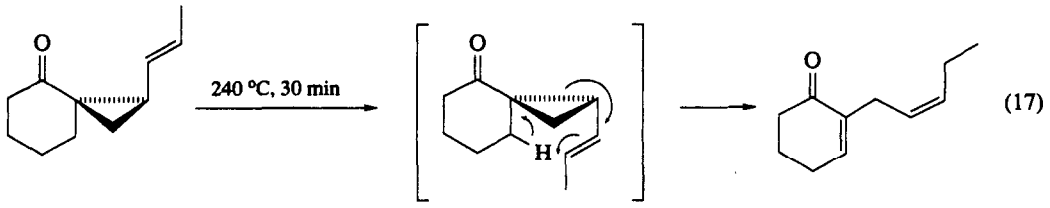
(ii) *Limited scope.* Synthetically significant substrates sometimes resist rearrangement within the range of reasonable reaction temperatures. For example, while the rearrangement of (**56**; equation 16) proceeds smoothly at 332 °C, the isomeric vinylcyclopropane (**58**; in which the requisite rearrangement conformation is sterically disfavored) is totally inert under these conditions, and at higher temperatures undergoes polymerization.[35]

(iii) *Side reactions.* The intervention of side reactions further limits the scope of the thermal vinylcyclopropane rearrangement. In particular, cyclopropanes with *syn*-vinyl and α-CH-bearing groups are subject to homo 1,5-hydrogen shifts leading to 1,4-dienes, and rarely undergo satisfactory vinylcyclopropane rearrangement. The activation energy for this concerted retro-ene process is typically 31 to 33 kcal mol^{-1}, significantly lower than the energy usually required for the VCP rearrangement.



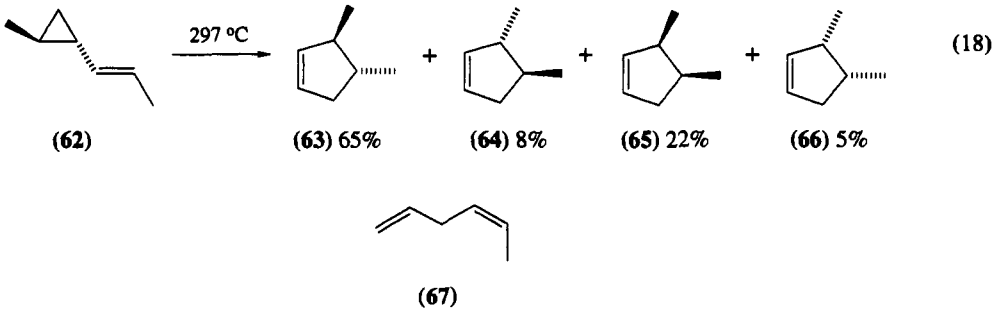
(56) (57) (58) (16)

Even in vinylcyclopropane derivatives in which the vinyl group is *anti* to the CH group, thermolysis often leads to 1,4-dienes as a result of isomerization to the *syn* isomer, followed by 1,5-shift (*e.g.* equation 17).[36]



(59) (60) (61) (17)

(iv) *Stereochemical ambiguities.* As illustrated with equation (18), the thermal VCP rearrangement generally proceeds with modest stereoselectivity.[37] A problem in some cases is that at the high reaction temperatures diastereomerization of the initial cyclopropane occurs more rapidly than rearrangement. Note that in the reaction depicted in equation (18) the major product formed is in fact the diene (**67**), the result of homo 1,5-sigmatropic hydrogen shift (1,4-diene:total cyclopentenes = 13:1).



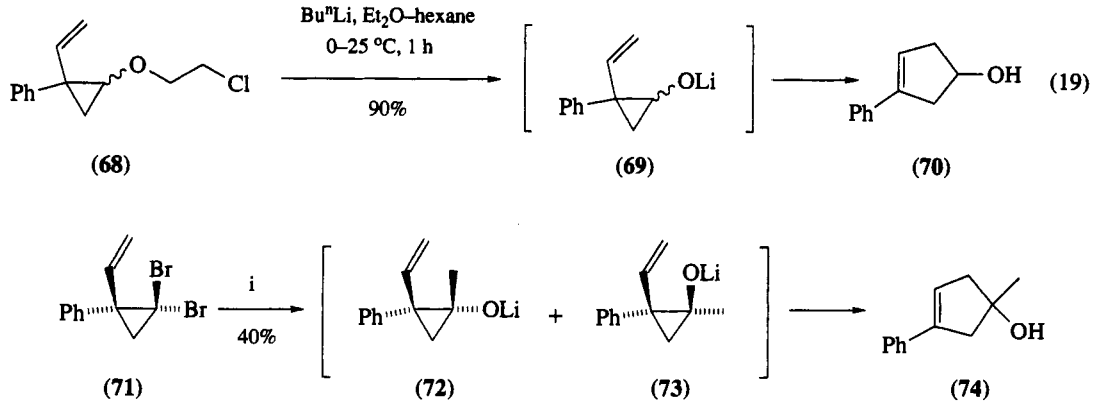
(62) (63) 65% (64) 8% (65) 22% (66) 5% (18)

(67)

8.3.2.2 Oxyanion-accelerated Vinylcyclopropane Rearrangements

The first example of a charge-accelerated vinylcyclopropane rearrangement was reported by Danheiser *et al.* in 1980.[38] Cleavage of the diastereomeric 2-chloroethoxy ethers (**68**; equation 19) with *n*-butyllithium[39] at 0 °C generated the vinylcyclopropanol lithium salts (**69**), which rearranged smoothly to the cyclopentenol (**70**) upon warming to room temperature. The facility of this oxyanion-accelerated process stands in dramatic contrast to the high temperatures required to effect conventional thermal vinylcyclopropane rearrangements. Although electron-donating substituents had previously been shown to increase the rate of the VCP rearrangement, even these systems require temperatures in excess of 200 °C for efficient reaction. For example, the activation energies for the rearrangement of 1-methoxy-2-vinylcyclopropane and 1-dimethylamino-2-vinylcyclopropane have been determined to be 39 and 31 kcal mol^{-1}, respectively.[40]

As outlined in Scheme 5, tertiary cyclopropanol salts are also subject to the oxyanion-accelerated VCP rearrangement. In this sequence the requisite vinylcyclopropanol salts are conveniently prepared from readily available 1,1-dibromocyclopropanes by sequential halogen–metal exchanges, followed first by alkylation,[41] and then by oxygenation.[42] Products resulting from alternative 1,5-hydrogen shift (retro-ene) pathways were not detected in these reactions.

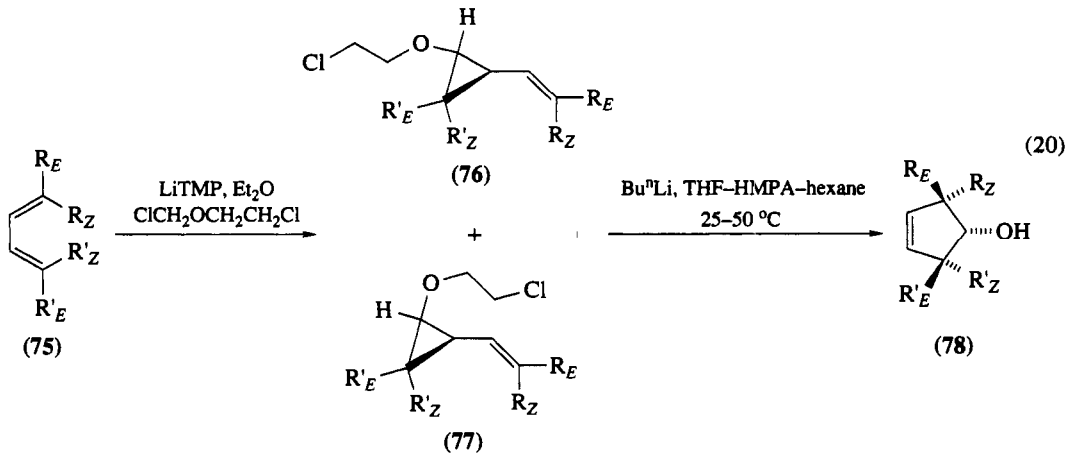


i, 1 equiv. Bu^{n}Li, −100 °C, then 1 equiv. MeI, then 2 equiv. Bu^{t}Li (−78 °C), then bubble in O_2, warm to 25 °C

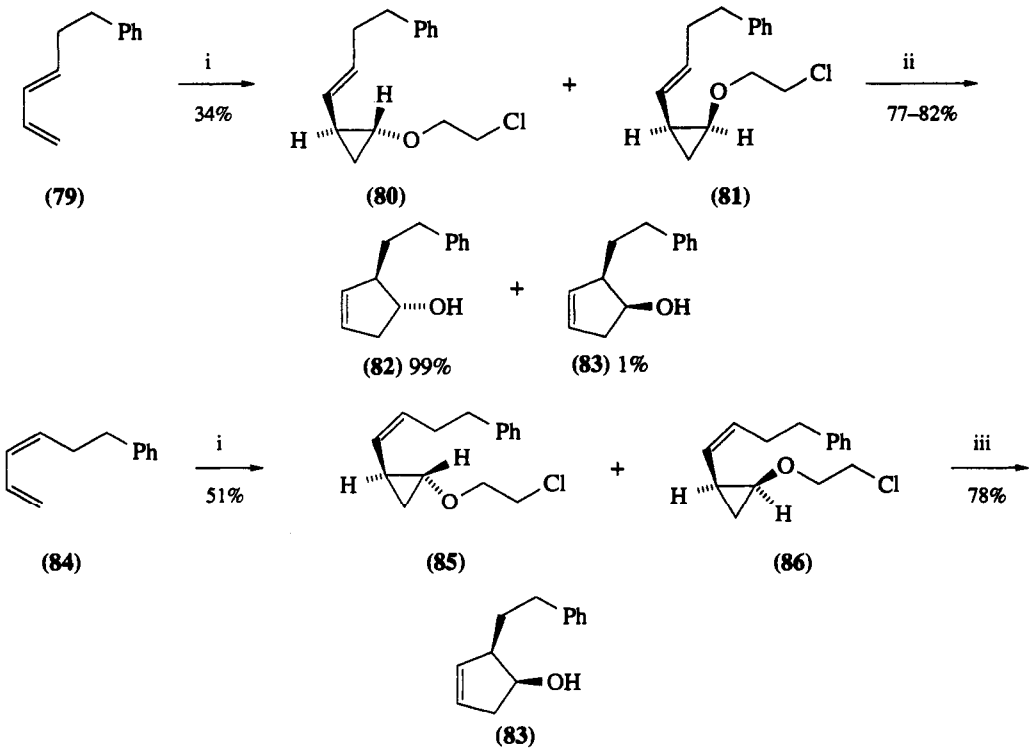
Scheme 5

Further studies on the scope and stereochemical course of the oxyanion-accelerated vinylcyclopropane rearrangement were reported in 1981.[43] This paper introduced a general [4 + 1] annulation strategy for the synthesis of cyclopentene derivatives in which the anion-accelerated VCP rearrangement functions as the key step. In this report, the accelerated version of the vinylcyclopropane rearrangement was also shown to proceed with remarkably high stereoselectivity, in further contrast to the thermal process.

For the purposes of synthetic planning, the overall transformation may be viewed as the suprafacial *exo* cycloaddition of hydroxycarbene across the termini of a conjugated diene (equation 20). Operationally, the annulation is accomplished in two steps. The first step involves the stereospecific *syn* addition of 2-(chloroethoxy)carbene[44] to the 1,3-diene to produce a mixture of vinylcyclopropanes (**76**) and (**77**). Exposure of these isomeric ethers to *n*-butyllithium in a mixture of THF, hexane, and HMPA at 0 to 50 °C then effects ether cleavage[39] and rearrangement of the resulting lithium salts in a single step. The intermediate *syn*- and *anti*-2-vinylcyclopropanol salts rearrange by topologically different pathways to afford, in most cases, a single cyclopentenol.



Application of the [4 + 1] strategy to (*E*)- and (*Z*)-6-phenyl-1,3-hexadiene illustrates the stereochemical course of the annulation (Scheme 6). Addition of 2-(chloroethoxy)carbene in each case occurs exclusively at the less-substituted double bond to afford a mixture of *syn*- and *anti*-2-vinylcyclopropyl ethers. Rearrangement of the corresponding lithium salts then furnishes (**82**) [99:1 mixture of (**82**) and (**83**) from the (*E*)-diene (**79**)] and (**83**) [exclusive product from the (*Z*)-diene (**84**)] in accord with the paradigm expressed in equation (20). Separate rearrangement of pure (**80**) and (**81**) revealed that the trace of *cis*-substituted cyclopentenol produced from the (*E*)-diene originates entirely in the rearrangement of the *syn* isomer (**81**). In addition, the stereochemical integrity of the lithium salts derived from (**82**) and (**83**) upon prolonged heating suggests that these cyclopentenols are the kinetic products of rearrangement.



i, LiTMP, Et_2O, $ClCH_2OCH_2CH_2Cl$; ii, Bu^nLi, THF–HMPA–hexane, 25 °C, 1 h;
iii, Bu^nLi, THF–HMPA–hexane, 50 °C, 1 h

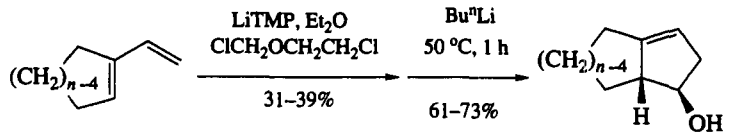
Scheme 6

A variety of other conjugated dienes participate in the [4 + 1] annulation with stereochemistry in accord with the predictions of equation (20). The 1-vinylcycloalkenes (**87**)–(**89**) can be viewed as (*E*)-substituted dienes, and are thus expected to yield the *exo*-alcohols (**90**)–(**92**). In each of these cases carbene addition generates a mixture of four intermediate 2-vinylcyclopropyl ethers, each of which then rearranges to produce exclusively the predicted stereoisomer. Application of the annulation to the endocyclic (*Z,Z*)-dienes (**93**) and (**94**) also generates in each case a single bicyclo[*n*.2.1]alkenol, and the (*E,E*)-diene (**97**) similarly reacts to afford exclusively the cyclopentenol (**98**; Scheme 7).

In contrast to the very high stereoselectivities observed for the reactions discussed above, the mixture of vinylcyclopropanol salts obtained from (*E,Z*)-2,4-hexadiene (**99**) rearranges to the predicted cyclopentenol (**102**) with a preference of only 4:1. Separate rearrangement of the vinylcyclopropyl ethers (**100**) and (**101**; Scheme 8) suggests that the paradigm expressed in equation (20) cannot be applied to systems incorporating C-3 substituents *syn* to the vinyl group on the cyclopropane ring. Note, however, that the desired VCP rearrangement does occur smoothly in this system, and no retro-ene cleavage of the cyclopropane ring was observed to take place as in the case of analogous thermal reactions.

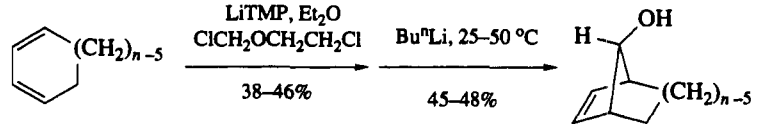
The stereochemical course of the oxyanion-accelerated vinylcyclopropane rearrangement can be explained on the basis of several alternative mechanisms.

(i) *Concerted 1,3-sigmatropic shift mechanism.* Four stereochemically distinct pathways can be distinguished for a concerted 1,3-sigmatropic shift: suprafacial migration across the π-system with either inversion (*si* pathway) or retention (*sr*) at the migrating center, and antarafacial rearrangement with either inversion (*ai*) or retention (*ar*) at the migrating center. Three effects have been suggested to contribute to determining the relative energies for these alternative pathways: (a) conservation of orbital symmetry (Woodward and Hoffmann)[19] predicts that the transition states for the *si* and *ar* pathways should be of lower energy than those for the *sr* and *ai* modes of reaction; (b) the Berson–Salem subjacent orbital effect[45] predicts stabilization of the transition states for the orbital symmetry disfavored *sr* and *ai* pathways due to interaction of the π-orbital of the migrating carbon and the subjacent HOMO bonding orbital of the allylic system; (c) as discussed earlier, Carpenter predicts that a charged substituent should stabilize the orbital symmetry disfavored pathway in a sigmatropic rearrangement more than it stabilizes the symmetry favored one.[10,46]



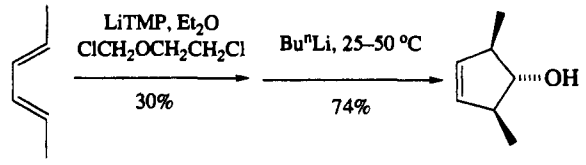
(87) $n = 5$
(88) $n = 6$
(89) $n = 7$

(90) $n = 5$
(91) $n = 6$
(92) $n = 7$



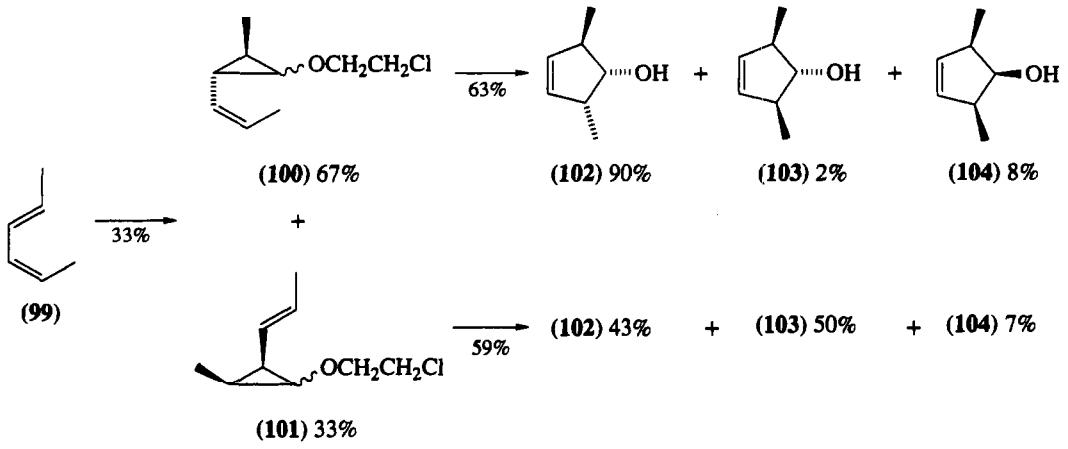
(93) $n = 6$
(94) $n = 7$

(95) $n = 6$
(96) $n = 7$



(97) (98)

Scheme 7



(100) 67% (102) 90% (103) 2% (104) 8%

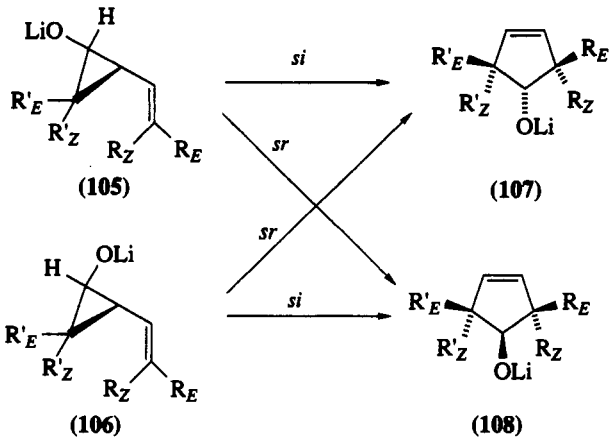
(99) + (101) 33%

(102) 43% + (103) 50% + (104) 7%

Scheme 8

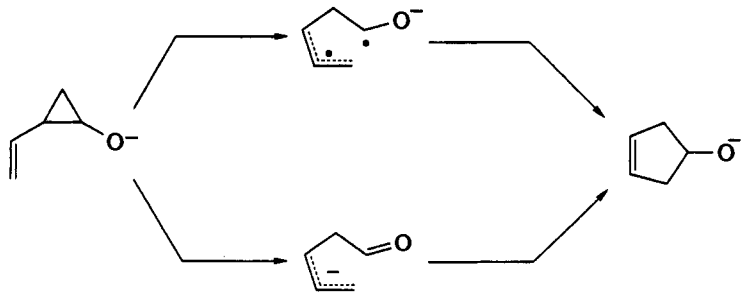
Scheme 9 shows the possible rearrangement products from suprafacial 1,3-sigmatropic migration of the isomeric vinylcyclopropanol salts (**105**) and (**106**). The '*exo* suprafacial' annulation product generally observed (equation 20) corresponds to cyclopentenol (**107**) in this scheme. Conservation of orbital symmetry requires that the *si* pathway should be favored for the isomer (**105**) in which the oxyanion substituent is *anti* to the vinyl group on the cyclopropane ring. However, migration with inversion at C-1 is sterically disfavored for the isomeric salt (**106**) in which the vinyl and oxyanion substituents are oriented *syn* on the cyclopropane ring; the clockwise somersaulting action required at the migrating atom would force the solvated lithium alkoxide into the allylic framework in this transition state. This isomer consequently rearranges *via* the subjacent orbital stabilized *sr* pathway. Thus, both (**105**) and (**106**) are expected to rearrange *via* topologically different concerted pathways to afford the same cyclopentenol (**107**).

(ii) *Stepwise mechanisms.* These can also be proposed to account for the oxyanion-accelerated vinylcyclopropane rearrangement (Scheme 10). However, these stepwise pathways involving diradical and allylic anion aldehydes are only compatible with the observed stereochemical results provided that cyclization of the intermediates occurs faster than conformational interconversions. The observation that the



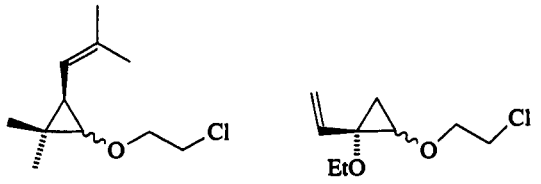
Scheme 9

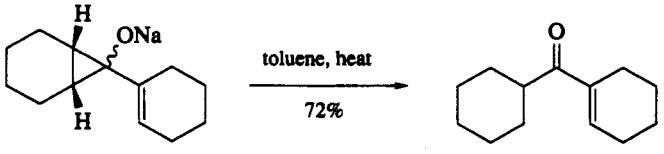
rearrangements of (**101**) and the vinylcyclopropanes derived from (**97**) result in different product distributions, excludes mechanisms involving freely rotating acyclic intermediates, since in that case both reactions would proceed through a common intermediate and therefore yield the same results.



Scheme 10

Several unsuccessful oxyanion-accelerated vinylcyclopropane rearrangements have also been noted. For example, the lithium alkoxides derived from the highly substituted 2-vinylcyclopropyl ethers (**109**) failed to undergo rearrangement even after prolonged heating at 66 °C. Treatment of (**110**; derived from 2-ethoxybutadiene) with *n*-butyllithium resulted in the formation of complex mixtures in which no cyclopentenol could be detected. Fragmentation of the oxyanion intermediate apparently occurs more rapidly than 1,3-sigmatropic rearrangement in this system. Finally, several reports have appeared indicating that the alkali metal salts of 1-vinylcyclopropanols are not subject to accelerated vinylcyclopropane rearrangement.[47,48] For example, thermolysis of (**111**) in toluene gave the fragmentation product (**112**) with no evidence of VCP rearrangement.[48]

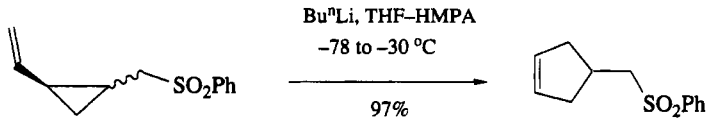




(21)

8.3.2.3 Carbanion-accelerated Vinylcyclopropane Rearrangements

The ability of carbanionic substituents to accelerate the vinylcyclopropane rearrangement was reported by Danheiser and coworkers in 1985.[49] α-Sulfonyl carbanions proved to be the most effective activating groups for these reactions. For example, exposure of (**113**; equation 22) to 1.2 equiv. of *n*-butyllithium in 5:1 THF–HMPA at –78 °C generated the corresponding lithium derivative, which rearranged smoothly upon warming to –30 °C to afford the cyclopentene (**114**) in 97% yield. The carbanion-accelerated vinylcyclopropane rearrangement thus occurs with even greater facility than the oxyanion-accelerated version of the reaction.



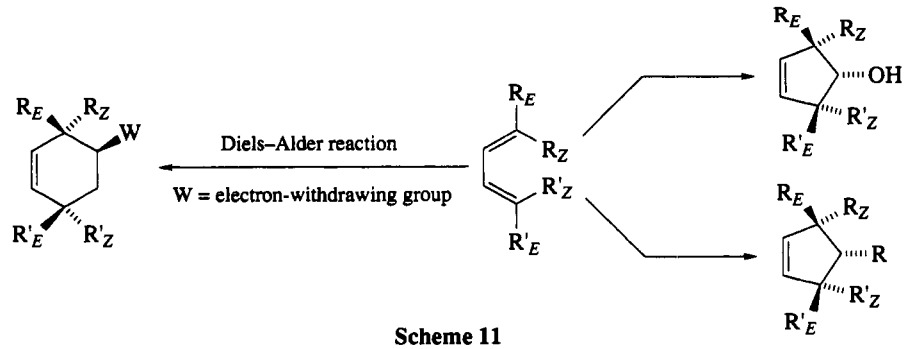
(22)

(**113**) (**114**)

The use of HMPA as cosolvent is crucial to the success of these reactions; in its absence no rearrangement was observed to occur, even after warming to higher temperatures. Interestingly, if the lithium derivative of (**113**) is quenched at –78 °C with methanol, then the (vinylcyclopropyl)methyl sulfone is recovered, but the ratio of *syn* and *anti* diastereomers is significantly different from that in the starting material (an increase in the amount of the *anti* isomer is observed). Also noteworthy is the observation that the rearrangement of the corresponding potassium derivative is complicated by the formation of acyclic by-products such as (**115**). These results suggest the possibility that heterolytic cleavage of the metallated (vinylcyclopropyl)methyl sulfones is occurring in these reactions, and that the accelerated VCP rearrangement may proceed *via* a stepwise fragmentation–conjugate addition pathway.

(**115**)

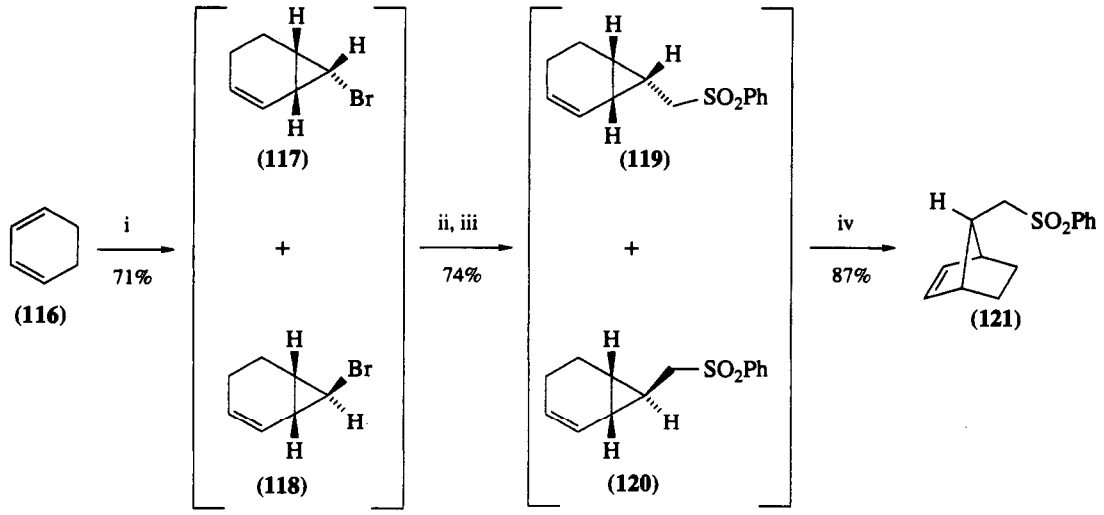
From the perspective of synthetic analysis, the anion-accelerated vinylcyclopropane rearrangement provides a method, analogous to the Diels–Alder reaction, for the conversion of conjugated dienes to cyclopentene derivatives. As outlined in the previous section, the oxyanion-accelerated version of the reaction serves as the key step in a process which results in the effective 1,4-addition of hydroxycarbene about the termini of a 1,3-diene (Scheme 11). The carbanion-accelerated vinylcyclopropane rearrangement comprises the pivotal step in a second-generation version of this [4 + 1] annulation strategy, which extends the method to include the synthesis of cyclopentene derivatives bearing a variety of functionalized substituents in place of the hydroxy group on the new five-membered ring.



Scheme 11

A typical annulation sequence (utilizing 1,3-cyclohexadiene as the diene component) is outlined in Scheme 12. Addition of monobromocarbene (generated from CH_2Br_2 and NaHMDS by the method of Martel)[50] furnished the isomeric bromocyclopropanes (**117**) and (**118**). Phenylthiomethylation was then achieved by coupling the Grignard derivatives with iodomethyl phenyl sulfide in the presence of 0.05 equiv. of Li_2CuCl_4[51] in THF–Et_2O at –30 to 25 °C. Next, chemoselective oxidation of the resulting sulfides was accomplished using MoO_5·HMPA·H_2O,[52] or alternatively, with MCPBA or potassium hydrogen persulfate ('oxone').[53] Exposure of the resulting pair of sulfones (**119**) and (**120**) to 1.2 equiv. of

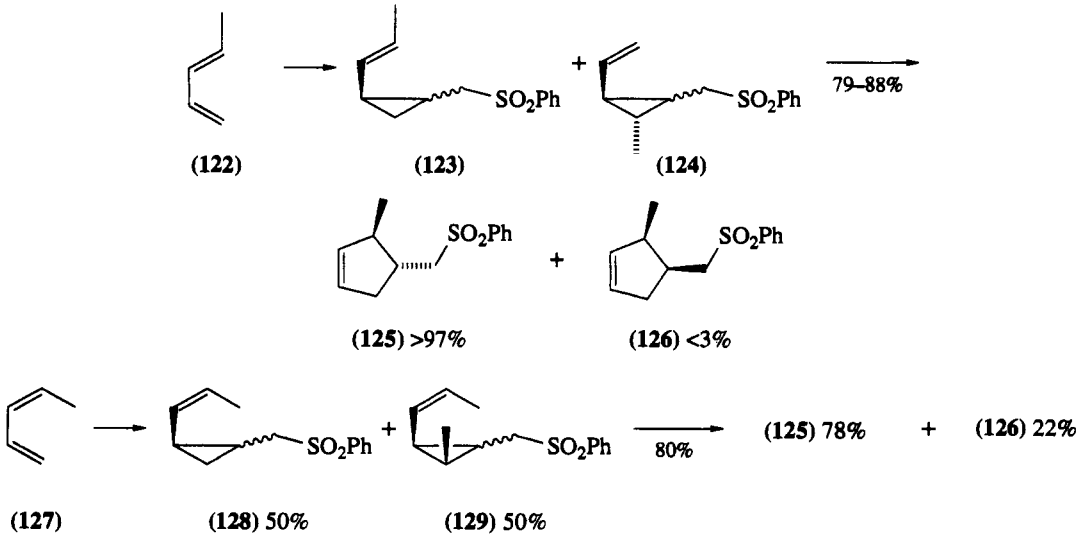
Bu^nLi in THF–HMPA at –78 °C, followed by warming to room temperature, then furnished the expected norbornene (**121**) as a single stereoisomer in 87% yield.



i, NaHMDS, CH_2Br_2, pentane; ii, Bu^tLi, $MgBr_2$, $PhSCH_2I$, cat. Li_2CuCl_4, THF–Et_2O; iii, MoO_5–HMPA–H_2O, CH_2Cl_2; iv, Bu^nLi, THF–HMPA, –78 to 25 °C

Scheme 12

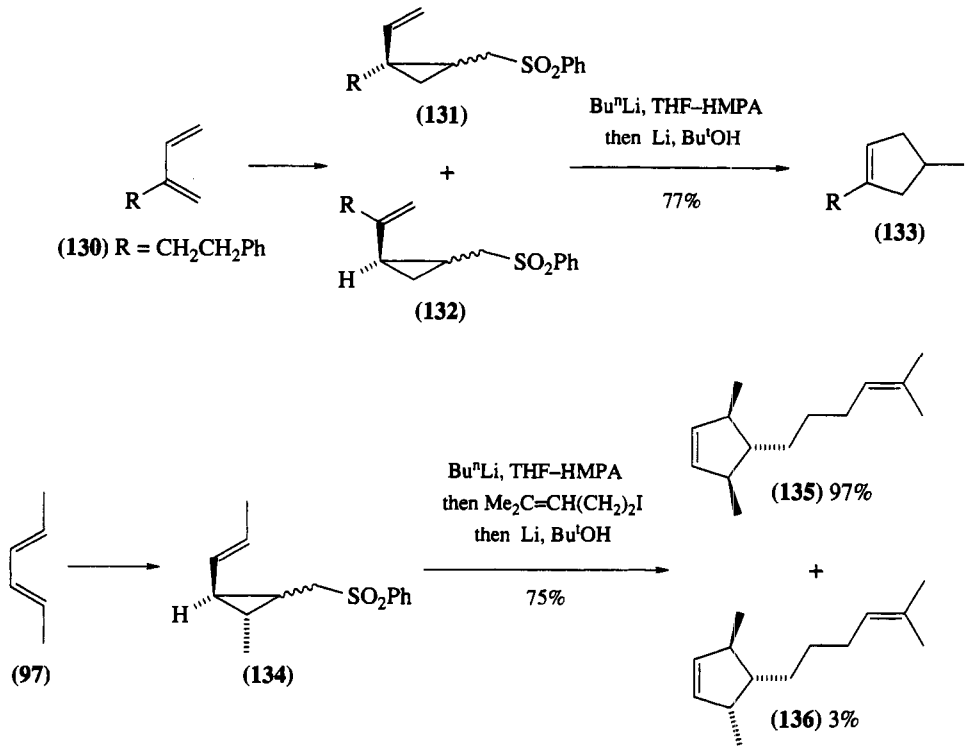
As illustrated with the above example, a notable feature of this annulation method is its stereoselectivity. As in the earlier version of the method, the overall annulation process can be viewed as accomplishing the effective suprafacial *exo* cycloaddition of a substituted carbene to the conjugated diene (Scheme 11). However, the generality of this stereochemical control does not appear to be as impressive as in the previous oxyanion-based strategy. Thus, whereas rearrangement of the (vinylcyclopropyl)methyl sulfones derived from (*E*)-1,3-pentadiene affords almost exclusively the predicted *trans*-substituted cyclopentene, annulation employing (*Z*)-1,3-pentadiene produces a mixture of cyclopentenes in which the expected *cis*-substituted isomer is the minor product (Scheme 13).



Scheme 13

The synthetic utility of this annulation methodology is significantly enhanced by the fact that the cyclopentenylmethyl sulfone anions generated in the rearrangement step can be trapped *in situ* with a variety of organic electrophiles, and that desulfonylation can then be conveniently achieved in the same flask under mild conditions. The transformations outlined in Scheme 14 illustrate this strategy. Thus, re-

arrangement of the lithium derivatives of (**131**) and (**132**) occurs upon warming from –78 to –20 °C; addition of excess *t*-butanol and lithium metal then effects reductive desulfonylation to afford (**133**) in good overall yield. Alternatively, the rearranged cyclopentenylmethyl sulfone anion can also be alkylated prior to reduction, as illustrated in the transformation of (**134**) to (**135**).



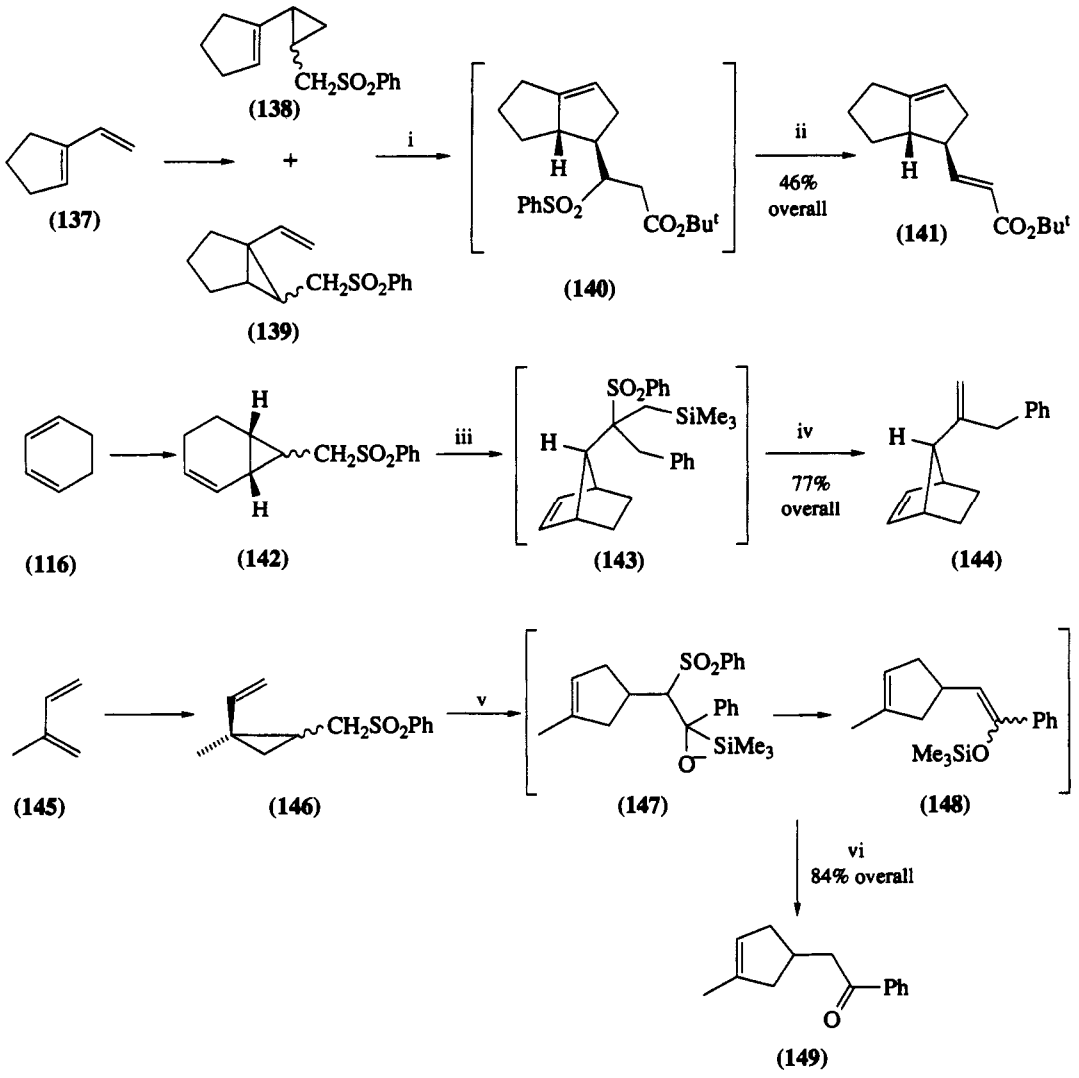
Scheme 14

Cyclopentene derivatives with unsaturated appendages are also available *via* this general annulation strategy; representative examples are presented in Scheme 15. In these several transformations desulfonylation is achieved using base-induced β-elimination, *via* the fluoride-promoted elimination of β-silyl sulfones,[54] and by means of Brook rearrangement chemistry according to the method of Reich.[55] In summary, a wide variety of complex functionalized cyclopentenes are available using this versatile [4 + 1] annulation method. The sulfonyl group serves a dual role in this strategy as a carbanion-stabilizing group: first to accelerate the vinylcyclopropane rearrangement, and then to facilitate the functionalization of the resulting cyclopentene derivative.

8.3.2.4 Carbocation-accelerated Vinylcyclopropane Rearrangements

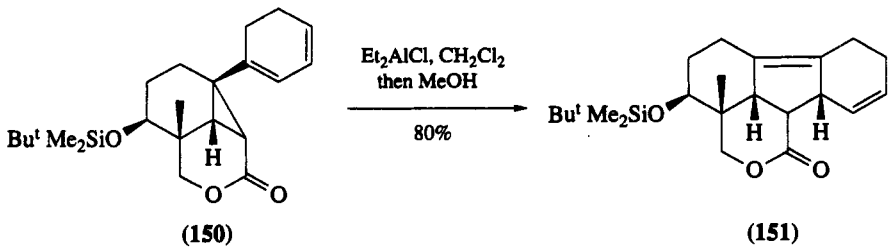
Several vinylcyclopropane to cyclopentene rearrangements have been reported in which a cationic substituent appears to facilitate the reaction. For example, exposure of (**150**; equation 23) to excess diethylaluminum chloride at 0 °C for 12 min furnished (**151**), which served as a key intermediate in Corey and Myers' synthesis of the plant hormone antheridogen-An.[56] Attempts to effect this transformation thermally were unsuccessful. In a similar fashion, treatment of (**152**; equation 24) with boron tribromide induced VCP rearrangement of this compound at room temperature, probably *via* initial cleavage to the allylic carbocation (**153**).[57] The reaction of the analogous vinylcyclopropane lacking a phenyl group failed to go to completion under these conditions.

Dinnocenzo and Conlon have described the remarkable effect of one-electron oxidation on the rate of certain vinylcyclopropane rearrangements.[58] Exposure of several 1-*p*-anisyl-2-vinylcyclopropane derivatives to a catalytic amount of tris(4-bromophenyl)aminium hexafluoroantimonate in acetonitrile at room temperature was found to induce ring expansion to form cyclopentenes (equation 25); temperatures in excess of 200 °C are required for the conventional thermal rearrangement of these systems. At this time it is uncertain whether these reactions follow concerted mechanisms, or are stepwise processes involving trimethylene cation radical intermediates.

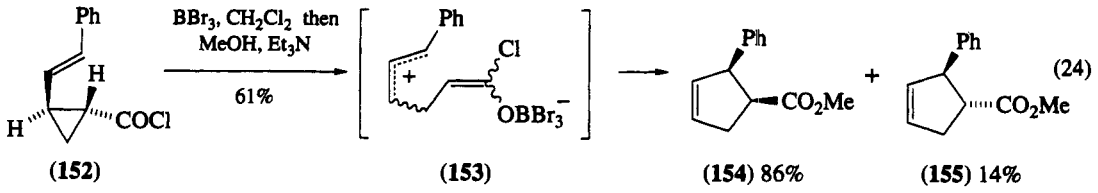


i, Bu^nLi, THF–HMPA, –78 to 25 °C, then add $BrCH_2CO_2Bu^t$, –78 to 25 °C; ii, DBU, –78 to 25 °C; iii, Bu^nLi, –78 to 25 °C, then add sequentially Me_3SiCH_2I, Bu^nLi, and $PhCH_2Br$, –78 to 25 °C; iv, $Bu^n{}_4NF$; v, Bu^nLi, –78 to 25 °C, then add $PhCOSiMe_3$, LiBr; vi, KF, H_2O

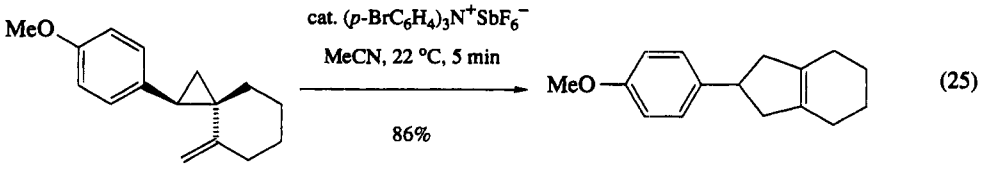
Scheme 15



(23)



(152) (153) (154) 86% (155) 14% (24)



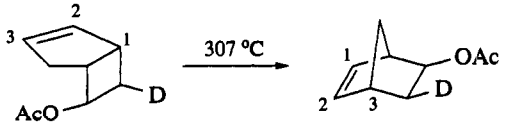
(156) (157) (25)

8.3.3 CHARGE-ACCELERATED REARRANGEMENTS OF CYCLOBUTANES

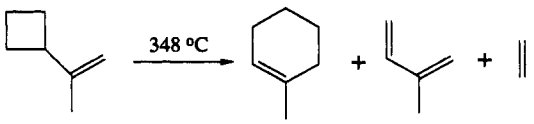
8.3.3.1 Vinylcyclobutane Rearrangements

8.3.3.1.1 Introduction

In the three decades since its discovery,[59] the vinylcyclobutane to cyclohexene rearrangement has been the subject of numerous mechanistic studies,[60] including Berson's elegant investigation of the stereochemical course of 1,3-sigmatropic rearrangements.[45c,61] In this classic study, Berson and Nelson demonstrated that the (necessarily) suprafacial rearrangement of the bicyclo[3.2.0]heptene (**158**; equation 26) occurs with inversion of configuration at the migrating carbon, in full accord with the predictions of orbital symmetry. However, in spite of this attention, to date the vinylcyclobutane (VCB) rearrangement has seen limited application as a practical method for the synthesis of cyclohexene derivatives. High temperatures are generally required to effect the rearrangement, and the scope of the reaction is further limited by the intervention of side reactions such as fragmentation, as illustrated in equation (27).[62]



(158) (159) (26)

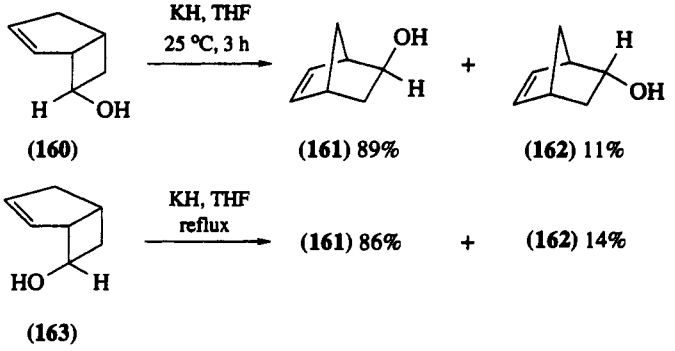


(27)

8.3.3.1.2 Oxyanion-accelerated rearrangement of 2-vinylcyclobutanol derivatives

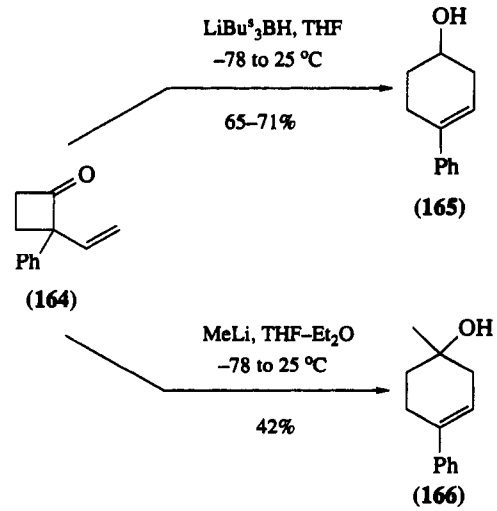
The first example of an oxyanion-accelerated vinylcyclobutane rearrangement was reported by Wilson and Mao in 1978.[63] Exposure of *exo*-bicyclo[3.2.0]hept-2-en-7-ol (**160**) to excess potassium hydride in THF at room temperature for 3 h afforded a mixture (8:1) of *exo*- and *endo*-norbornenol in addition to unrearranged starting material (Scheme 16). Although the *endo*-bicycloheptenol (**163**) was stable under these conditions, 1,3-rearrangement did occur upon heating or in the presence of added 18-crown-6. Once again the major norbornenol produced was the *exo* isomer (**161**). These stereochemical results were interpreted as being consistent with a concerted mechanism, in which the *exo* isomer (**160**) rearranges *via* a suprafacial inversion (*si*) pathway as in the thermal 1,3-sigmatropic shifts (equation 26) studied earlier

by Berson. The *endo* isomer (**163**), however, rearranges *via* the alternate *sr* pathway; in this case Wilson suggests that the transition state for orbital symmetry favored *si* migration is destabilized by steric interactions similar to those discussed earlier (Section 8.3.2.2) in the context of the oxyanion-accelerated VCP rearrangement. Wilson and Mao noted further that, since the thermodynamic ratio of (**161**) to (**162**) is approximately 6:1, it is also possible that a stepwise mechanism may be operating in these reactions.

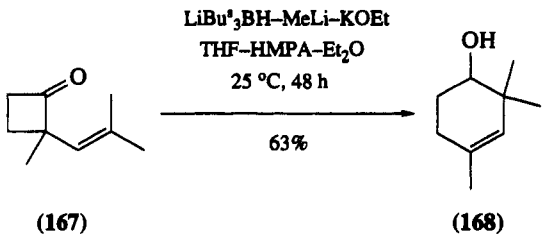


Scheme 16

Further studies defining the scope and stereochemical course of the oxyanion-accelerated vinylcyclobutane rearrangement were subsequently carried out in the laboratories of Danheiser[64] and Cohen.[65] Potassium, sodium[66] and even lithium alkoxides have been employed as the activating substituent in these reactions. For example, Danheiser has described a ring expansion strategy which involves the addition of lithium tri-*s*-butylborohydride or an alkyllithium reagent to a 2-vinylcyclobutanone derivative. The resultant cyclobutanol lithium salt rearranges at room temperature to afford the expected cyclohexenol, generally in good yield, as illustrated in Scheme 17. In contrast to these results, the lithium alkoxides produced by reduction of the isobutenyl derivative (**167**) resisted rearrangement even at 70 °C in the presence of HMPA. However, it was found that VCB rearrangement can be achieved in this and other difficult cases by means of the corresponding potassium salts, which are conveniently generated *in situ* from 2-vinylcyclobutanones under the conditions described in equation (28).

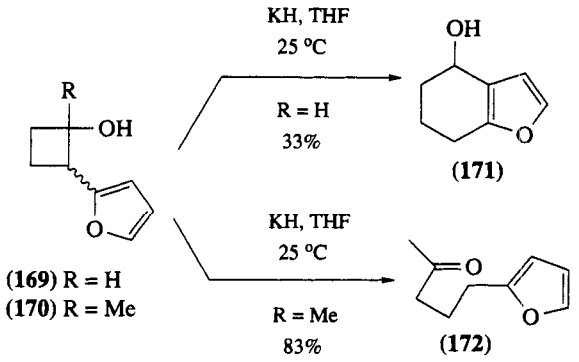


Scheme 17

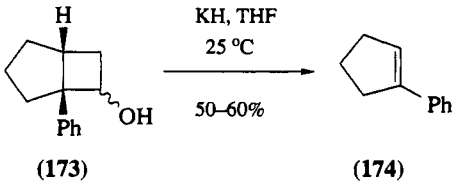


(28)

Certain arylcyclobutane derivatives also appear to be subject to oxyanion-accelerated 1,3-sigmatropic rearrangement. Cohen and coworkers found that exposure of the diastereomeric 2-(2-furyl)cyclobutanols (**169**; Scheme 18) to potassium hydride in THF at room temperature results in rearrangement to the tetrahydrobenzofuran (**171**), albeit in modest yield.[65a] However, under the same conditions the tertiary alcohol (**170**) suffers fragmentation to ketone (**172**), presumably *via* heterolytic cleavage of the alkoxide followed by proton transfer. Similar findings have been reported by Snider and Niwa; these workers also examined the chemistry of the phenylcyclobutanol derivative (**173**).[67] Treatment of this secondary alcohol with potassium hydride in THF led to fragmentation, with no evidence for 1,3-sigmatropic rearrangement being obtained (equation 29).



Scheme 18

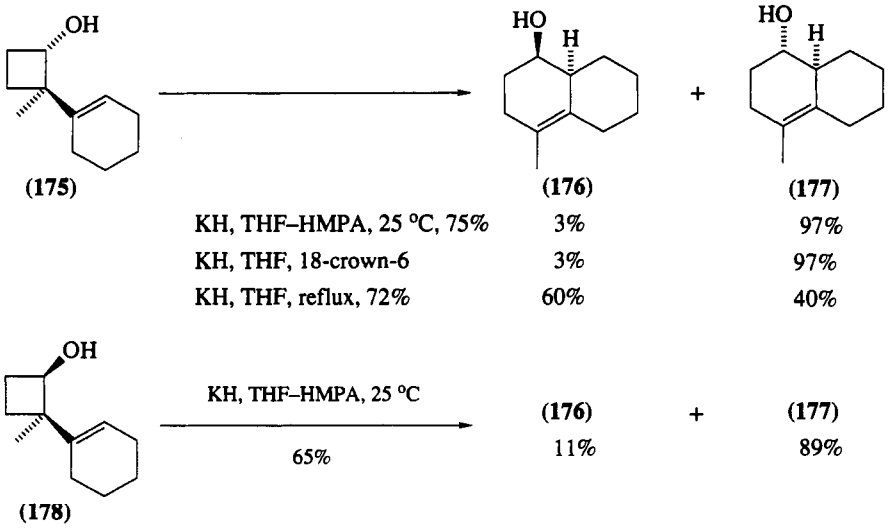


(29)

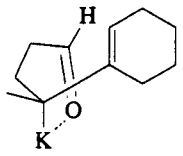
The oxyanion-accelerated vinylcyclobutane rearrangement is in many cases a highly stereoselective process, although the mechanistic basis of this stereoselectivity is not completely understood. Complicating the problem is the fact that epimerization of the intermediate vinylcyclobutanol salt takes place, at least in some cases, faster than 1,3-rearrangement.[65] Some generalizations with predictive value can be made, however. As in the case of the vinylcyclopropanes discussed in Section 8.3.2.2, systems in which the hydroxy group is *anti* to the vinyl substituent appear to rearrange preferentially by suprafacial inversion pathways. On the other hand, the overall stereochemical course of the reactions of the corresponding cyclobutanes with *syn* hydroxy and vinyl groups appears to be suprafacial retention. It should be noted, however, that these generalizations only appear to be applicable to reactions carried out in highly dissociating media.

The transformations of the epimeric vinylcyclobutanols (**175**) and (**178**), studied by both Danheiser[64] and Cohen,[65] are representative (Scheme 19). In this case, both the *syn*- and *anti*-vinylcyclobutanol potassium salts rearrange to form mainly the *exo*-alcohol (**177**), provided that the reaction is carried out in the presence of HMPA[64] or 18-crown-6.[65] However, note that exposure of the *syn*-2-vinylcyclobutanol (**178**) to potassium hydride in THF at room temperature for 4 d led to its epimerization to the more stable *anti* isomer (**175**); very little rearrangement took place under these conditions. Interestingly, in the absence of complexing agents the rearrangement of (**175**) (which proceeds only upon heating) affords a mixture of products in which the *endo* isomer (**176**) predominates. Cohen has suggested that the chelated species (**179**) may be involved as an intermediate leading to the *endo*-alcohol in the case of the reaction carried out in THF alone.

The transformations summarized in Scheme 20 provide further insight into the stereochemical course of the oxyanion-accelerated VCB rearrangement. 1,3-Migration of the '*anti*-type' vinylcyclobutanol salt (**181**) leads to the *exo*-alcohol (**182**) *via* rearrangement with inversion at the migrating carbon, while rearrangement of the *syn* isomer (**185**) takes place predominantly with retention of configuration to afford (**183**). Although these results are in accord with the stereochemical predictions for concerted 1,3-sigma-

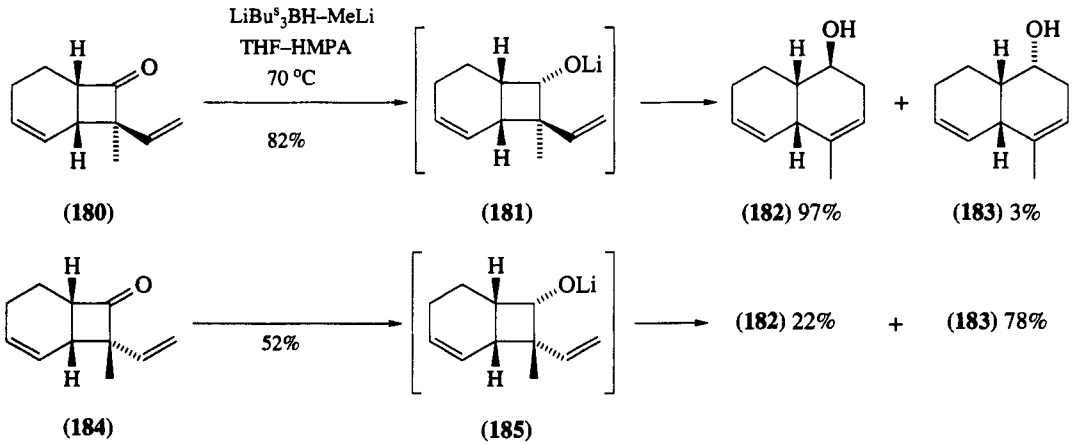


Scheme 19



(179)

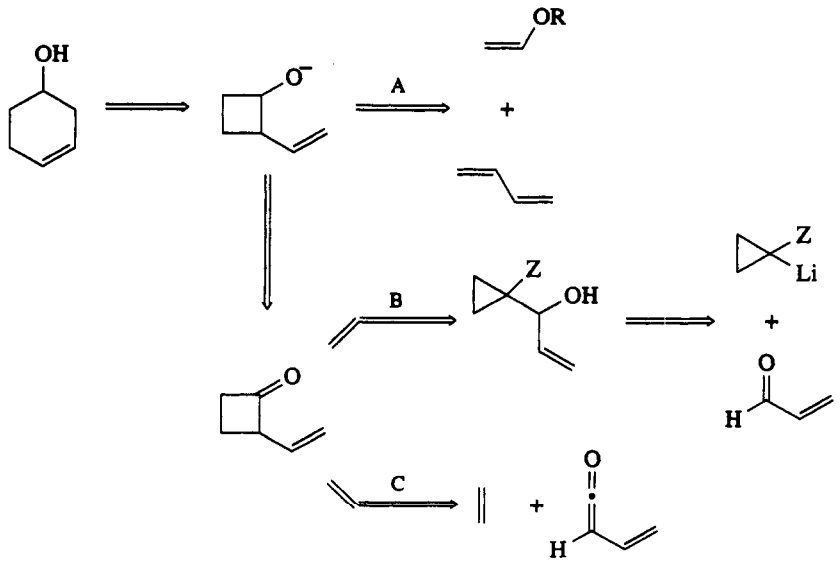
tropic rearrangements, it is likely that in most if not all cases the accelerated VCB rearrangement follows a stepwise pathway involving allylmetal aldehyde intermediates.



Scheme 20

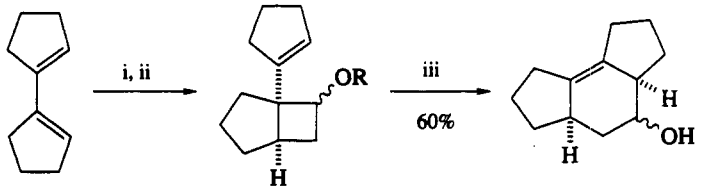
The accelerated vinylcyclobutane rearrangement functions as the key step in several useful strategies for the assembly of functionalized six-membered carbocycles. As outlined in Scheme 21, these strategies are conveniently classified according to the approach used to synthesize the pivotal vinylcyclobutanol intermediate.

Bauld and coworkers have examined the cation radical cycloadditions of 1,3-dienes with electron-rich alkenes and found that, under photosensitized electron-transfer conditions, [2 + 2] cycloaddition is in many cases favored over Diels–Alder addition. Thus, as illustrated in equation (30), 1,1′-dicyclopentenyl (**186**) reacts with β-chloroethyl vinyl ether under electron transfer conditions to afford the cyclobutane adduct (**187**), which was cleaved to the cyclobutanol (**188**) in 70% yield upon treatment with *n*-butyllithium. Oxyanion-accelerated VCB rearrangement then provided (**189**) as a mixture of diastereomers in



Scheme 21

60% yield.[68,69] This transformation represents the only example of the implementation of strategy A (Scheme 21) which has been reported to date.



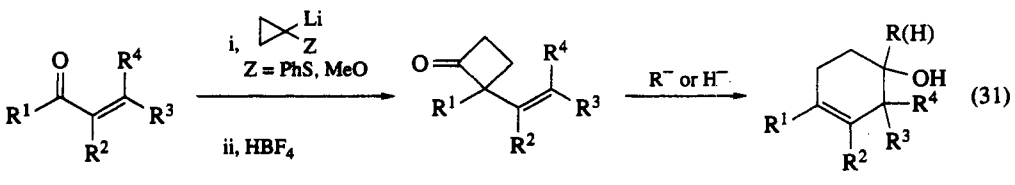
(30)

(186) **(187)** R = CH_2CH_2Cl **(189)**
(188) R = H

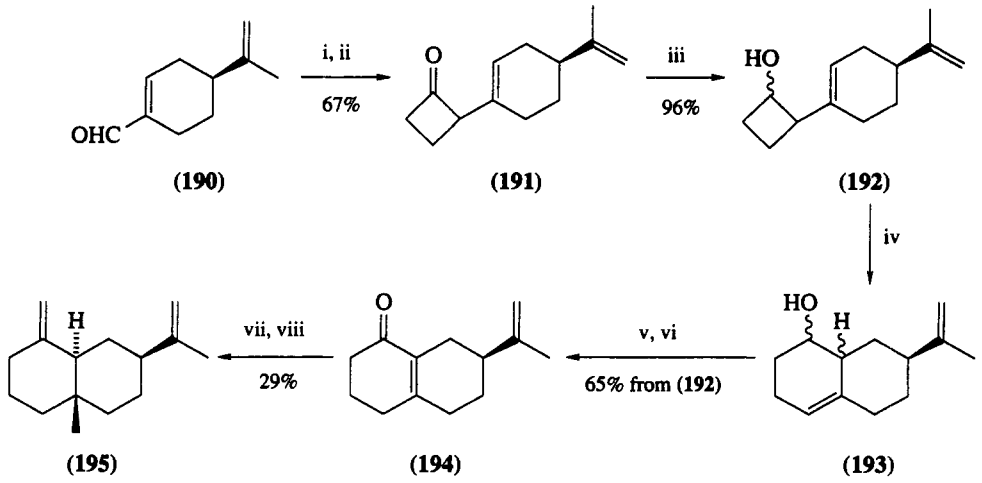
i, $H_2C{=}CHOCH_2CH_2Cl$, *hν*, 1,4-dicyanobenzene, CH_2Cl_2; ii, Bu^nLi, Et_2O–HMPA; iii, KH, THF, reflux

Thus far, the most widely employed route to 2-vinylcyclobutanones has involved the addition of the 1-lithio derivative of thiophenyl- or methoxy-cyclopropane to an α,β-unsaturated carbonyl compound, followed by acid-promoted ring expansion of the resulting cyclopropylcarbinol (strategy B in Scheme 21).[70] In conjunction with the oxyanion-accelerated VCB rearrangement, this approach provides a useful three-step [3 + 3] annulation route to 3-cyclohexenol derivatives (equation 31).[64,65] Scheme 22 outlines the application of this strategy to the synthesis of the eudesmane sesquiterpene (–)-β-selinene.[65a] Addition of 1-lithio-1-methoxycyclopropane to (–)-perillaldehyde and subsequent acid-catalyzed rearrangement[70c] furnished the cyclobutanone (**191**) in 67% overall yield. Reduction with lithium aluminum hydride then produced (**192**) as an 82:18 mixture of *cis* and *trans* isomers. Exposure of this mixture of vinylcyclobutanols to excess potassium hydride in THF at reflux next induced 1,3-rearrangement to afford (**193**), which without purification was oxidized and isomerized to the conjugated enone (**194**) in 65% overall yield. Conjugate addition of $MeCuBF_3$ and Wittig methylenation completed the synthesis of (–)-β-selinene.

Strategy C in Scheme 21 employs the [2 + 2] cycloaddition of vinylketenes and 1,3-dienes to generate the requisite 2-vinylcyclobutanone intermediates for oxyanion-accelerated VCB rearrangement. The sequence presented in Scheme 23 illustrates this two-step [4 + 2] annulation strategy, the overall result of



(31)

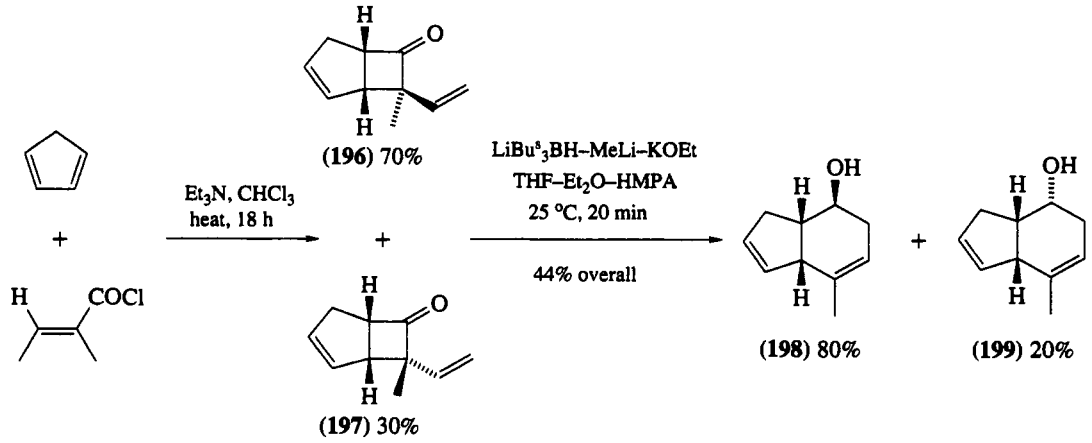


i, 1-lithio-1-methoxycyclopropane, THF; ii, 48% HBF_4, THF; iii, $LiAlH_4$, Et_2O; iv, KH, THF, reflux, 1 h; v, Jones oxidation; vi, Al_2O_3 chromatography; vii, $MeCuBF_3$, Et_2O; viii, $Ph_3P{=}CH_2$, DMSO

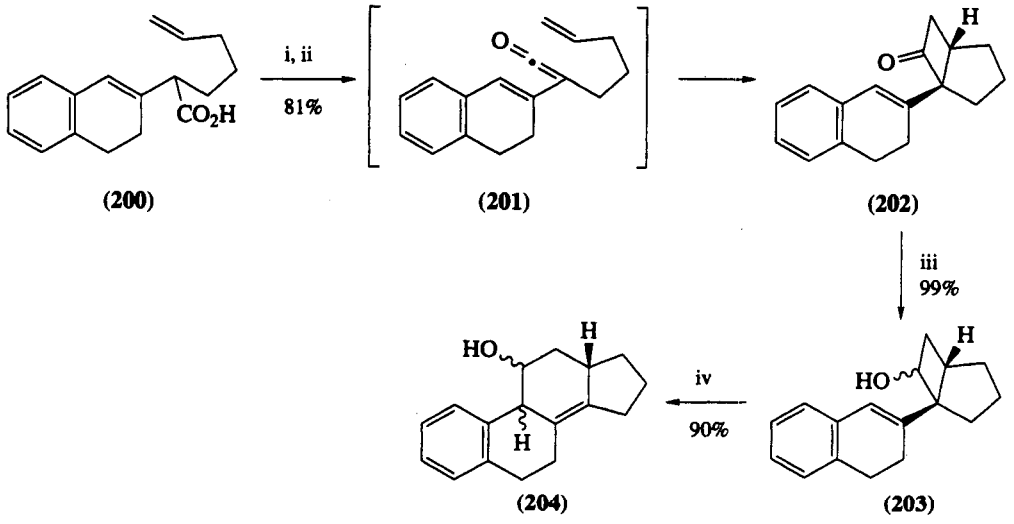
Scheme 22

which is a suprafacial addition with respect to the two-carbon (alkene) component.[64] The vinylketenes required for the [2 + 2] cycloaddition step are conveniently generated *via* the 1,4-dehydrohalogenation of α,β-unsaturated acid chlorides. It should be noted, however, that the scope of this reaction is limited to the more ketenophilic alkenes; simple alkenes such as 1-hexene react slowly with vinylketenes at 90 °C to produce the desired 2-vinylcyclobutanones in relatively low yield. On the other hand, the intramolecular addition of unactivated alkenes to ketenes is a more efficient process, and Snider and coworkers have recently employed this strategy to prepare the tetracyclic vinylcyclobutanone derivative (**202**; Scheme 24).[71] Reduction of this ketone with sodium borohydride furnished the cyclobutanols (**203**) as a 19:1 mixture of diastereomers, which were then converted to the corresponding potassium salts in the usual fashion by treatment with excess potassium hydride. The oxyanion-accelerated VCB rearrangement proceeded smoothly in this case at only 0 °C, and produced the tetracyclic steroid model compound (**204**) in 90% yield. The stereochemistry of the two isomers (78:22) which were obtained could not be determined from the data available.

In summary then, the oxyanion-accelerated rearrangement of 2-vinylcyclobutanol derivatives is now established as an attractive method for achieving two-carbon ring expansion under relatively mild conditions. In conjunction with the efficient synthetic routes to vinylcyclobutanones outlined in Scheme 21, this version of the VCB rearrangement provides several strategically novel annulation methods for the construction of six-membered carbocycles.[72]



Scheme 23

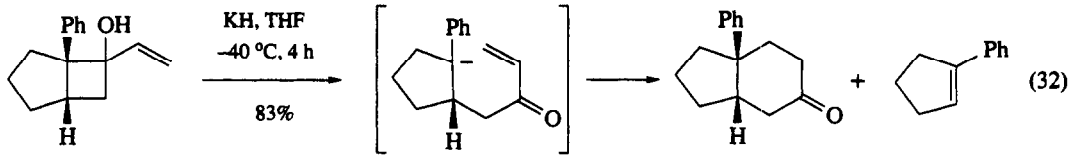


i, $(COCl)_2$, benzene, 55 °C; ii, Et_3N, toluene, reflux; iii, $NaBH_4$, MeOH, 25 °C; iv, KH, THF, 0 °C, 2 h

Scheme 24

8.3.3.1.3 Oxyanion-accelerated rearrangement of 1-vinylcyclobutanol derivatives

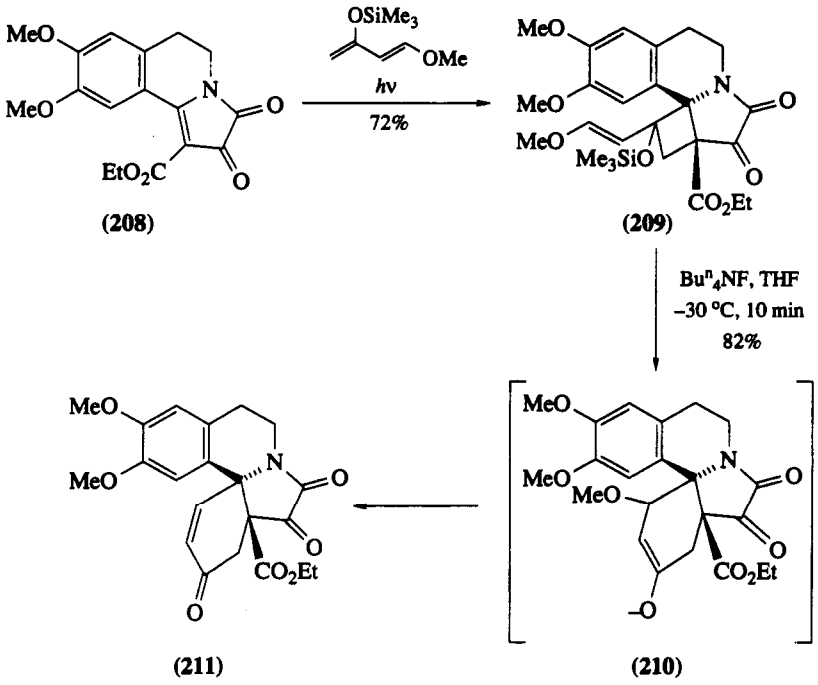
The substitution of an oxyanion substituent at carbon-1 of a vinylcyclobutane ring has been shown to facilitate the 1,3-rearrangement of this system, leading to a cyclohexanone enolate. These ring expansions appear to follow stepwise reaction pathways involving initial heterolytic cleavage to form an anionic α,β-unsaturated ketone intermediate, which then cyclizes *via* internal Michael addition to generate the six-membered ring. Only 1-vinylcyclobutanol derivatives that bear an anion-stabilizing group at carbon-2 are subject to the reaction. The transformation outlined in equation (32) is representative.[67] Addition of vinyllithium to 1-phenylbicyclo[3.2.0]hept-7-one produced the requisite vinylcyclobutanol (**205**) as a single diastereomer (stereochemistry not assigned) in 51% yield. At –40 °C the potassium salt of this cyclobutanol rearranged to the enolate derivative of (**207**), presumably *via* initial heterolytic cleavage to the benzylic carbanion (**206**). This intermediate was also observed to undergo further fragmentation (eliminating the enolate derivative of methyl vinyl ketone), and 1-phenylcyclopentene was isolated as a by-product of the ring expansion in 15% yield.



(**205**) (**206**) (**207**) 82% (**174**) 18%

Similar 1,3-rearrangements involving more highly functionalized 2-aryl-1-vinylcyclobutanol derivatives have been studied by Sano and coworkers;[73] Scheme 25 outlines the application of this process in an interesting synthetic approach to the erythrina alkaloids.[73c] [2 + 2] Photocycloaddition of 1-methoxy-3-trimethylsiloxybutadiene to (**208**) provided the requisite vinylcyclobutanol silyl ether (**209**) in 72% yield. Exposure of (**209**) to TBAF at –30 °C for several minutes then induced ether cleavage and 1,3-rearrangement of the resulting salt to afford the enolate (**210**), which upon elimination of methoxide provided the desired enone (**211**) in 82% overall yield. By contrast, the thermal VCB rearrangement of (**209**) required heating above 110 °C, and produced (**211**) (after enol ether hydrolysis) in only 38% yield.[74]

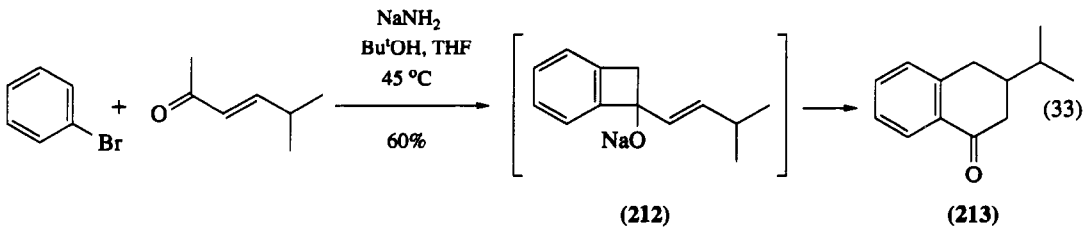
1-Vinylbenzocyclobutanol salts also undergo stepwise anion-accelerated 1,3-rearrangements to form six-membered rings. For example, Caubere has used the 'arynic condensation' of ketone enolates with benzyne to generate benzocyclobutanol salts such as (**212**; equation 33) which rearrange at 45 °C to form α-tetralones.[75] Swenton has employed related rearrangements in his elegant annulation approaches to the anthracyclinone and tetracycline antibiotics.[76] For example, addition of (**215**; from the corresponding



Scheme 25

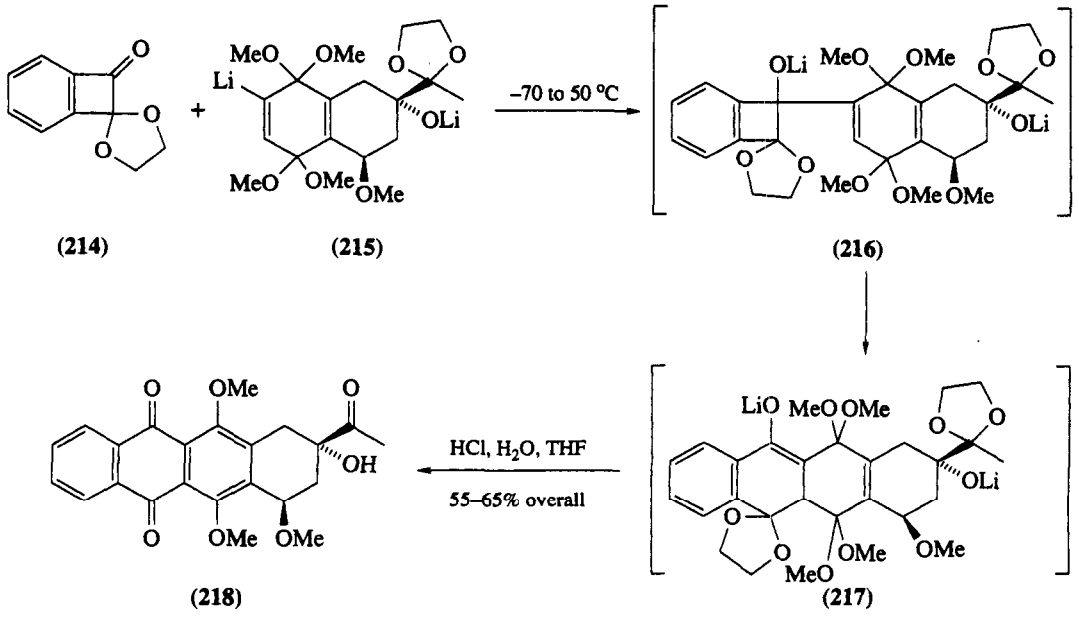
bromide using 2 equiv. of *n*-butyllithium) to benzocyclobutenedione monoketal (**214**) furnished the vinylcyclobutane (**216**), which rearranged at 50 °C to produce the tetracyclic quinone (**218**) in 55–65% overall yield after ketal hydrolysis (Scheme 26). This annulation product served as an intermediate for the synthesis of the antitumor antibiotic 4-demethoxydaunomycinone.

In the reactions discussed above an aromatic ring stabilizes the negative charge which develops at the C-2 position of the original cyclobutane ring. Cohen has demonstrated the ability of certain sulfur substituents to function in a similar capacity.[77] For example, ring expansion of the potassium salt derived from (**220**) proceeded smoothly in THF–HMPA upon warming from –11 °C to room temperature to afford 4-thiophenylcyclohexanone in 60% yield (equation 34).



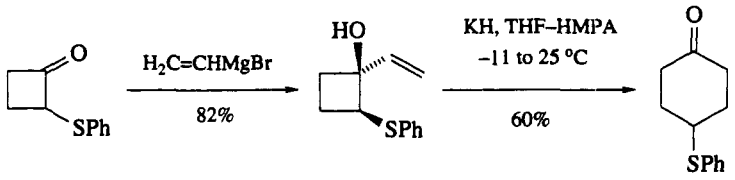
8.3.3.1.4 Azaanion-accelerated vinylcyclobutane rearrangements

Bauld and coworkers have developed a strategy for the effective [4 + 2] cycloaddition of a vinylamine to a conjugated diene which features an azaanion-accelerated vinylcyclobutane rearrangement as a key step.[69,78] Equation (35) illustrates this interesting approach to 3-cyclohexenylamine derivatives. Under photosensitized electron transfer conditions, the cation radical [2 + 2] cycloaddition of *N*-methyl-*N*-vinylacetamide takes place smoothly with a wide range of conjugated dienes. No [4 + 2] adducts are detected in these reactions, even with *s-cis*-dienes such as 1,3-cyclohexadiene. Base-promoted hydrolysis then furnishes cyclobutylamines such as (**222**; 3.2:1 mixture of *anti* and *syn* isomers), which rearrange to the desired cyclohexenes upon heating in THF in the presence of excess potassium hydride.

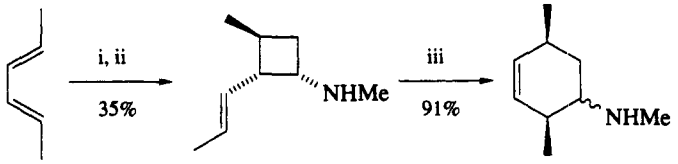


(214) (215) (216) (217) (218)

Scheme 26



(219) (220) (221) (34)



(222) (223) (35)

i, *N*-methyl-*N*-vinylacetamide, 1,4-dicyanobenzene, *hν*, MeCN, 72 h;
ii, KOH, NH_2NH_2, $HOCH_2CH_2OH$, 110 °C; iii, KH, THF, reflux, 1 h

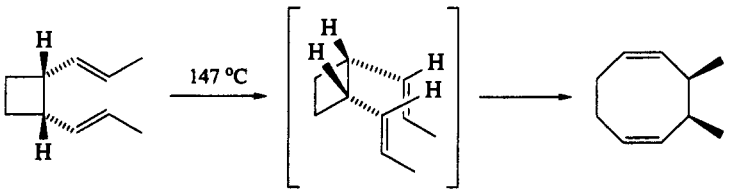
8.3.3.2 Divinylcyclobutane Rearrangements

8.3.3.2.1 Introduction

The isolation of a variety of biologically important natural products with structures incorporating eight-membered rings has led to increased interest in the search for new methodology for the synthesis of cyclooctane derivatives. Traditionally, the most popular synthetic routes to cyclooctanes have involved one- and two-carbon ring expansions and the cleavage (or fragmentation) of bi- and poly-cyclic systems already incorporating eight-membered rings.[79] Methods based on the cyclization of acyclic precursors have also been explored, but usually are only marginally successful due to unfavorable enthalpic and entropic factors. Recently, the 3,3-sigmatropic rearrangement of 1,2-divinylcyclobutane derivatives has emerged as an attractive and generally successful strategy for the preparation of cyclooctane derivatives. Charge-accelerated versions of the reaction proceed under unusually mild conditions and have further

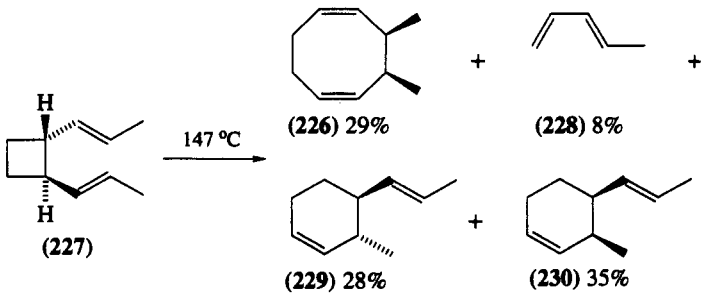
expanded the scope and synthetic utility of this strategy. This section reviews the general features of the divinylcyclobutane (DVCB) rearrangement, which is also discussed in detail in Chapter 7.1, this volume.

The thermal DVCB rearrangement was first reported by Vogel in 1958.[80] Subsequent extensive physical organic studies by Berson and other workers elucidated the important mechanistic features of the reaction.[81] Driven by the release of cyclobutane ring strain, this Cope rearrangement often proceeds at significantly lower temperatures (generally in the range 60–140 °C) than analogous reactions involving acyclic 1,5-dienes. As illustrated in equation (36), *cis*-divinylcyclobutanes rearrange *via* boat-like transition states to afford *cis,cis*-1,5-cyclooctadienes.[81e] In these systems the chair-like geometry normally favored for the acyclic Cope rearrangement is difficult to achieve, and in any event would lead to the formation of severely strained *cis,trans*-cyclooctadienes. The analogous rearrangements of *trans*-divinylcyclobutane derivatives are generally carried out at somewhat higher temperatures (140–210 °C), and often produce complex mixtures of several products (*e.g.* Scheme 27).[81e] In this example the major reaction pathway followed is 1,3-sigmatropic rearrangement leading to the cyclohexenes (**229**) and (**230**); [2 + 2] cycloreversion (producing *trans*-piperylene) is also observed as a side reaction. Interestingly, the Cope rearrangement of the *trans*-divinylcyclobutane produces the same cyclooctadiene (**226**) formed in the reaction of the *cis*-divinylcyclobutane (**224**). The rearrangement of the *trans* compound is believed to take place by an indirect mechanism involving initial epimerization to (**224**), followed by sigmatropic rearrangement.



(36)

(224) (225) (226)



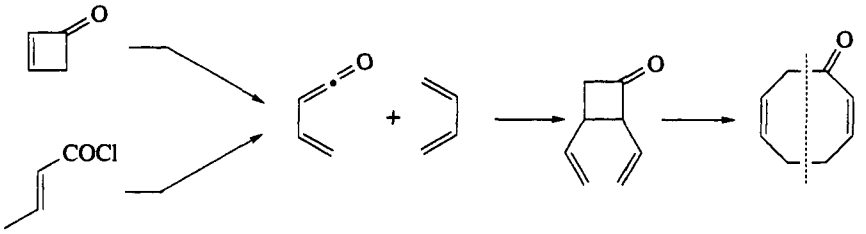
(227) (226) 29% (228) 8% (229) 28% (230) 35%

Scheme 27

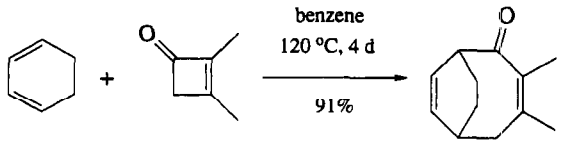
The application of the divinylcyclobutane rearrangement to the synthesis of functionalized cyclooctane derivatives began to receive serious attention in the early 1980s. The general synthetic strategies which have emerged from these studies are conveniently classified according to the method used to prepare the key 1,2-divinylcyclobutane intermediates. The most important strategies devised to date are based on: (i) the thermal [2 + 2] cycloaddition of vinylketenes with 1,3-dienes; (ii) photochemical [2 + 2] diene–diene cycloadditions; and (iii) the addition of vinyl organometallic compounds to 2-vinylcyclobutanones, which are themselves generally prepared *via* the acid-promoted rearrangement of cyclopropylcarbinols as discussed in Section 8.3.3.1.2.

The first approach, based on thermal vinylketene–diene cycloadditions, was independently developed in three laboratories and first reported in 1982.[82–84] The overall transformation constitutes a powerful [4 + 4] annulation strategy for the synthesis of eight-membered carbocycles (Scheme 28). Several options are available for the generation of the requisite vinylketene intermediates. One approach, employed by Danheiser and coworkers,[82] involves the 4π-electrocyclic ring opening of cyclobutenones and is illustrated in equation (37). Thermolysis of the cyclobutenone (**231**) in benzene at 120 °C produces isopropenylmethylketene, which combines with 1,3-cyclohexadiene in a regiospecific [2 + 2] cycloaddition. At the elevated reaction temperature the resulting 2,3-divinylcyclobutanone then undergoes 3,3-sigmatropic rearrangement to afford the eight-membered ring annulation product. The overall transformation thus in-

volves a cascade of three pericyclic reactions, each step representing a different major class of pericyclic process.



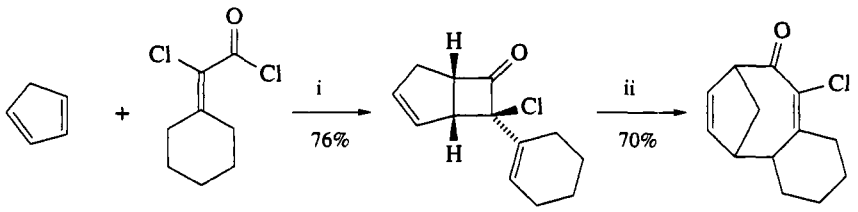
Scheme 28



(116) (231) (232)

(37)

A related [4 + 4] annulation strategy relies on the base-promoted 1,4-dehydrochlorination of α,β-unsaturated acid chlorides;[82,83] the transformation outlined in Scheme 29 (reported by Dreiding and coworkers)[83] illustrates this approach. In some cases it is possible to effect all three steps — ketene generation, [2 + 2] cycloaddition, and Cope rearrangement — in a single synthetic operation.[82]



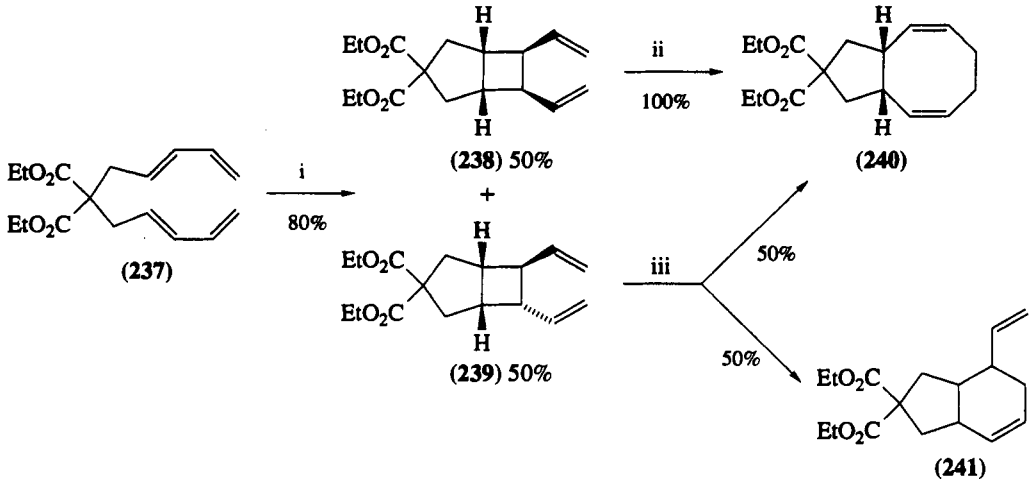
(233) (234) (235) (236)

i, Et_3N, $CHCl_3$, 25 °C, 15 h; ii, xylene, 145 °C, 4 h

Scheme 29

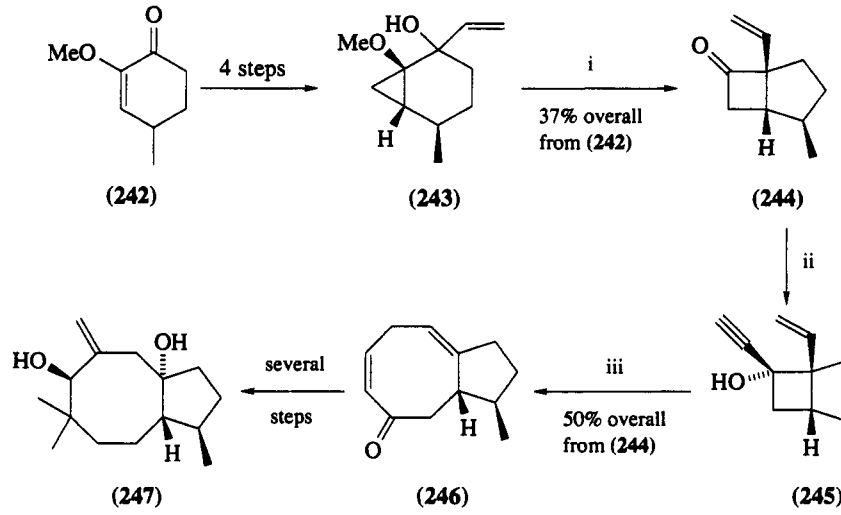
In principle, the photoinduced diene–diene [2 + 2] cycloaddition reaction should provide a particularly expeditious route to 1,2-divinylcyclobutanes. Unfortunately, these diene–diene cycloadditions generally produce complex mixtures of regio- and stereo-isomeric dimers and have little practical value in synthesis. Recently, Wender and Correia demonstrated that the intramolecular variant of the reaction circumvents these selectivity problems and provides an efficient route to substrates for DVCB rearrangements.[85] The transformations outlined in Scheme 30 illustrate this approach. Irradiation of tetraene (**237**) furnished the *cis*- and *trans*-divinylcyclobutanes (**238**) and (**239**) as a 1:1 mixture in 80% yield. Thermolysis of *cis* isomer (**238**) in benzene at 130 °C then afforded the desired cyclooctadiene in nearly quantitative yield. More vigorous conditions (200 °C) were required for rearrangement of the *trans*-divinylcyclobutane, and in this case the product of 1,3-rearrangement (**241**; mixture of 4 isomers) was formed along with the desired Cope rearrangement product.

Finally, a third synthetic approach to 1,2-divinylcyclobutanes employs the addition of vinylmetal reagents to 2-vinylcyclobutanones which are available using the methods discussed earlier in Section 8.3.1.2. A novel variant of this strategy was exploited by Gadwood and his coworkers in their total synthesis of the cyclooctanoid sesquiterpene poitediol (**247**).[86] As outlined in Scheme 31, the key step in this synthesis involved the addition of lithium acetylide to (**244**) and oxy-Cope rearrangement of the resulting alkynylvinylcyclobutanol at 50 °C to afford the bicyclo[6.3.0]undecadienone (**246**) in 50% overall yield. The initial product of this remarkably facile 3,3-sigmatropic rearrangement is a high-energy 1,2,5-cyclooctatrienol derivative; rapid enol–ketone tautomerization produces the final cyclooctadienone product.



i, *hν*, hexane, Ph_2CO (sensitizer); ii, benzene, 130 °C, 4 h; iii, benzene, 200 °C, 24 h

Scheme 30



i, BF_3–Et_2O, Et_2O, 0 °C, 10 min; ii, LiC≡CH, THF, –30 °C; iii, THF, 50 °C, 3 h

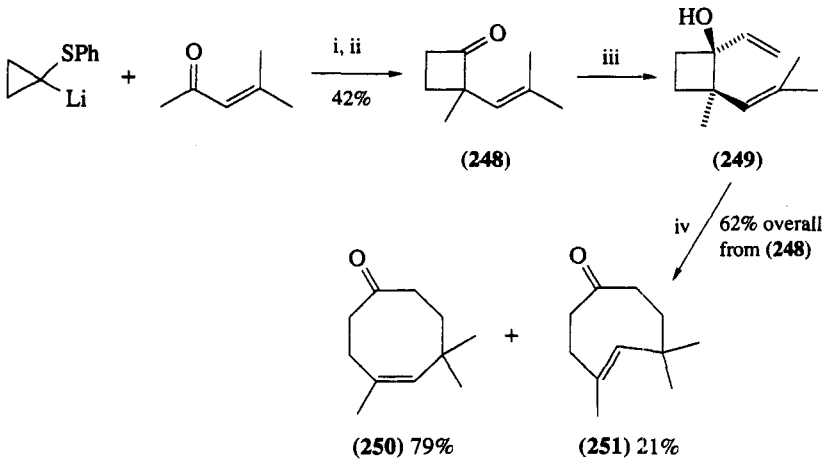
Scheme 31

8.3.3.2.2 Anion-accelerated divinylcyclobutane rearrangements

In principle, the oxyanion-accelerated version of the divinylcyclobutane rearrangement might offer several advantages over the thermal reaction discussed in the preceding section. Particularly attractive is the prospect of achieving the ring expansion of both *cis*- and *trans*-divinylcyclobutane derivatives under relatively mild conditions without the intervention of troublesome side reactions. In fact, these hopes have to a large extent been realized, and the anion-accelerated DVCB rearrangement constitutes a key step in several useful strategies for the synthesis of substituted cyclooctanes.

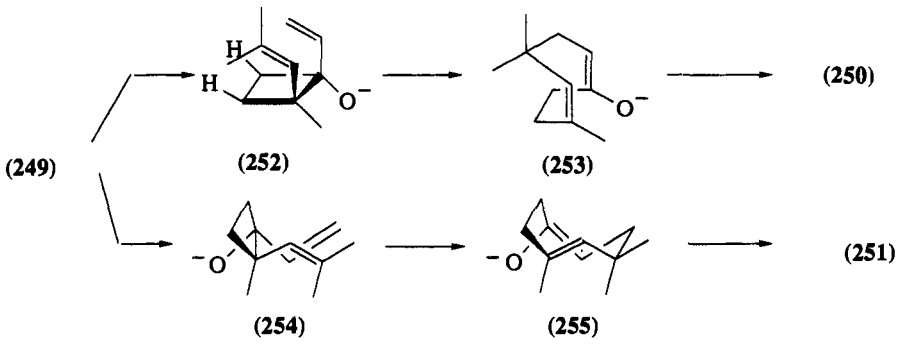
The first examples of the oxyanion-accelerated DVCB rearrangement were observed in the laboratories of Kahn,[87] Levine[88] and Gadwood.[89] Particularly noteworthy are the studies of Gadwood and Lett, who reported their systematic investigation of the scope and stereochemical course of the reaction in 1982.[89] As illustrated with the example in Scheme 32, Gadwood and Lett elected to assemble all of their rearrangement substrates *via* the addition of alkenylmetal compounds to 2-vinylcyclobutanones; the latter were conveniently prepared from α,β-enones according to the method of Trost.[70] Exposure of the *trans*-divinylcyclobutanol (**249**) to potassium hydride in THF at room temperature led to its rapid rear-

rangement to a mixture of *cis*- and *trans*-cyclooctenones. Presumably this Cope rearrangement proceeds *via* the initial isomerization of (**249**) to the corresponding *cis*-divinylcyclobutanol salt. The success of this reaction stands in contrast to the results of the thermal rearrangement of related *trans*-divinylcyclobutanes, which as discussed in the preceding section, generally afford significant quantities of 1,3-sigmatropic rearrangement products in addition to the desired cyclooctadienes. Another interesting feature of the oxyanion-accelerated rearrangement of (**249**) is the appearance of the *trans*-cyclooctenone (**251**) as a minor product of the reaction. This isomer is presumably formed *via* the chair-like conformation (**254**); steric interactions between the *endo* terminal methyl groups and the cyclobutane ring protons appear to destabilize the normally favored boat-like transition state conformation (**252**). Related oxyanion-accelerated DVCB rearrangements favoring the formation of (*E*)-cyclooctenones have been reported by Frei and coworkers.[90]



i, THF, 0 °C; ii, *p*-TsOH, benzene, reflux, 1.5 h; iii, H_2C=CHLi, Et_2O, –78 °C; iv, KH, THF, 25 °C, 45 min

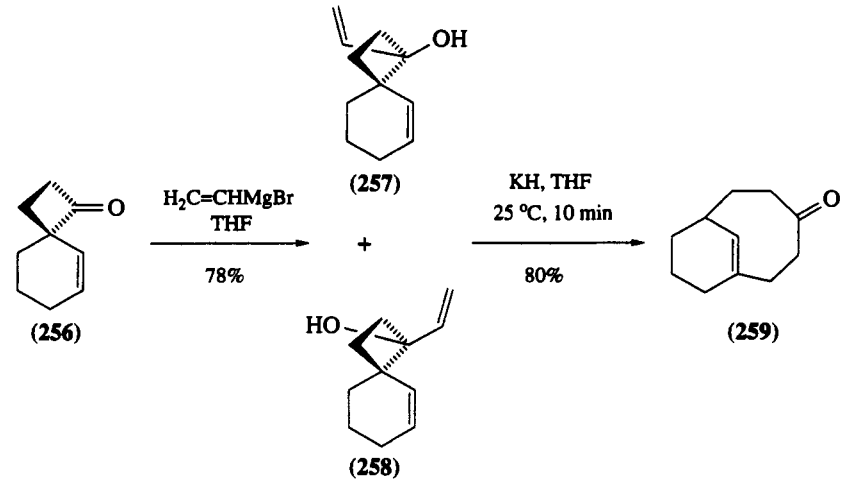
Scheme 32



Scheme 33

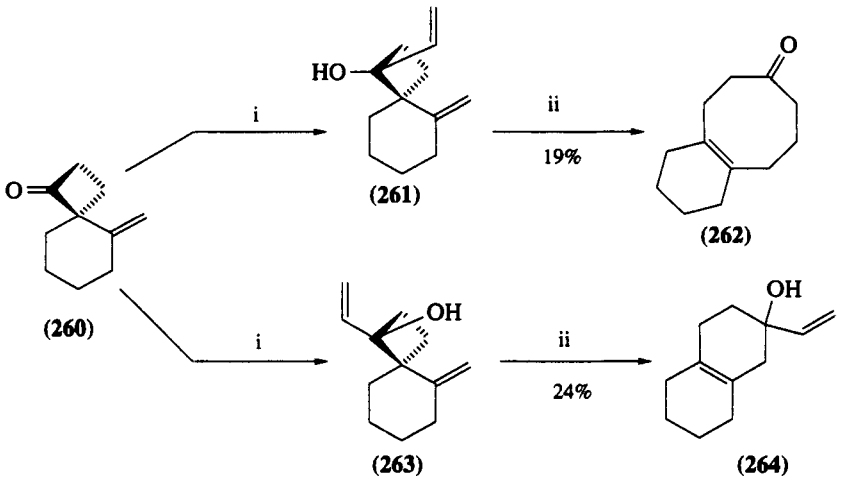
Gadwood and Lett also described the rearrangement of several divinylcyclobutanols derived from the spirononenone (**256**); similar reactions had been studied earlier by Kahn[87] and by Levine.[88] The potassium salts obtained from both the *cis*- and *trans*-divinylcyclobutanols (**257**) and (**258**) rearranged smoothly at room temperature to produce the interesting bridgehead alkene containing bicyclo[5.3.1]undecenone (**259**) in excellent yield (Scheme 34). Once again, cyclohexene by-products resulting from alternative 1,3-sigmatropic rearrangement pathways were not detected in this reaction.

The chemistry of the divinylcyclobutanols derived from 5-methylenespiro[3.5]nonanone (**260**) proved to be more complicated than the reactions described above. As expected, the oxyanion-accelerated 3,3-sigmatropic rearrangement of the *cis* isomer (**261**) was extremely facile as a consequence of the rigid *s-cis* orientation of the exocyclic methylene group (Scheme 35). The rearrangement of the *trans* isomer, however, produced none of the desired Cope product; instead this cyclobutanol salt underwent exclusive 1,3-rearrangement to afford the cyclohexenol derivative (**264**). It is uncertain whether this transformation



Scheme 34

proceeds *via* a concerted mechanism or involves a stepwise pathway initiated by heterolytic cleavage to an allylmetal ketone intermediate.

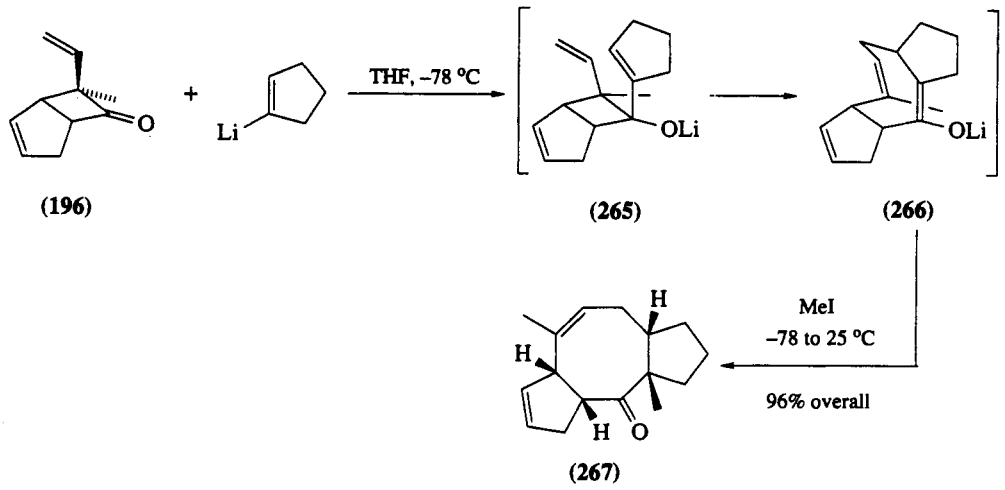


i, H_2C=CHLi, Et_2O, –78 °C, 15 min, then quench at –78 °C with AcOH; ii, KH, THF, 25 °C, 30 min

Scheme 35

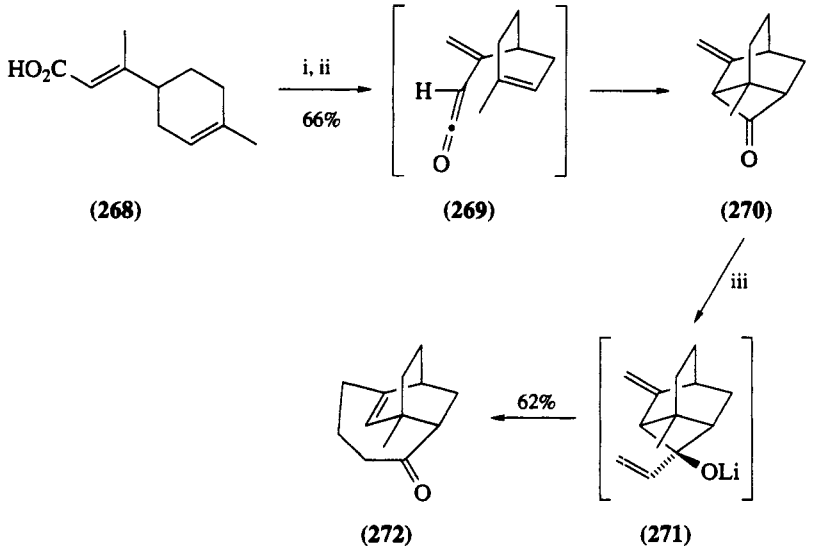
A second attractive strategy for the synthesis of eight-membered carbocycles utilizes the [2 + 2] cycloaddition of vinylketenes in conjunction with the oxyanion-accelerated DVCB rearrangement. Paquette and coworkers have examined the application of this strategy to the synthesis of the dicyclopenta[*a*,*d*]cyclooctane ring system which is incorporated in the structures of the ophiobolane and related sesterterpenes.[91] As discussed earlier (see Scheme 23), the addition of methylvinylketene to cyclopentadiene provides a 70:30 mixture of diastereomeric cycloadducts; separation of these isomeric vinylbicycloheptenones can be accomplished by means of high-pressure liquid chromatography. Addition of cyclopentenyllithium to the *exo*-vinyl isomer (**196**) at –78 °C then produces the cyclobutanol salt (**265**), which undergoes spontaneous Cope rearrangement at this temperature to furnish the enolate (**266**). Alkylation with methyl iodide then affords the desired tricyclic product (**267**) in 96% overall yield (Scheme 36).

Intramolecular vinylketene cycloadditions have also found use as an efficient method for the preparation of divinylcyclobutanols suitable for accelerated oxy-Cope rearrangement. A typical reaction sequence is outlined in Scheme 37.[92] In this case the cyclobutanol salt produced by addition of vinyllithium to (**270**) at –78 °C was observed to undergo 3,3-sigmatropic rearrangement simply upon warming to room temperature; the tricyclic enone (**272**) incorporating a *trans*-cyclooctene ring was thus formed in 62% overall yield from (**270**).



(196) (265) (266) (267)

Scheme 36



(268) (269) (270) (271) (272)

i, $(COCl)_2$, benzene, 25 to 55 °C; ii, Et_3N, toluene, reflux, 3 h; iii, $H_2C{=}CHLi$, THF, –78 to 25 °C

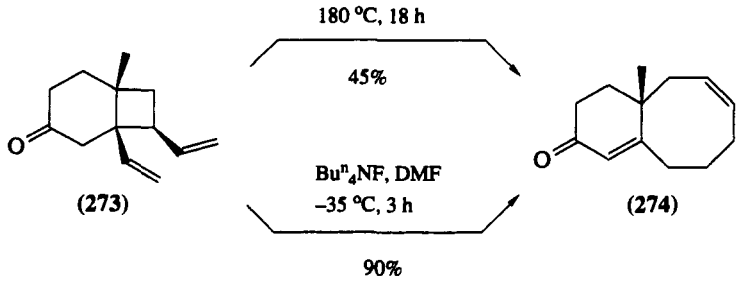
Scheme 37

Finally, a recent study by Majetich and Hull has demonstrated the feasibility of the carbanion-accelerated divinylcyclobutane rearrangement.[93] Whereas the thermal rearrangement of the divinylcyclobutane (**273**; Scheme 38) required extended heating at 180 °C and proceeded in modest yield, the corresponding enolate was shown to rearrange smoothly at –35 °C in 90% yield. As illustrated in Scheme 39, the enolate-accelerated DVCB rearrangement can be employed in tandem with the intramolecular fluoride-promoted Michael addition of allylsilanes to provide an attractive route to a variety of fused bicyclic cyclooctane derivatives.

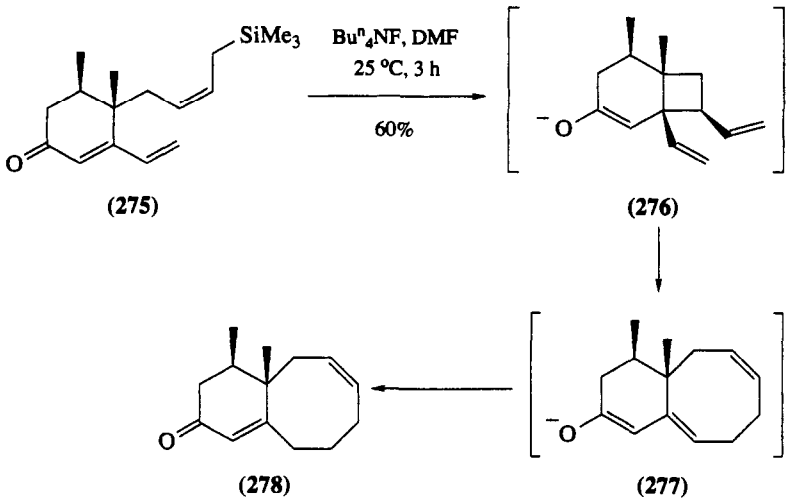
8.3.3.3 Cyclobutene Rearrangements

8.3.3.3.1 Introduction

The electrocyclic ring opening of cyclobutenes has found considerable use as a method for the synthesis of 1,3-dienes. The reaction has recently been reviewed by Marvell[94] and is also the subject of



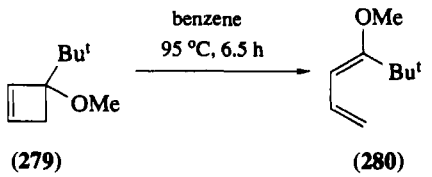
Scheme 38



Scheme 39

Chapter 6.1, this volume. Several important synthetic strategies feature the electrocyclic cleavage of a cyclobutene derivative as a key step. Particularly noteworthy in this regard is the thermolysis of benzocyclobutenes, which serves as a convenient method for the generation of *o*-quinodimethanes. These highly reactive conjugated dienes readily participate in both inter- and intra-molecular Diels–Alder reactions, and the tandem electrocyclic cleavage–cycloaddition strategy provides a powerful method for the preparation of a wide range of complex six-membered ring-containing compounds. The application of this strategy in elegant total syntheses of a variety of steroids, alkaloids and lignan antitumor agents is well documented.[95]

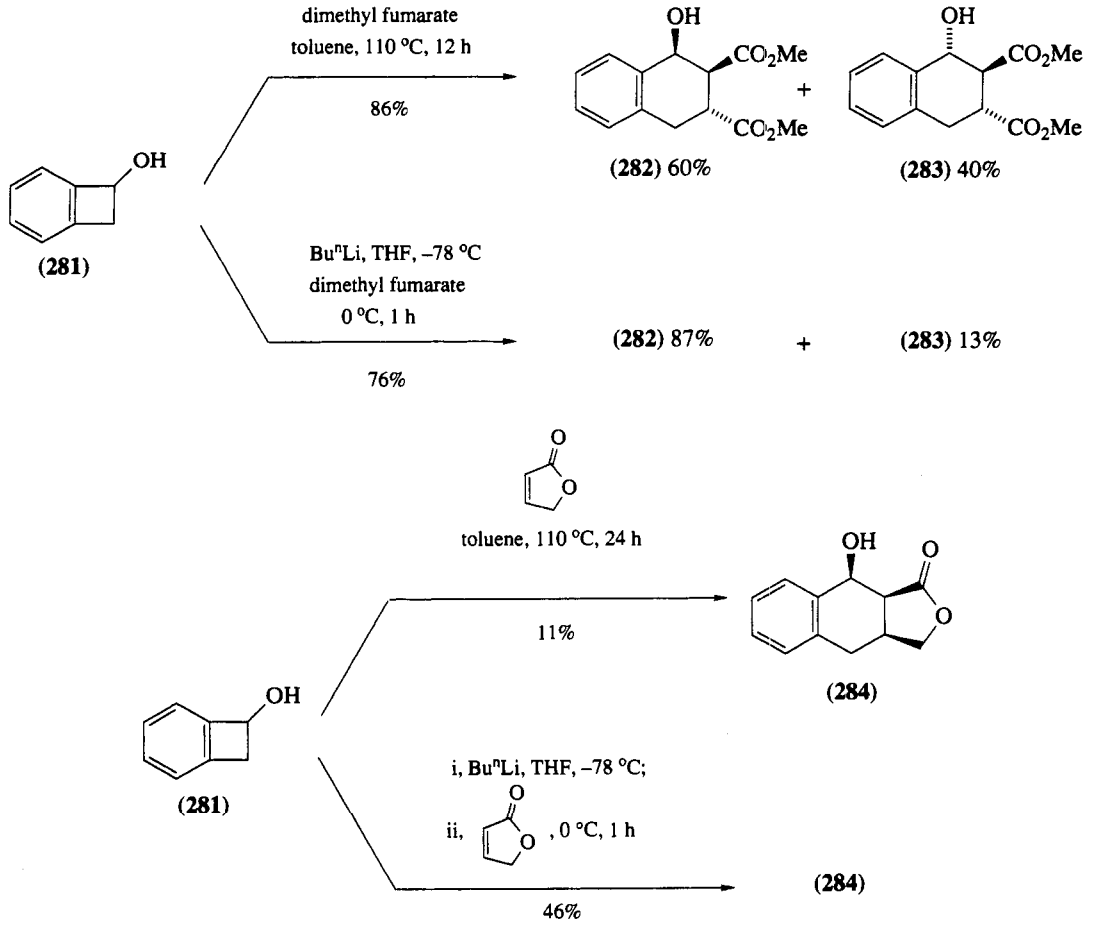
Cyclobutene thermolyses are typically performed at temperatures ranging from 80 to 200 °C. Carpenter's model (see Section 8.3.1.2)[9] suggests that electron-donor substituents at C-3 of the four-membered ring should enhance the rate of electrocyclic ring cleavage. This prediction has received experimental verification; for example, the activation energy for the ring opening of 3-ethoxycyclobutene was determined to be 9 kcal mol^{-1} lower than that required for the parent system.[96] A particularly interesting recent development is the finding that these conrotatory electrocyclic processes occur with a strong preference for the 'outward' rotation of C-3 donor substituents, as illustrated with the transformation outlined in equation (38).[97]



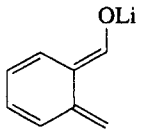
(38)

8.3.3.3.2 Anion-accelerated electrocyclic cleavage of cyclobutenes

The ability of both oxyanionic and carbanionic substituents to facilitate the electrocyclic ring opening of cyclobutenes has now been documented.[98] For example, the oxyanion-accelerated electrocyclic cleavage of benzocyclobutenes has been examined by Choy and Yang;[99] some of their results are summarized in Scheme 40. Addition of 1.1 equiv. of *n*-butyllithium to the benzocyclobutenol (**281**) in THF at –78 °C and subsequent warming to –25 °C led to the formation of a burgundy red solution believed to contain the oxyanion-substituted *o*-quinodimethane (**285**). Efficient Diels–Alder cycloadditions were observed to take place when the electrocyclic cleavage reaction was carried out in the presence of electron-deficient dienophiles such as dimethyl fumarate and γ-crotonolactone (Scheme 40). These cycloadditions proceed under considerably milder conditions than the analogous thermal reactions, and in many cases exhibit increased selectivity for the formation of the *endo* Diels–Alder adducts.



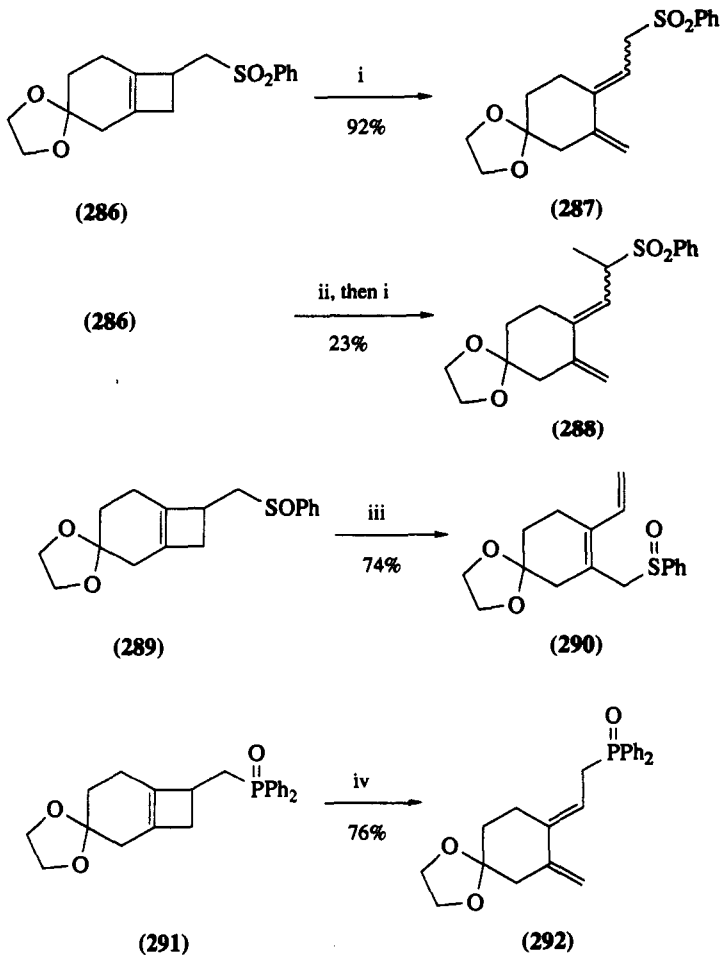
Scheme 40



(285)

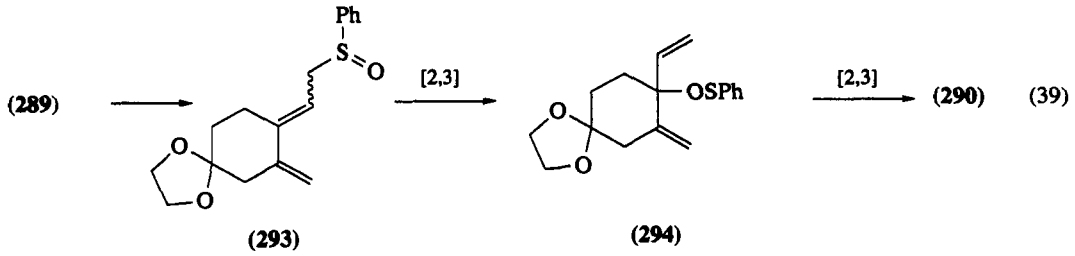
Kametani and his group have described several examples of carbanion-accelerated cyclobutene ring openings.[100] As outlined in Scheme 41, cyclobutenes substituted with arylsulfonyl-, arylsulfinyl- and diphenylphosphinoyl-stabilized carbanions all undergo extraordinarily facile electrocyclic cleavage at temperatures below –20 °C. It is unclear whether these reactions follow concerted mechanisms or involve heterolytic cleavage of the cyclobutene ring. The formation of the peculiar rearranged products such as

(**290**) in reactions in the sulfoxide series has been explained on the basis of a mechanism involving sequential 2,3-sigmatropic rearrangements (equation 39).



i, 1.2 equiv. Bu^{n}Li, THF, –78 to –30 °C, 10 min; ii, 1.2 equiv. Bu^{n}Li, THF, then 1.2 eqiuv. MeI, –78 °C; iii, LDA, THF, –78 °C to –30 °C; iv, 7 equiv. LDA, THF, –20 °C, 16 h

Scheme 41



(39)

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9.1
The Pauson–Khand Reaction

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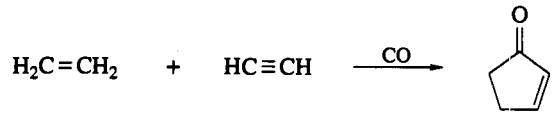
9.1.1 GENERAL CONSIDERATIONS

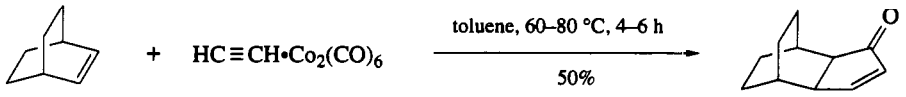
9.1.1.1 Introduction

Although the *a priori* development of multicomponent cycloaddition reactions involving selective incorporation of three or more different molecules may seem to be a daunting task, numerous such reactions exist.[1] Indeed, study of the chemistry of transition metals in the presence of organic π-systems over the past four decades has led to the serendipitous discovery of a marvelous array of multicomponent processes. More recently, as a fuller understanding of mechanisms of transition metal reactions has evolved, the intentional development of still more remarkably powerful reactions has taken place.[2] Among the several systems that have been found to be suitable for the cocycloaddition of alkynes, alkenes and carbon monoxide,[3–5] the most extensively studied is the one first reported in detail by Khand and Pauson in 1973,[6] a cyclopentenone synthesis from the three components and $Co_2(CO)_8$, a formal [2 + 2 + 1] cycloaddition (equation 1). This reaction was discovered in the course of a study aimed principally at the preparation and characterization of various alkene and alkyne complexes derived from $Co_2(CO)_8$. During the subsequent half-dozen years or so the Pauson group was virtually alone in pursuing the development of this reaction, carrying out a number of extensive series of studies of remarkable breadth and depth. The Pauson–Khand reaction has now taken a place amidst the more conventional methodological approaches to the challenging cyclopentenone ring system, is a focus of study by a number of research groups and has been used in synthetic applications by many more.

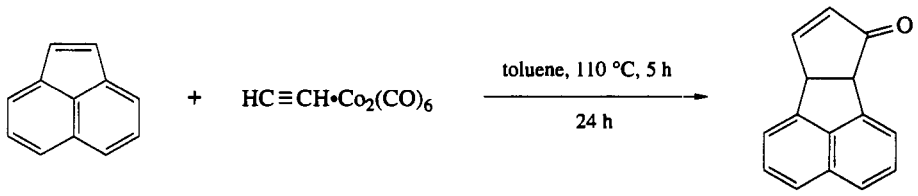


(1)

The reaction is carried out in one of two principal ways. In the more common stoichiometric method, the alkyne is allowed to react with $Co_2(CO)_8$ at room temperature over the course of several hours in hydrocarbon or ethereal solvent to generate the thermally stable, readily characterized complex $Co_2(CO)_6{\cdot}RC{\equiv}CR'$.[7] This in turn reacts under moderate heating with a wide variety of alkenes to generate cyclopentenones, giving typical yields in the 30–60% range (equations 2 and 3).[8,9] The reaction is normally carried out under an atmosphere of either nitrogen or carbon monoxide; if the alkyne in $Co_2(CO)_6{\cdot}RC{\equiv}CR'$ is a gas, it is typically incorporated into the atmosphere above the reaction mixture as well. Depending on the reactivity of the substrate, reaction times range from hours to days at temperatures between 70 and 110 °C for all but the most unreactive alkenes. The use of pressure above 1 atm is usually unnecessary, although improvements in yields have occasionally been noted when the reaction is carried out in a sealed tube.

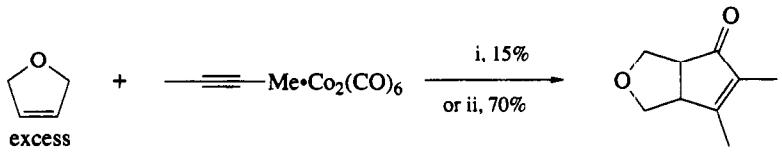


(2)



(3)

When the reaction involves a gaseous alkyne, it is often both feasible and advantageous to carry it out in a catalytic fashion by stirring a mixture of alkene and *ca.* 10 mol % $Co_2(CO)_8$ in an inert solvent under a 1:1 alkyne/carbon monoxide atmosphere. Provided that potential side reactions involving the alkene and $Co_2(CO)_8$ do not compete, the continuous supply of excess alkyne allows trapping and recycling of reactive cobalt-containing fragments to occur, while also compensating for independent side reactions that consume the alkyne, such as trimerization to benzene derivatives. The result is substantially improved yields in the most favorable cases (equation 4).[10]



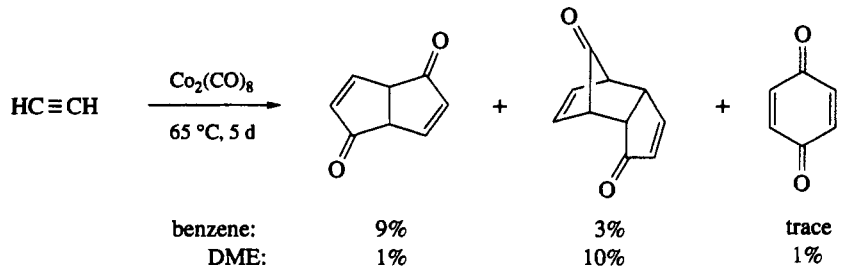
(4)

i, toluene, 110 °C, 8 h, N_2; ii, isooctane, 85 °C, 8 d, 1:1 CO/2-butyne

9.1.1.2 Scope of the Reaction

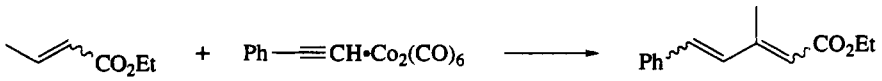
The scope of the Pauson–Khand reaction with respect to substrate structure is considerable. Virtually all alkynes that have been tried participate, except derivatives of propynoic acid. Most satisfactory are acetylene itself and simple terminal alkynes, including arylalkynes. Internal alkynes give consistently lower yields of cyclopentenones. The scope of the reaction with respect to the alkene is typically somewhat more limited. Strained cyclic alkenes are the best substrates, typically reacting at 60–80 °C over a period of several hours. Steric hindrance around the double bond exerts a significant deleterious effect on the cycloaddition. In particular, tri- and tetra-substituted double bonds, and double bonds containing large allylic substituents, even when contained in a strained ring, frequently give cyclopentenones only in low yields, if at all. This is apparently due to a reduction in the ability of the alkene to compete with additional molecules of alkyne for reaction with the initially formed $Co_2(CO)_6{\cdot}RC{\equiv}CR'$ complex. As a result, reactions such as alkyne trimerization, and multicomponent cycloadditions involving only alkyne

and carbon monoxide, normally only minor side reactions, become the principal processes taking place, leading to a variety of products (equation 5).[11] Simple acyclic alkenes and unstrained cyclic alkenes are also generally poor substrates, rarely giving cyclopentenones in yields better than 40%. Several techniques for improving yields of cyclopentenones in these less favorable situations have been employed, and these will be described in the appropriate sections.



(5)

As examples that follow will reveal, the Pauson–Khand reaction possesses substantial functional group tolerance. It is completely compatible with a wide range of functionality including ethers, alcohols, tertiary amines, sulfides, ketones, ketals, esters, tertiary amides, and aromatic rings including benzene, furan and thiophene. Partial tolerance of the following groups has also been observed: alkyl and aryl halides, vinyl ethers and esters, and less reactive alkenes and alkynes in the presence of more reactive unsaturation.[12] Cyclopentenone formation generally appears not to be adversely affected by conjugation of either substrate π-system with another carbon–carbon π-bond. However, a few examples of reduced or anomalous reactivity have been reported in substrates bearing other allylic or propargylic functionality. Most noticeably, alkenes conjugated with electron-withdrawing substituents react very differently. Formal addition of a vinylic C—H bond across the triple bond of the alkyne results in the formation of 1,3-dienes (equation 6).[13] A possible mechanistic relationship between this process and the formation of cyclopentenones will be presented in the section that follows.



(6)

Excellent background material on the Pauson–Khand reaction is available in reviews published by Pauson in 1977, 1985 and 1988.[14–16]

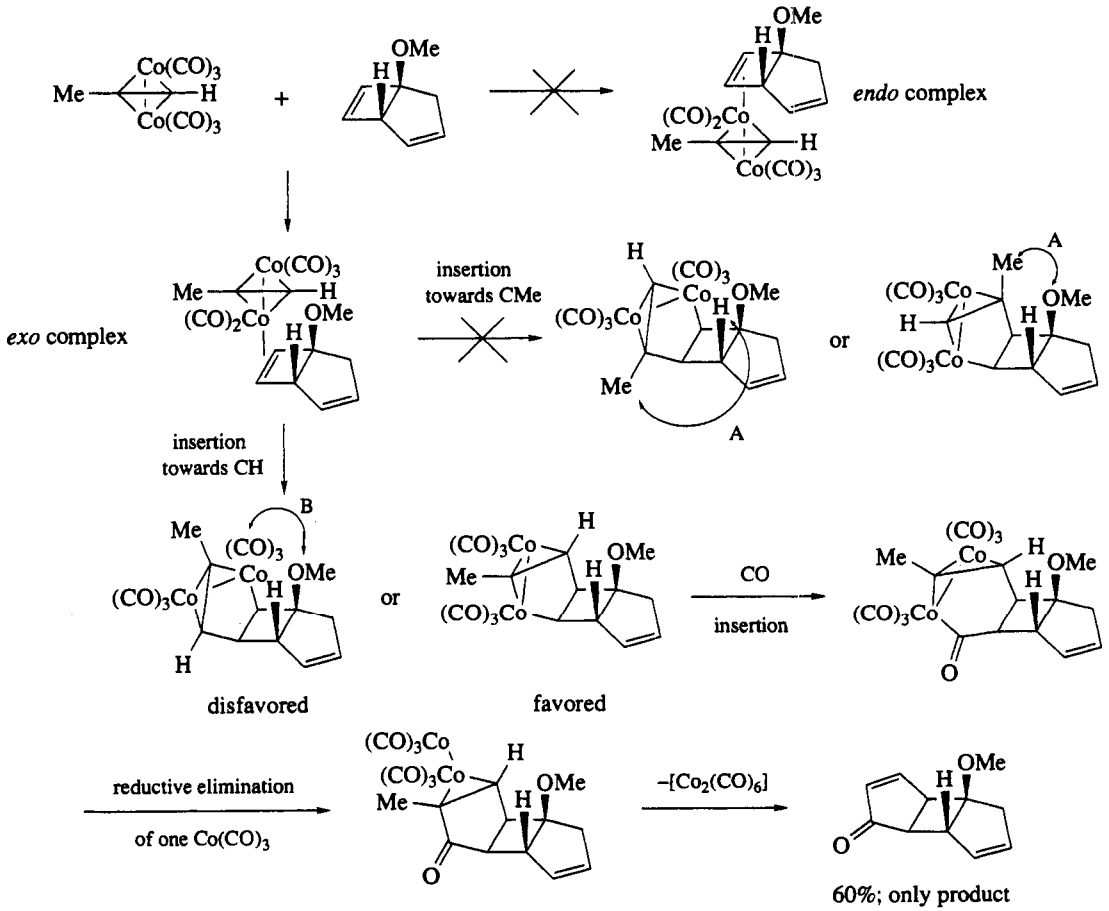
9.1.2 MECHANISM: REGIO- AND DIASTEREO-SELECTIVITY

Direct studies of the mechanism of the Pauson–Khand reaction have been limited to the observations made very early on by the Pauson group indicating the unambiguous intermediacy of the $Co_2(CO)_6$·RC≡CR′ complex in the process. Although alkene complexes derived from $Co_2(CO)_8$ are well known, if limited in number, they have been shown not to give rise to cyclopentenones upon treatment with alkynes.[6] Attempts to observe intermediates spectroscopically beyond the alkyne complexation stage have been unsuccessful; invariably the only species detected during the course of the reaction are the final products themselves. It is most reasonable to assume that, whatever the mechanistic sequence that follows alkyne complexation, the rate-determining step occurs early in the sequence, precluding the build-up of any subsequent intermediates to observable levels.

Nevertheless, although direct mechanistic evidence beyond the alkyne complexation stage is lacking, a hypothesis has been inferred from observations of regio- and stereo-chemistry in a large number of examples of Pauson–Khand cycloaddition.[17] This is illustrated using the reaction between the $Co_2(CO)_6$·propyne complex and 1-methoxybicyclo[3.2.0]hepta-3,6-diene, reported by Pauson and coworkers in 1977 (Scheme 1).[18] In common with the majority of transition metal mediated organic cycloaddition reactions known at the present time, the principal controlling interactions appear to be steric in nature. Complexation of the alkene to cobalt *via* a standard dissociative mechanism initiates the sequence. With bicyclic alkene substrates such as the one shown, the less hindered *exo* face of the π-bond preferentially complexes to the metal. This process is almost certainly reversible. The step that follows, insertion of the complexed face of the alkene π-bond into one of the formal cobalt–carbon bonds of the

alkyne complex, is thought to be both the rate- and product-determining step. Both regio- and stereochemistry are kinetically controlled, chiefly by steric interactions in this irreversible insertion process. In the example shown, the diastereofacial selectivity upon alkene complexation is preserved upon insertion, a stereospecific process that leads exclusively to a *cis-exo* ring fusion. This result is nearly universally observed with bicyclic alkenes, including those employed in the first reported examples of the reaction: norbornene, norbornadiene and several of their derivatives.[6]

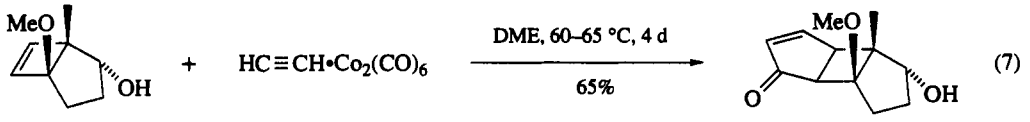
During the insertion into the cobalt–carbon bond, regiochemistry with respect to both alkyne and alkene is determined. The incipient carbon–carbon bond is most susceptible to steric crowding; for example, a 1,3-pseudodiaxial interaction (A in Scheme 1) develops between the substituent on the alkyne carbon and any allylic group on the alkene. As a result, if the alkyne is unsymmetrical, insertion and carbon–carbon bond formation proceed exclusively at the alkyne carbon possessing the smaller substituent (*i.e.* H in a terminal alkyne, leading eventually to a 2-substituted enone). With steric hindrance at the alkyne carbon thus removed, a second 1,3-pseudodiaxial interaction comes into play, capable of exerting regiocontrol of an alkene unsymmetrically substituted at the allylic positions. This interaction (B in Scheme 1) involves an allylic substituent with the $Co(CO)_3$ moiety. In order to minimize this interaction, the alkene carbon bearing the larger allylic substituent inserts away from the cobalt, thus forming the new carbon–carbon bond with the alkyne carbon. Subsequent CO insertion, reductive elimination of one cobalt, and decomplexation of the other give the final product.



Scheme 1

Briefly summarized, the less-hindered face of the alkene inserts into the less-hindered formal cobalt–carbon bond of the starting complex, with the orientation of alkene insertion placing the larger allylic substituent away from cobalt. The overall result is: (i) *cis-exo* ring fusion stereochemistry; (ii) alkyne regiochemistry placing the larger alkyne substituent α to the new ketone carbonyl and (iii) alkene regiochemistry placing the larger allylic substituent *anti* to the new ketone carbonyl. The first two preferences are strong ones; indeed, no exceptions to the second are known. As to the third, it should be pointed out that the bicyclo[3.2.0]hept-6-ene system is an unusually regioselective substrate. Indeed, the steric sensi-

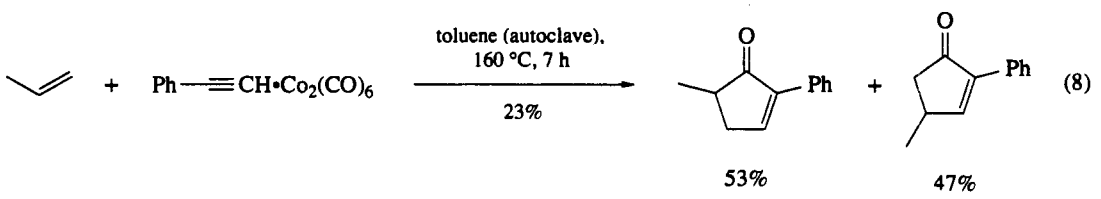
tivity of this system is strikingly illustrated in the total reversal of regiochemistry upon replacement of a ring fusion hydrogen with methyl, which is effectively larger than methoxy (equation 7).[19]



(7)

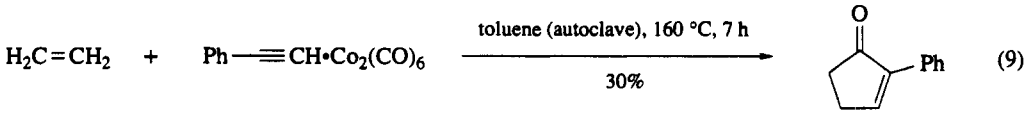
In general, however, the issue of alkene regiochemistry is still incompletely resolved, as it is dependent on both the nature of the alkene as well as the alkyne. Thus, while the systems depicted in Scheme 1 and equation (7) are totally regioselective, most other types of bicyclic alkenes give mixtures of regioisomers, although the isomer predicted on the basis of the analysis above always predominates. Furthermore, regiocontrol with simpler alkenes is more difficult to predict. Simpler terminal alkenes themselves display little or no regioselectivity upon reaction with acetylene or terminal alkynes, although incorporation of the alkyne remains totally regioselective (equation 8).[20,21] In addition, alkyne regiocontrol remains high even in reactions with ethylene itself, even though some of the steric interactions alluded to earlier are obviously absent (equations 9 and 10).[16] Krafft has suggested that steric effects may play a controlling role prior to insertion, by favoring specific configurational and conformational isomers of the alkene complex for subsequent reaction. Thus of the three possible configurational isomers at pseudooctahedral cobalt, the one most likely to lead to insertion contains the alkene complexed *trans* to the bond between cobalt and the substituted alkyne carbon, avoiding a steric interaction with the latter. Insertion can therefore only occur into the other cobalt–carbon bond, fixing the alkyne regiochemistry (Scheme 2, R′ = H). With most terminal alkenes, there will be little preference between the two possible reactive conformations about the cobalt–alkene bond, resulting in no regioselectivity in alkene incorporation (*cf.* equation 8). However, if the R′ group on the alkene is sufficiently large, conformation (**2**) is preferred (Scheme 2), placing the large group *anti* to the cobalt–carbon bond. This results in a preference for the 5-substituted cyclopentenone, as has been observed by Pauson in the case of 3,3-dimethyl-1-butene (*t*-butylethylene; equation 11).[16]

Strong support for this picture has been provided by Krafft in the observation of greatly increased alkene regioselectivity in Pauson–Khand cycloadditions with internal alkynes (equation 12).[21] As above, the site of coordination of the alkene determines alkyne regioselectivity, while the conformation of the coordinated alkene prior to insertion determines alkene regioselectivity. The presence of groups larger than hydrogen on both alkyne carbons introduces unavoidable steric interactions biasing the system towards alkene insertion from a conformation similar to conformation (**2**) in Scheme 2. This more detailed analysis has only been applied to terminal alkenes, in which steric differentiation between the alkene carbons is large. Comparable application to bicyclic systems such as those discussed earlier (*i.e. cis*-disubstituted alkenes) will be more complicated. Steric differentiation is much smaller, and, in addition, it will

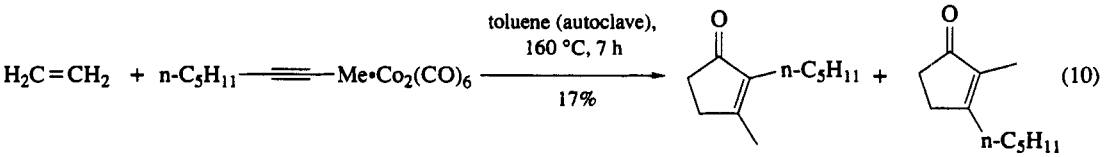


53% 47%

(8)

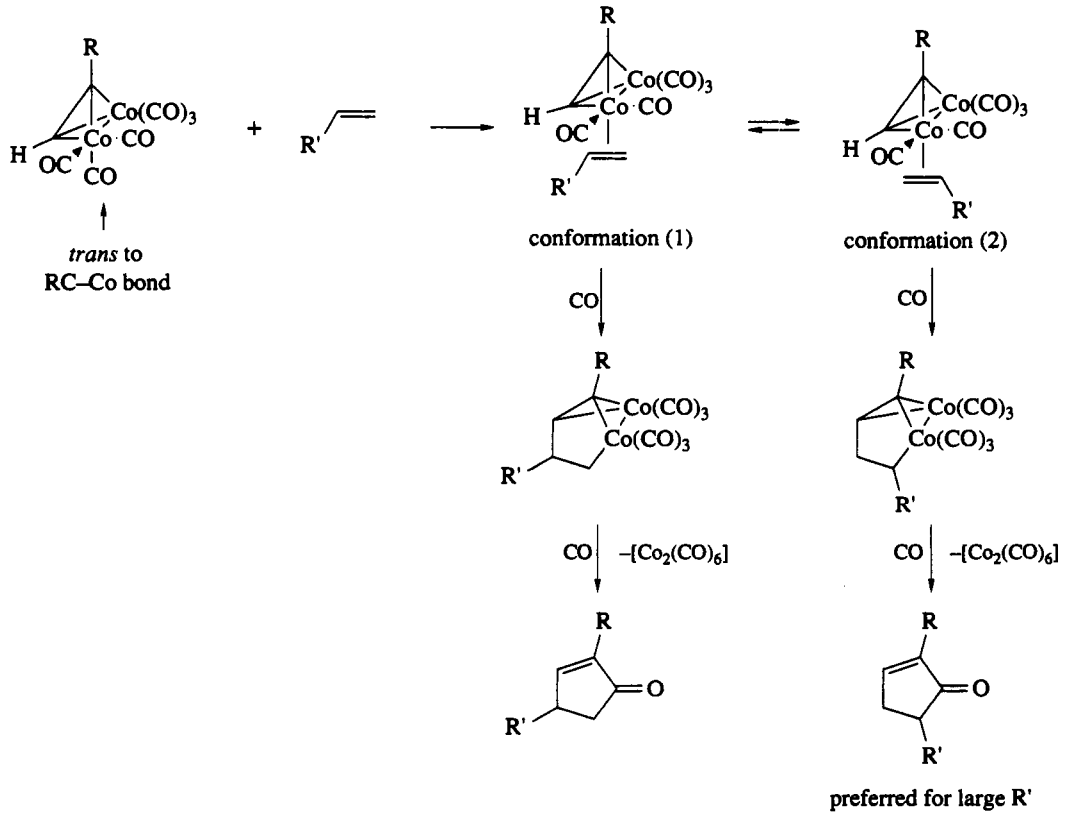


(9)

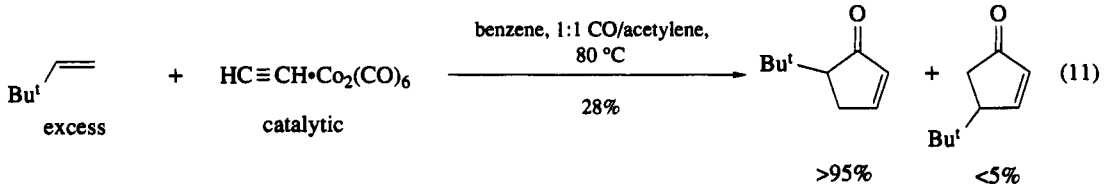


93% 7%

(10)

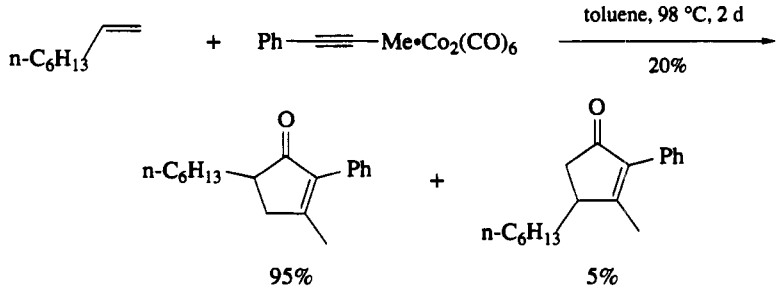


Scheme 2



(11)

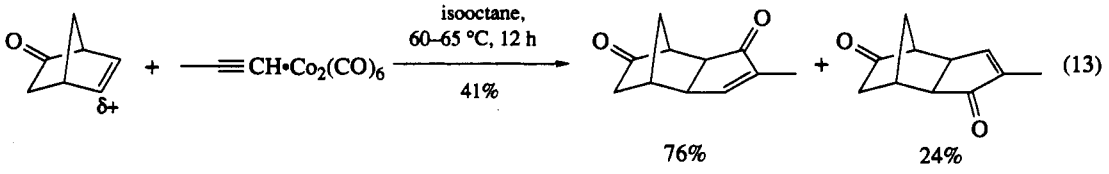
be necessary to consider the effects on regiochemistry of the chirality of both the allylically substituted alkene as well as the alkene–alkyne–cobalt complex, in which the cobalt becomes a stereocenter, thus introducing an additional diastereoselection problem in the formation of the complex itself. At present, the simpler analysis based upon pseudoaxial interactions will have to suffice.



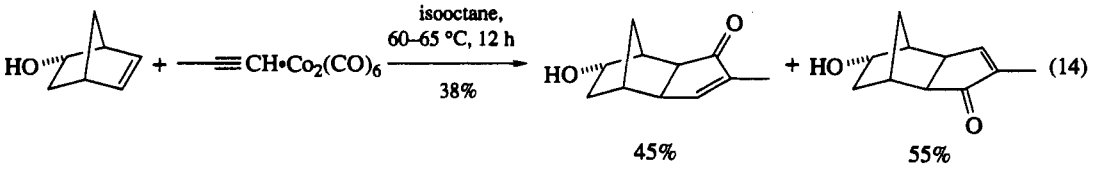
(12)

Electronic effects on alkene regioselectivity in the Pauson–Khand reaction have also been observed. The regioselectivity observed in cycloadditions of norbornen-2-ones has been interpreted as arising from an electronic preference for attachment of the δ^+ C-5 of the alkene to an alkyne carbon rather than cobalt in the bond-forming insertion step (equation 13). In these systems electronic and steric effects have been separated by carrying out identical reactions with the corresponding norbornen-2-ols, in which the

alkene-polarizing homoconjugation interaction has been removed. The observation of *ca.* 1:1 product ratios from the latter (equation 14) supports the interpretation given above, and is consistent with earlier results from the Pauson group involving reactions of styrene derivatives (see Section 9.1.3.1).[22]

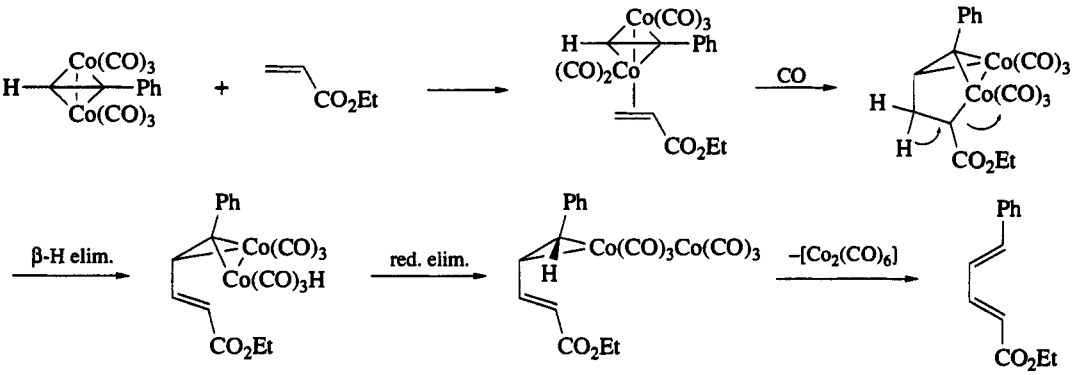


(13)



(14)

As already mentioned, alkenes attached to electron-withdrawing groups react anomalously, giving 1,3-dienes (equation 6).[13] The reaction is completely regioselective, with the new carbon–carbon bond forming between the less-hindered alkyne carbon and the less-hindered alkene carbon, which also happens to be the δ^+ polarized alkene carbon. It is therefore reasonable to assume that complexation of the alkene and subsequent insertion still occur as illustrated in Scheme 1, and are controlled by the same steric and electronic factors. The electron-withdrawing group in every example of this reaction is π-conjugating. This probably renders a β-hydrogen elimination/reductive elimination sequence competitive with CO insertion, by providing a driving force for regeneration of the alkene (Scheme 3).

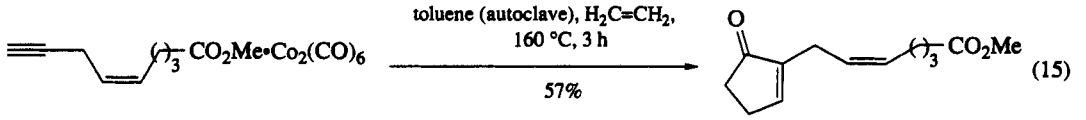


Scheme 3

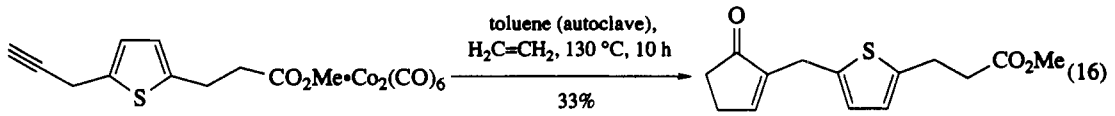
9.1.3 INTERMOLECULAR PAUSON–KHAND REACTION

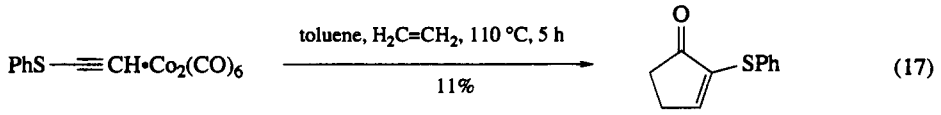
9.1.3.1 Reactions involving Acyclic Alkenes: Chemo-, Regio- and Diastereo-selectivity

Application of the Pauson–Khand reaction to simple acylic alkenes has been limited by both low reactivity and lack of regiocontrol in incorporation of the alkene. Among simple alkenes, ethylene provides the most consistently useful results. Yields with terminal alkynes range from 30–60% (equations 9,15 and 16);[23,24] internal alkynes have also been used with some success (equation 10).[16] Forcing conditions (toluene, 130–160 °C, 60–80 atm, autoclave) are usually required for best results, although it has been recently demonstrated that the reaction proceeds, albeit slowly, at reduced pressures and temperatures (equation 17).[16,25]

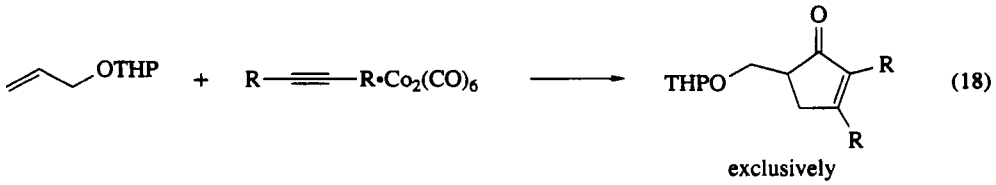


(15)

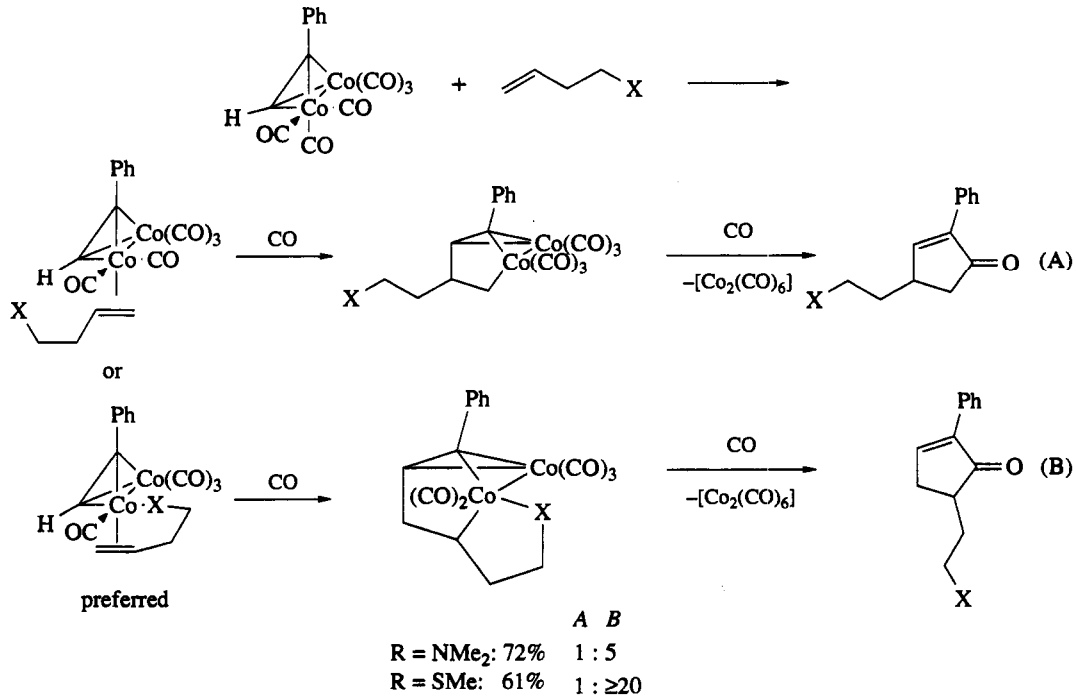




As already mentioned, terminal alkenes usually give modest yields but no regioselectivity in reaction with terminal alkynes. Isolated examples of regiocontrol have been reported in the case of allyl ethers (equation 18);[16,26] note that the R = Me situation is consistent with Krafft's results (equation 12).[21] In the case of R = H, a remarkable and unexplained effect is observed in which the regioselectivity is totally lost when reaction is carried out in a nonaromatic solvent. On the other hand, of considerable potential is another recent observation by Krafft that alkenes containing groups capable of acting as soft ligands at a homoallylic position give both enhanced yields and regioselectivities. This is thought to result from coordination of the heteroatom to cobalt prior to insertion, thereby fixing the conformation of the alkene to favor the 5-substituted product (Scheme 4).[27] Reduced but still usable (*ca.* 3:1) selectivity is observed when the heteroatom is one carbon further removed from the double bond. For optimal yields in these situations it is necessary to exclude carbon monoxide from the atmosphere above the reaction.



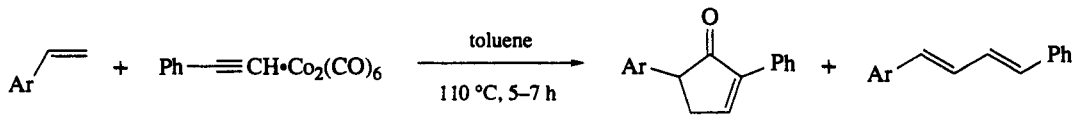
R = H: benzene, 80 °C, 8 h, 48%; R = Me: toluene, 110 °C, 8 h, 32%



Scheme 4

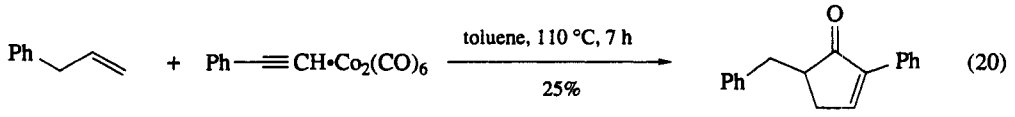
Conjugated acyclic dienes (in contrast to cyclic dienes, Section 9.1.3.2), like alkenes conjugated to electron-withdrawing groups, give only linear oligomerization, resulting in acyclic polyene products.[14]

Styrene derivatives have been extensively studied and are intermediate, giving both dienes and 5-arylcyclopentenones, both with complete regioselectivity, consistent with expectations. Attempts to explain and control chemoselectivity in such systems have been made in several studies by the Pauson group. Initial notions that chemoselectivity might be related to electron-withdrawing capability of the aryl substituent have not been supported by the evidence. For a variety of styrene derivatives containing *para* substitution the product ratio of cyclopentenone to linear diene varies in no readily interpretable way with the nature of the substituent, nor does complexation of the strongly electron-withdrawing $Cr(CO)_3$ unit to the arene have a consistent effect (equation 19).[20,28,29] Fragmentary data indicate that alkyl alkynes give more cyclopentenone and less diene than do aryl alkynes in reactions with styrenes. Allylarenes (3-arylpropenes) also give 5-substituted cyclopentenones with complete regioselectivity, for no obvious reason (equation 20).



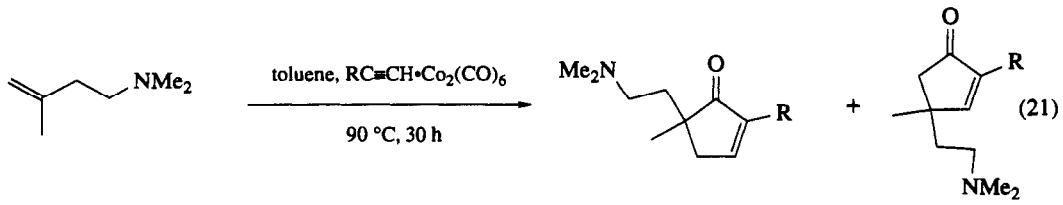
(19)

Ar = Ph:	31%	77%	23%
Ar = Ph•Cr(CO)$_3$:	69%	54%	46%
Ar = *p*-Tol:	39%	33%	67%
Ar = *p*-Tol•Cr(CO)$_3$:	68%	57%	43%
Ar = *p*-ClC$_6$H$_4$:	29%	55%	45%
Ar = *p*-ClC$_6$H$_4$•Cr(CO)$_3$:	29%	0%	100%



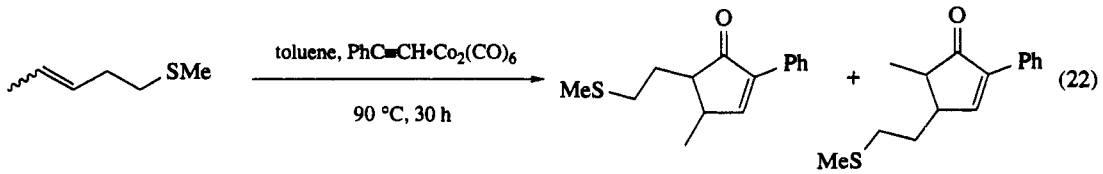
(20)

Considerably less work has been carried out with more heavily substituted acyclic alkenes; for all practical purposes these cannot at present be considered useful substrates. A significant exception exists in the reactivity of the homoallylically derivatized systems of Krafft; again, greatly improved yields are observed along with impressive regioselectivity but no diastereoselectivity (equations 21 and 22). It is not known at what stage stereochemistry at the saturated α-carbon is lost.[27]



(21)

R = Ph:	77%	95%	5%
R = Bu:	60%	94%	6%

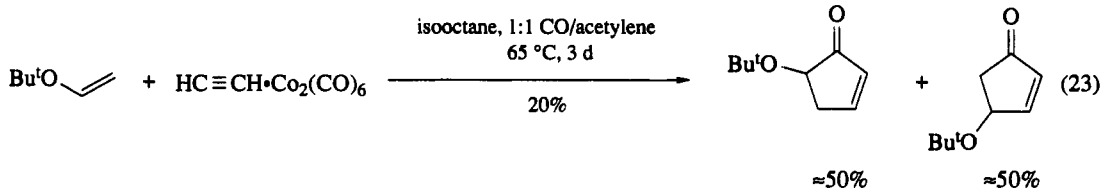


(22)

(*E*)-alkene:	40%	87% (*trans*/*cis* = 12:1)	13%
(*Z*)-alkene:	73%	≥97% (*trans*/*cis* = 19:1)	≤3%

Limited work has revealed that vinyl and allyl halides cyclize only in low yield, and the products suffer halogen loss in the process.[20] Also, unlike allyl ethers, vinyl ethers and esters are only marginally

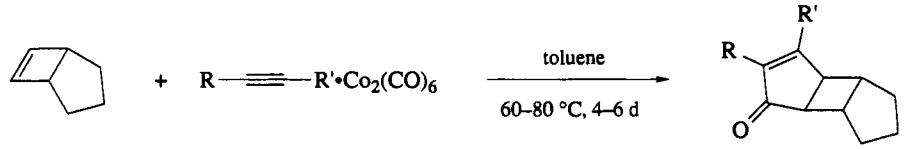
suitable substrates for Pauson–Khand cycloaddition (equation 23).[30] Part of the difficulty lies in the sensitivity of both the substrates and the products to decomposition under the reaction conditions.



(23)

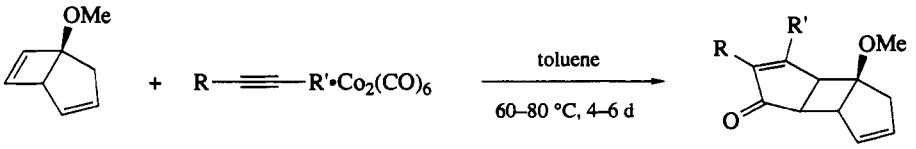
9.1.3.2 Reactions involving Monocyclic and Fused Bicyclic Alkenes: Chemo- and Regio-selectivity

The first alkenes studied as substrates for Pauson–Khand cycloaddition were strained bicyclics containing the double bond in four- or five-membered rings. Simple cyclobutenes do not appear to have been examined as substrates, but bicyclo[3.2.0]hept-6-enes have been used with considerable success. Pauson found the parent system to be generally reactive towards both terminal and internal alkynes, forming the expected *cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]dec-4-en-3-ones *via exo* face selective cycloaddition (equation 24). As mentioned earlier, total regioselectivity was obtained in the case of substrates with ring fusion (*i.e.* allylic) substitution, with the larger allylic group ending up *anti* to the newly introduced cyclopentenone carbonyl (Scheme 1; equations 7, 25 and 26).[18,19]



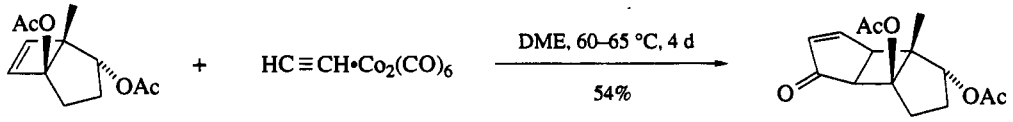
(24)

R = R' = H, 32%
R = Me, R' = H, 43%
R = Ph, R' = H, 43%
R = Ph, R' = Me, 30%



(25)

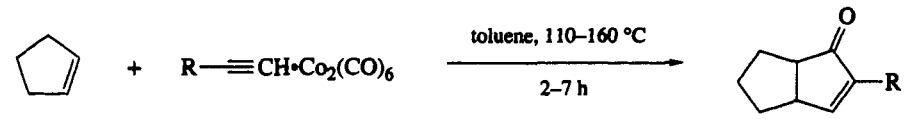
R = R' = H, 46%
R = Me, R' = H, 60%
R = Ph, R' = H, 30%
R = R' = Et, 44%



(26)

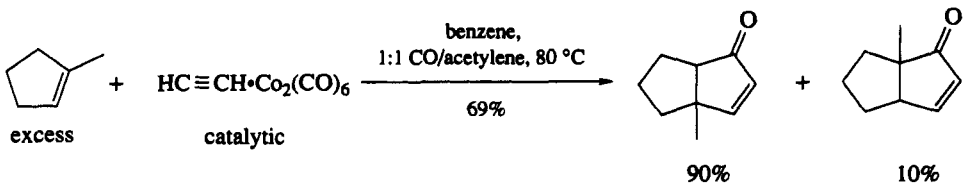
Although unstrained cyclic alkenes are generally less reactive than strained systems, cyclopentene and dihydrofuran are important exceptions. Required reaction temperatures are higher in some cases (120–160 °C), but no other special conditions are necessary and yields are frequently excellent. Cyclopentene itself reacts with terminal alkenes to give 30–60% yields of cyclopentenones (equation 27).[20,24] This reaction has seen extensive and imaginative development by de Meijere in the use of cyclopropylacetylenes as cycloaddition partners (see Section 9.1.3.4). Moreover, 1-methylcyclopentene, which reacts with acetylene to give <20% yields of cyclopentenones under normal conditions, becomes an excellent substrate when the catalytic modification of the cycloaddition procedure is used (equation 28).[16,25b] The remarkable regioselectivity may be due to a combination of (admittedly small) 1,3-pseudodiaxial interactions and electronic effects (*cf.* Scheme 1 and equation 13); recall that the Krafft conformational analysis involves interactions of internal alkynes only.

In contrast to acyclic dienes, cyclopentadienes and fulvenes react chemoselectively with alkynes to give cyclopentenones, the former in excellent yield but somewhat reduced regioselectivity, the latter less efficiently, although only one regioisomer is obtained (equations 29 and 30). Note that the favored posi-



(27)

R = Ph, 47%; R = SPh, 53%; R = $(CH_2)_6CO_2Me$, 33%

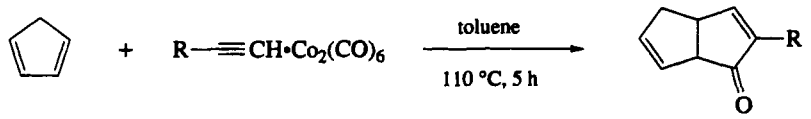


excess catalytic

(28)

90% 10%

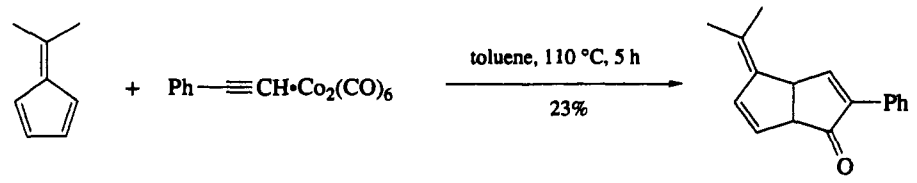
tion of conjugated unsaturation is the 5-position of the product, as was the case with styrene derivatives. Indene derivatives behave similarly. The fact that dienes are observed only as very minor products, if at all, reflects the clear superiority of the cyclopentene system over simple alkenes in Pauson–Khand annulation (equation 31). The same is true for acenaphthalene (equation 3), which also reacts with propyne and phenylacetylene to give exclusively cyclopentenones.[9]



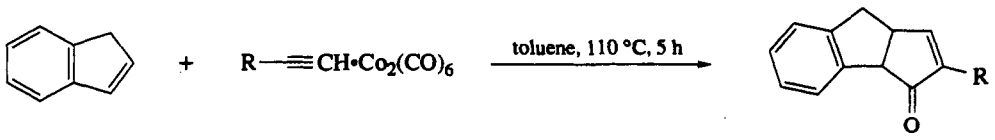
(29)

major product

R = Me, 55%; R = Ph, 60%



(30)

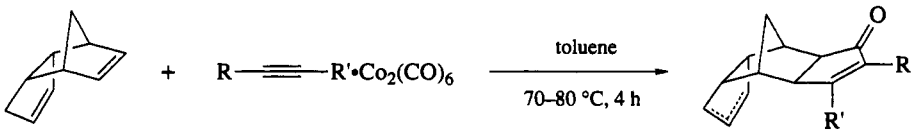


(31)

R = H, 31%; R = Me, 41%; R = Ph, 52% (+ 4% diene)

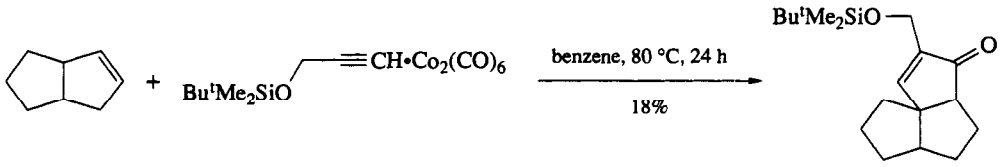
Other ring-fused cyclopentenes have been studied by both Pauson and Serratosa. Pauson's studies show the expected chemoselectivity when a cyclopentene is present together with a more reactive alkene moiety. In the system shown (equation 32), the cyclopentene is in fact totally inert under conditions required for the norbornene double bond to react.[12] Pentalene-derived substrates present an interesting variation on the basic theme. Serratosa's group has found an unexpected alkene isomerization to precede cycloaddition in the bicyclo[3.3.0]oct-2-ene system. Thermodynamics favors the double bond between C-2 and C-3; however, the double bond at C-1 is more reactive in spite of its increased steric hindrance. Under a variety of conditions, contrathermodynamic double bond isomerization is observed, and only products resulting from reaction of the double bond towards the ring fusion are observed (equation 33).[31] Note the regioselectivity, which is in the same direction as that observed for another trisubstituted alkene, 1-methylcyclopentene (equation 28). It is presumed that a standard hydrogen transfer mechanism involving π-allyl complexes mediates this process; certainly the presence of a tertiary allylic C—H bond in the starting alkene renders this feasible. Cyclopentenone yields in this system increase with temperature, but so do the yields of side products, including the corresponding cyclopentanones and products in which hydrogenolysis of the silyl ether has taken place. These reductions are further evidence for the intermediacy of metal hydrides, such as the ones that would mediate the aforementioned alkene isomeriza-

tion. The 2-methyl-substituted analog has been found to undergo similar reaction by Pauson: isomerization of the alkene again precedes cycloaddition (equation 34). Although the yield is low, the reaction is noteworthy as the only case in which a tetrasubstituted alkene gives an isolable enone product from a Pauson–Khand reaction. The lack of regioselectivity in the more symmetrical system is expected.[16,25b]

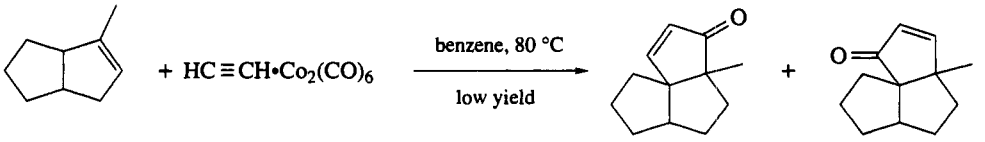


(32)

R = R' = H, 74%
R = Me, R' = H, 51%
R = Ph, R' = H, 57%
R = Ph, R' = Me, 32%

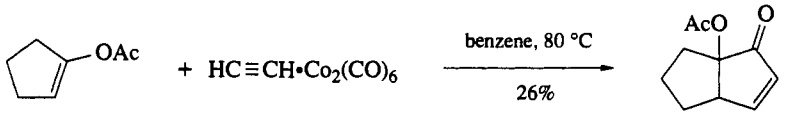


(33)

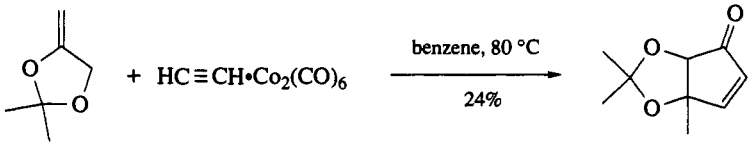


(34)

Regarding five-membered rings involving heteroatoms, 1-acetoxycyclopentene gives a single isolated product, although the conditions are such that the other regioisomer may not have survived (equation 35). Another case of alkene isomerization is presented in equation (36). Reaction from exclusively the internal double bond isomer again gives a single regioisomer; it is not known whether this results from the same factors controlling the reactions of other trisubstituted alkenes, or if this is another artifact arising from further chemistry under cycloaddition conditions.[16,25b]

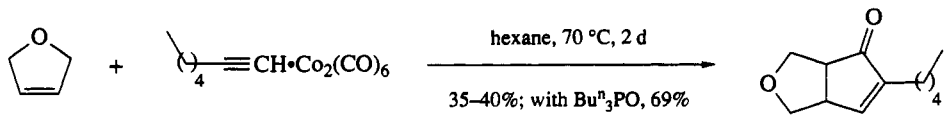


(35)

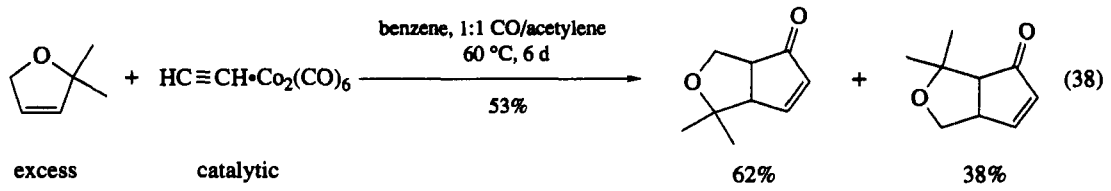


(36)

Dihydrofurans have seen considerable use as substrates in the Pauson–Khand reaction. The parent compound reacts in excellent yield with acetylene, terminal and internal alkynes. Yields in this system respond very well to the use of catalytic reaction conditions (equation 4). Another unusual experimental modification has also been found by Pauson to be useful in this system: addition of tri-*n*-butylphosphine oxide nearly doubles the product yield in certain cases (equation 37). The role of the added substance is unclear. Addition of phosphine oxide does not always improve reaction efficiency; at this time there are no guidelines to indicate when its use might be beneficial. Substituted dihydrofurans give somewhat lower but still acceptable yields; the poor regioselectivity in unsymmetrical cases is the more significant difficulty with these substrates (equation 38).[14,25a,32]

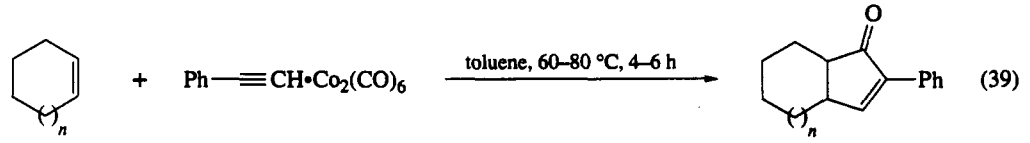


(37)



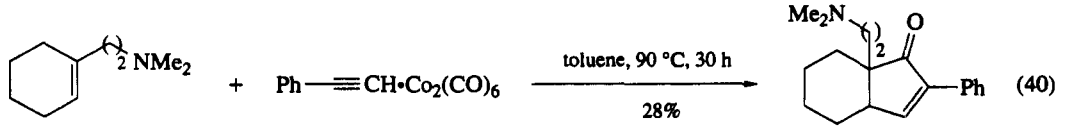
(38)

Alkenes in larger rings show acceptable reactivity in some cases but not others. For example, cycloheptene and cyclooctene give moderate yields of cyclopentenones upon reaction with phenylacetylene (equation 39), but none of the simple cycloalkenes reacts well with alkyl alkynes and cyclohexene itself is a very poor substrate.[20] Attachment of a 2-dimethylaminoethyl chain onto cyclohexene (*i.e.* homoallylic nitrogen) introduces useful reactivity (equation 40).[27] Dihydronaphthalene is also a usable substrate, perhaps due to reduced steric hindrance in the flattened ring. It displays the expected regioselectivity for a styrene analog (equation 41).[28] Cyclohexadienes do not give cyclopentenones directly under Pauson–Khand conditions. Instead, an apparently catalyzed Diels–Alder reaction takes place with the alkyne first, giving a bicyclo[2.2.2]octa-1,4-diene; this then participates in Pauson–Khand cycloaddition with additional alkyne (equation 42; Section 9.1.3.3). The product thus contains two molecules of starting alkyne, one of alkene and one of CO.[8]

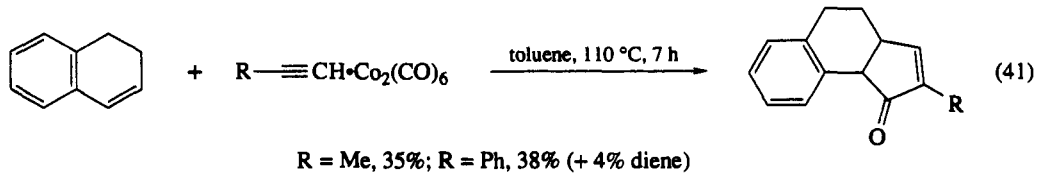


(39)

$n = 1$, 3%; $n = 2$, 41%; $n = 3$, 35%

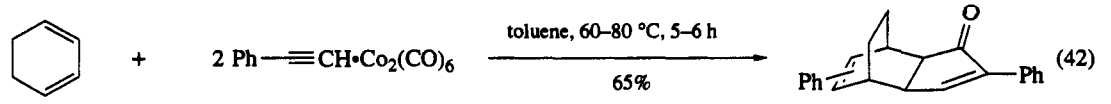


(40)



(41)

R = Me, 35%; R = Ph, 38% (+ 4% diene)



(42)

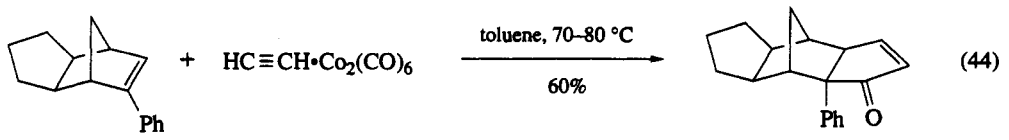
9.1.3.3 Reactions involving Bridged Bicyclic Alkenes: Regio- and Diastereo-selectivity

Five-membered ring alkenes contained in bridged bicyclic or polycyclic systems are by far the most extensively studied substrates for intermolecular Pauson–Khand reaction. Comprehensive surveys carried out by the Pauson group identified many of the key features of the process in these substrates.[6,12] Norbornene is nearly ideal, displaying such a wide scope of reactivity towards alkynes that it is usable as a test of the suitability of an alkyne as a Pauson–Khand substrate (equation 43).[15,24,33] Yields of cyclopentenones, all of which are formed with complete regioselectivity and *exo*-diastereofacial stereoselectivity, range for internal alkynes typically between 20 and 40%, and for terminal alkynes from 30 to >70% using catalytic conditions. Monoaryl substitution on the double bond is tolerated to a certain extent as well (equation 44). Reactivity of norbornenones and norbornenols has been discussed (equations 13 and 14).[22]

Both double bonds in norbornadiene are similarly reactive, so yields of tricyclic enones are limited by continued reaction of the initial product.[6,12,24] Use of a large excess of the diene is a partial remedy. This

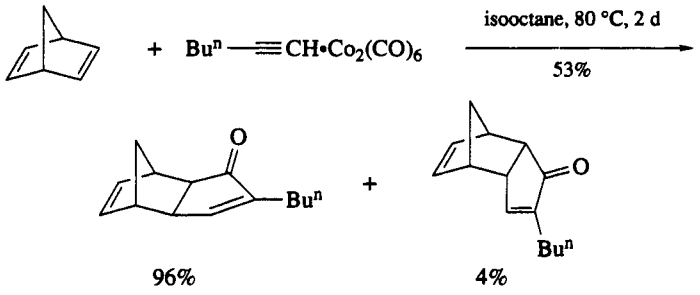
(43)

R = OEt, low yield; R = SPh, 59%; R = , 30%

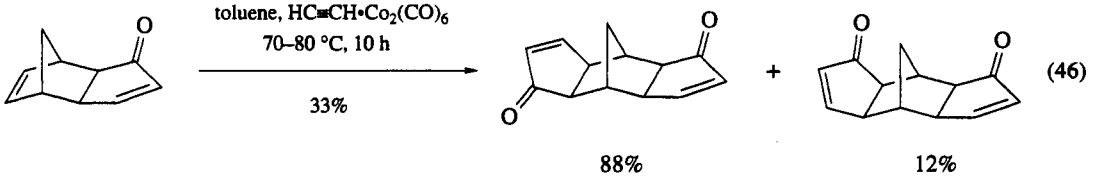


(44)

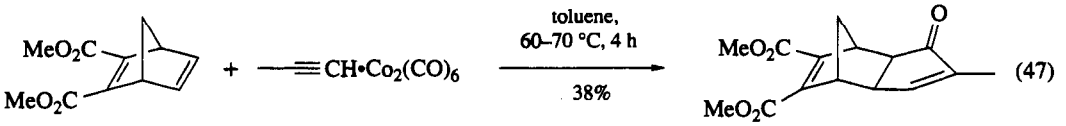
substrate is unique in affording small amounts of *endo*-fused products in some cases, probably as a result of reduced steric differentiation between the faces of the double bond (equation 45).[34] When cycloaddition is permitted to proceed at the second double bond, the result is low yield but regioselective formation of *anti*-diketones (equation 46). Chemoselectivity in systems containing less strained double bonds has been mentioned (equation 32);[12] this is also observed in systems with less electron rich double bonds (equation 47). Among heterocyclic analogs, 2,3-diaza-5-norbornene shows Pauson–Khand reactivity, but 7-oxanorbornadiene deoxygenates to an aromatic system.[14,15]



(45)

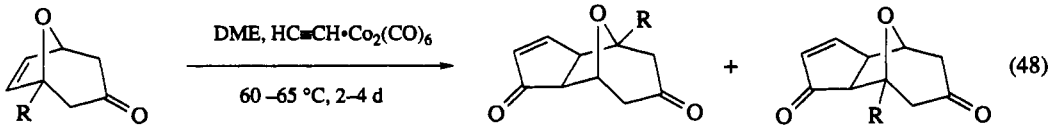


(46)



(47)

As bridged dihydrofuran analogs, 8-oxabicyclo[3.2.1]oct-6-enes are also useful substrates. Only low to moderate regioselectivity is observed in the cycloaddition of bridgehead substituted examples of these compounds (equation 48). In this system Pauson–Khand reactivity is eliminated by either further substitution on the double bond or even a bulky bridgehead substituent.[17] The analog containing an amide nitrogen in place of the oxygen bridge has also been cyclized successfully (equation 49).[35]

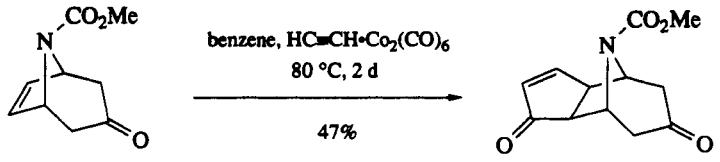


(48)

R = H, 45%
R = Me, 49%
R = Ac, 24%

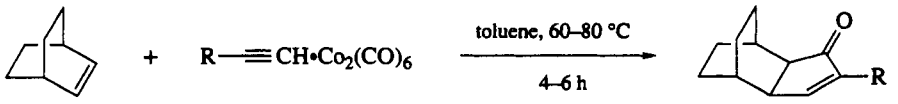
60%
75%

40%
25%



(49)

Bicyclo[2.2.2]octenes are good to excellent substrates, quite comparable to norbornene-based systems (equation 50).[8]

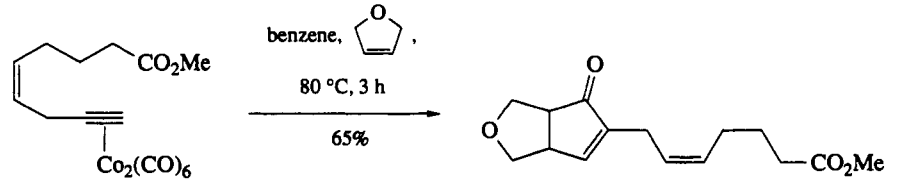


(50)

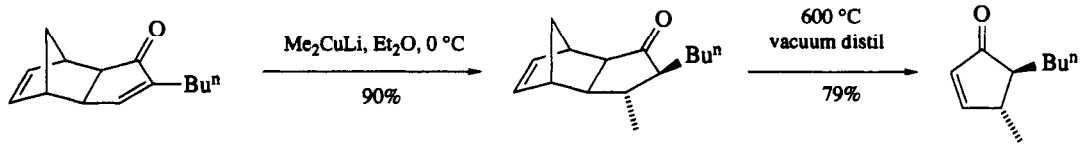
R = H, 50%; R = Me, 19%; R = Ph, 34%

9.1.3.4 Synthetic Applications

Numerous synthetic applications of the intermolecular Pauson–Khand reaction have been reported. Pauson has reported a number of very direct applications of cycloadditions of ethylene in the synthesis of prostanoids and jasmone analogs (*e.g.* equations 15 and 16).[23,24,36a] This is a reliable entry to 2-substituted cyclopentenones. The suitability of cyclopentene and dihydrofuran as substrates has permitted the extension of this work to the preparation of still further varieties of prostaglandin analogs (*e.g.* equations 27 and 51).[36b] Simple 4,5-disubstituted 2-cyclopentenones are not as directly accessible, but may be prepared from the cycloaddition products of norbornadiene (equation 45). A sequence of conjugate addition followed by retro-Diels–Alder reaction affords the product (Scheme 5).[34] Dihydrofuran cycloadditions have been used by Billington in the syntheses of the antibiotic methylenomycin B (Scheme 6),[26] as well as cyclomethylenomycin A (synthetic precursor to the antibiotic methylenomycin A), cyclosarkomycin (precursor to the antitumor agent sarkomycin)[10] and the iridoid Japanese hop ether.[32]

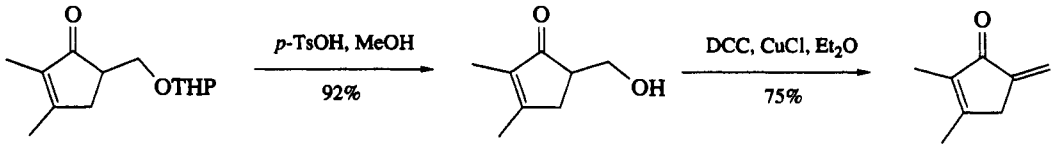


(51)



(from equation 45)

Scheme 5

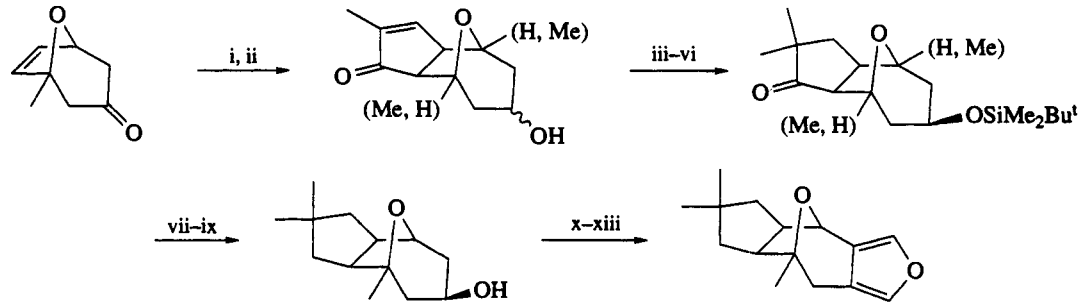


(from equation 18)

Scheme 6

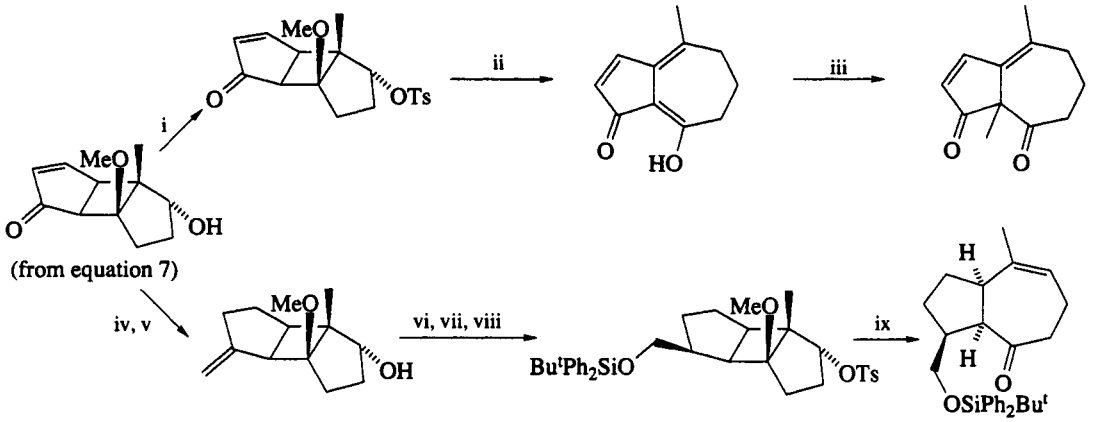
Variations on the hydrazulene skeleton have been approached *via* the Pauson–Khand reaction, several with high regio- and diastereo-selectivity. Pauson's cycloadditions of cycloheptene provided the first entries but were limited in scope and efficiency (equation 39).[20] Several synthetic equivalents of cycloheptenes displaying greater reactivity include 8-oxa- and 8-aza-bicyclo[3.2.1]oct-6-enes (equations 48 and

49),[17] and bicyclo[3.2.0]hept-6-enes (equation 7). Two syntheses of the sesquiterpene furanether B have been completed, based on cycloaddition reactions in the 8-oxa series (Scheme 7).[37] The bicyclo[3.2.0]heptenes provide especially versatile access to systems transformable into both the guaianolide and pseudoguaianolide natural product structural types (Scheme 8).[19]



i, $LiAlH_4$, Et_2O (96%); ii, $MeC{\equiv}CH{\bullet}Co_2(CO)_6$, benzene, 65–70 °C, 2 d (75%); iii, separate; iv, Bu^tMe_2SiCl, imidazole, DMF (98%); v, H_2, 5% Pd/C, EtOAc, MeOH (100%); vi, MeI, $KOBu^t$, Bu^tOH, benzene (100%); vii, $LiAlH_4$, Et_2O (100%); viii, NaH, then CS_2, then MeI, THF (100%); ix, $Bu^n{}_3SnH$, AIBN, toluene, 110 °C (50%); x, PCC, CH_2Cl_2; xi, EtOCHO, NaOMe, benzene (≈50%); xii, Bu^nSH, *p*-TsOH, benzene, 80 °C (100%); xiii, $Me_3S^+MeSO_4^-$, CH_2Cl_2, NaOH, H_2O, then HCl, THF (46%)

Scheme 7

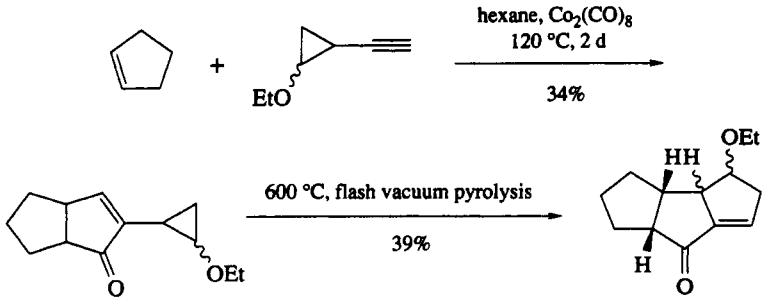


i, *p*-TsCl, pyridine, 0 °C (≈100%); ii, $NaHCO_3$, $CaCO_3$, pyridine, MeOH, H_2O, 65 °C (90%); iii, MeI, K_2CO_3, acetone, 55 °C (82%); iv, H_2, 5% Pd/C, MeOH (98%); v, $Ph_3P{=}CH_2$, $Ph_3PMe^+\ Br^-$, DMSO, 60 °C (88%); vi, $BH_3{\bullet}SMe_2$, THF, then NaOH, H_2O_2, 60 °C (90%); vii, Bu^tPh_2SiCl, Et_3N, DMAP (76%); viii, *p*-TsCl, pyridine, 0 °C (94%); ix, $NaHCO_3$, $CaCO_3$, pyridine, MeOH, H_2O, 65 °C (72%)

Scheme 8

In a novel combination of Pauson–Khand cycloaddition with vinylcyclopropane chemistry, de Meijere has described an entry to linearly fused triquinanes beginning with cyclopropylalkynes. Cyclopentenone formation has been carried out with a variety of substitution patterns on the cyclopropane, and moderate yields achieved with both norbornene and cyclopentene as substrates. Thermal vinylcyclopropane–cyclopentene rearrangement of the cycloaddition products leads to the final tricyclic system (Scheme 9).[33,38]

Serratosa's entry into the angularly fused triquinanes, mentioned earlier (equation 33), succeeds for terminal but not internal propargyl ethers. The *in situ* alkene isomerization that precedes cycloaddition renders synthesis of the bicyclo[3.3.0]oct-1-ene isomer unnecessary, making this a most direct synthetic process in spite of the modest yields.[31]

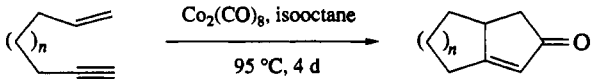


Scheme 9

9.1.4 INTRAMOLECULAR PAUSON–KHAND REACTION: DIASTEREOSELECTIVITY

9.1.4.1 Reactions involving Acyclic All-carbon Enynes

Enynes in which three or four atoms separate the double and triple bonds cyclize upon complexation to $Co_2(CO)_8$ and subsequent heating to give bicyclic enones (equation 52). With the exception of slightly elevated temperatures the conditions required are no different than those of the stoichiometric procedure described earlier for reactive substrates in intermolecular Pauson–Khand reactions. The intramolecular cycloaddition cannot in general be carried out under catalytic conditions. Hex-1-en-5-yne, which would give a four-membered ring upon intramolecular cycloaddition, instead undergoes alkyne trimerization exclusively.[39] The most extensively studied systems are those derived from hept-1-en-6-yne, as the products, bicyclo[3.3.0]oct-1-en-3-ones, are useful in the synthesis of numerous cyclopentane-based polycyclics.



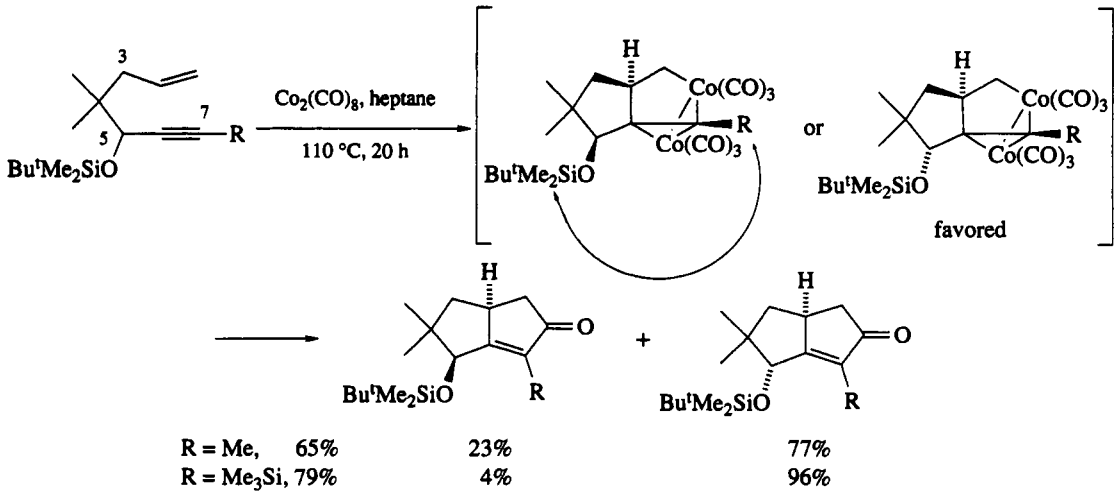
(52)

$n = 1$, 31%; $n = 2$, 35–40%

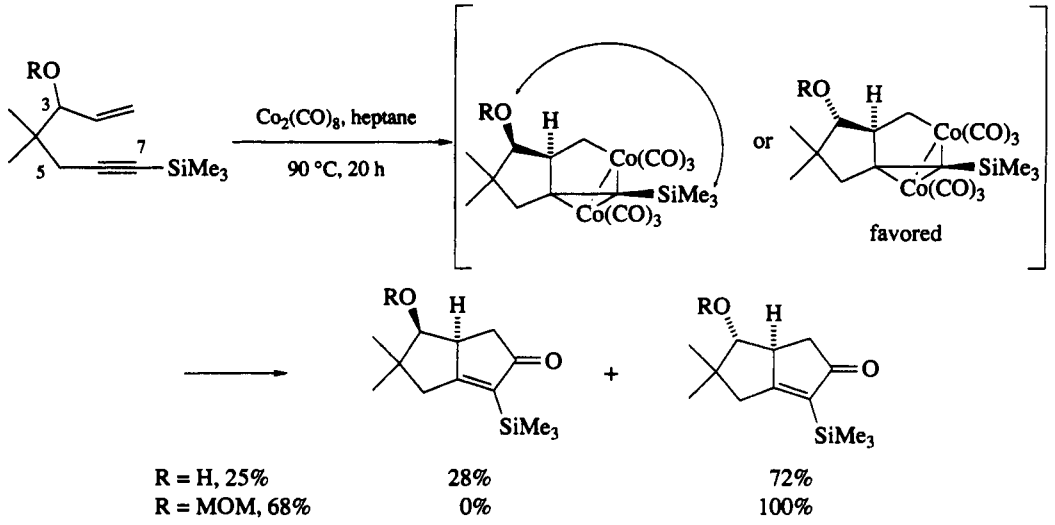
Considerable information on the effects of substitution on these reactions has been collected from the work of Magnus, Hua and Serratosa. Magnus carried out the first systematic examinations of the factors that contribute to diastereoselectivity in these reactions, and all three workers have compiled results bearing on the effects of substitution on yields and reaction rates. Toleration and effect of substitution in these cyclizations is a function of position. Indeed, the detailed effects of substitution on Pauson–Khand reactivity have been readily accommodated by a mechanism that is in all important aspects identical to that previously described.[40] As alkene insertion takes place into a cobalt–carbon bond of the enyne–hexacarbonyldicobalt complex, pseudodiaxial interactions develop between any substituent on the terminus of the alkyne (C-7) and those substituents at the allylic (C-3) and propargylic (C-5) positions of the original enyne that are positioned to end up on the *endo* face of the product. Thus the insertion is preferentially directed to place the larger of these substituents in *exo* orientations. The larger these substituents are, the greater the diastereoselectivity obtained (Schemes 10 and 11). It should be noted that later work of Serratosa suggests the operation of an additional process that may contribute to diastereoselectivity in the case of labile propargyl substituents (see Section 9.1.4.3).

Unprotected alcohols occasionally interfere with the intramolecular reaction. Although the *t*-butyldimethylsilyl protecting group has been most frequently used in these situations, it too is occasionally unsuitable, in which case the methoxymethyl (MOM) group is preferred.

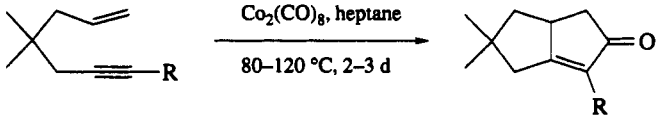
Comparison of equation (52) with Schemes 10 and 11 suggests that substitution at C-4 confers substantial benefit in terms of both yield and reaction time. This is most likely a result of a *gem*-dialkyl effect in which conformations placing the alkene and complexed-alkyne ends of the system in close proximity are rendered enthalpically more favorable by increasing substitution on the intervening atoms. The reduced contribution of $\Delta H^{\ddagger}$ to $\Delta G^{\ddagger}$ associated with alkene complexation allows it to better compete with intermolecular side reactions (*i.e.* trimerization of the otherwise more reactive alkyne moieties). Hua has made similar observations in simpler systems (equation 53).[41] No stereocontrol at C-4 is available, however, the position being too remote from the reaction centers (equation 54).[42]



Scheme 10

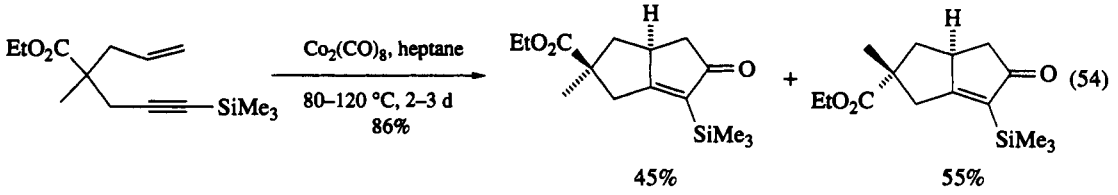


Scheme 11



(53)

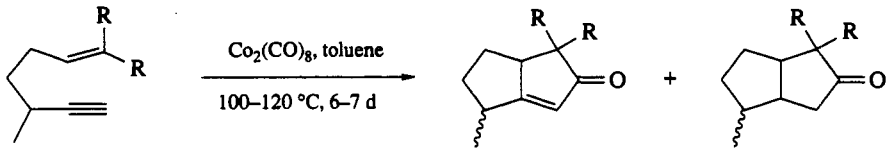
R = H, 58%; R = $CH_2OSiMe_2Bu^t$, 65%



(54)

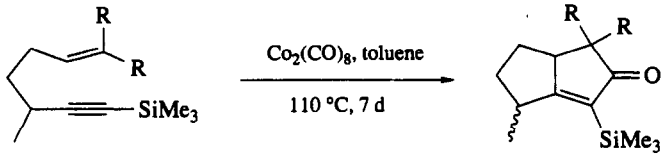
Recent work of Serratosa has identified limitations in substitution tolerance when substituents are lacking at C-4.[43] The formation of even modest yields of cycloaddition products require more forcing conditions, and double bond reduction becomes a significant process. Surprisingly, *gem*-dimethyl groups at C-1 are accommodated (equation 55). Without the *gem*-dialkyl assistance from groups at C-4, how-

ever, propargyl (C-5) substitution now becomes a liability, especially in conjunction with substitution at the alkyne terminus (equation 56). Diastereoselectivity was not determined in these low yield reactions, although mixtures of stereoisomers were obtained in each case.



(55)

R = H, 30% 83% 17%
R = Me, 23% 87% 13%

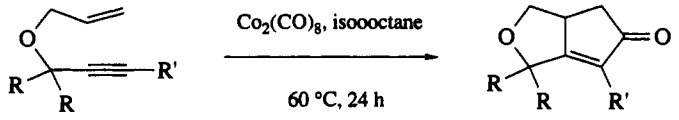


(56)

R = H, 15%; R = Me, 0%

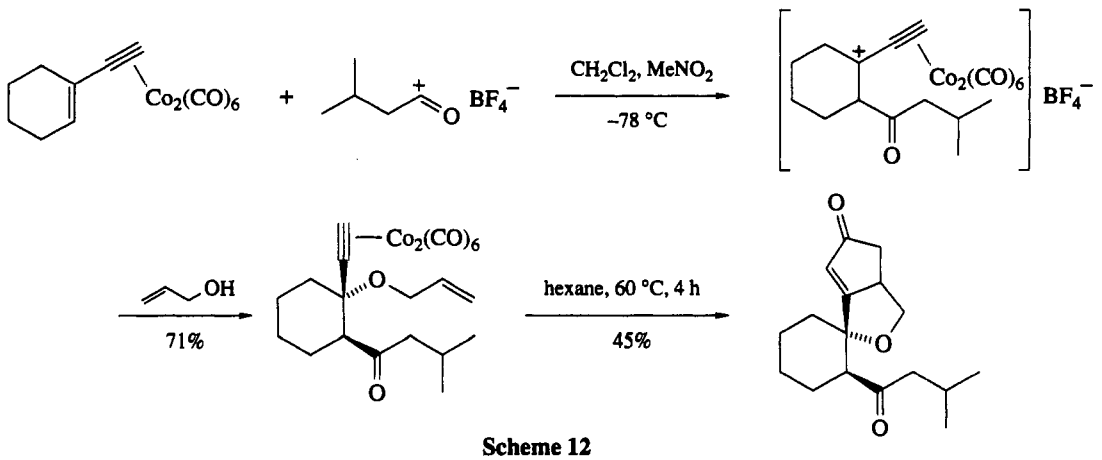
9.1.4.2 Reactions involving Acyclic Heteroatom-containing Enynes

The ready access of allyl propargyl ethers from $Co_2(CO)_6$-complexed propargyl cations, whose chemistry has been extensively developed by Nicholas,[44] has made them the most frequently studied heteroatom-containing substrates for intramolecular Pauson–Khand cycloaddition. Initial work by Billington established the feasibility of these systems as cycloaddition substrates, albeit in only moderate yields (equation 57).[45] The collaboration of Smit and Caple has also combined even more extensively developed versions of Nicholas chemistry with Pauson–Khand cycloaddition to access novel heteropolycyclics (Scheme 12).[46] Schreiber has demonstrated still another direction of development of Nicholas chemistry. Incorporation of an alkyne in a medium-sized ring is achieved by exploiting the 'bending' of the triple bond by cobalt complexation in the course of alkylative ring formation *via* the stabilized propargyl cation complex. The resulting system is then capable of inter- as well as intra-molecular Pauson–Khand cycloaddition (Scheme 13).[47]

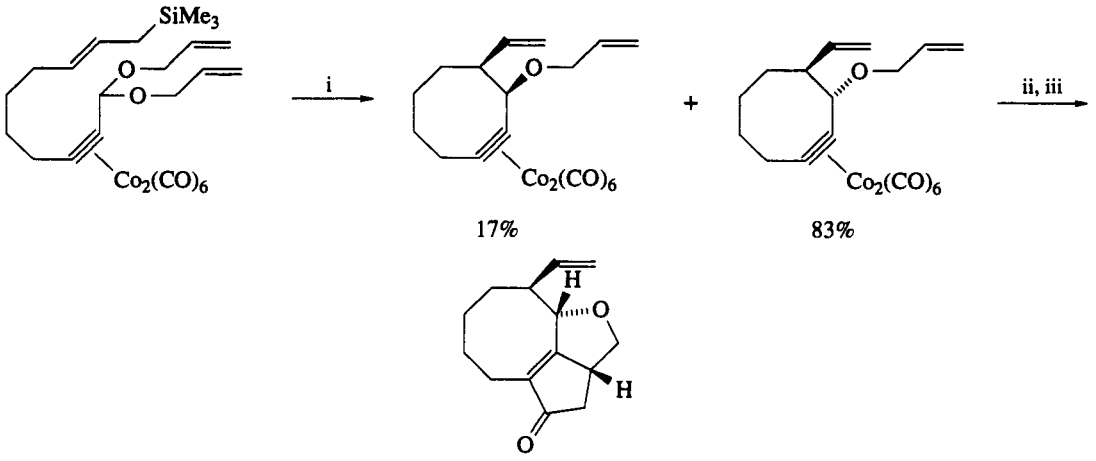


(57)

R = R' = H, 14%; R = Me, R' = H, 29%; R = H, R' = Me, 41%



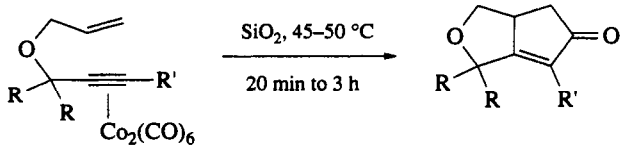
Scheme 12



i, BF_3•Et_2O, CH_2Cl_2, –78 °C to 25 °C; ii, separate and purify *trans* isomer; iii, CO, PhH, 60 °C, 4 h (85%)

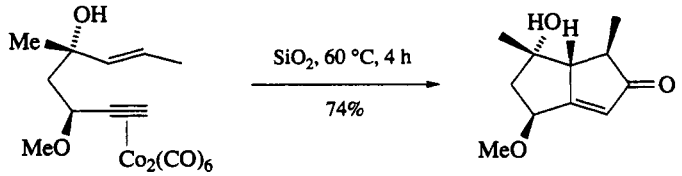
Scheme 13

In the course of work in the Smit and Caple groups the remarkable discovery was made that adsorption of the cobalt-complexed enyne ether onto silica gel enormously facilitates intramolecular Pauson–Khand cycloaddition. Reactions that in solution require 24 h heating at temperatures ranging from 60 to ≥100 °C may be carried to completion in under 2 h by gentle heating of the dry silica gel adsorbate under oxygen or air (equation 58).[48] Apparently adsorption to silica favors reactive conformations in a manner similar to that of bulky substitution, facilitating cycloaddition by means of a novel variant of the *gem*-dialkyl effect. As the examples show, the process is remarkably tolerant of substitution throughout the molecule, although bulky groups on the alkyne terminus do not appear to have been examined. Stereochemical aspects of the process are not clear from the published examples, although reasonable expectations would parallel the findings of Magnus in the all-carbon systems described previously: a tendency for substituents in allyl or propargyl positions to end up *exo* relative to the newly formed ring fusion. The technique is also applicable to ordinary enynes containing polar substituents and enynes containing heteroatoms other than oxygen (equations 59 and 60). Indeed, it is now known that heteroatoms, while helpful, are not necessary: even simple intermolecular cycloadditions of hydrocarbon substrates have been found to benefit from adsorption on various dry supports. Sonication also provides some acceleration, allowing reactions to be carried out at still lower temperatures (*e.g.* ≤45 °C).[25a,49]

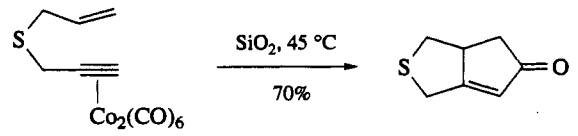


(58)

R = R' = H, 58%; R = Me, R' = H, 75%; R = H, R' = Me, 60%



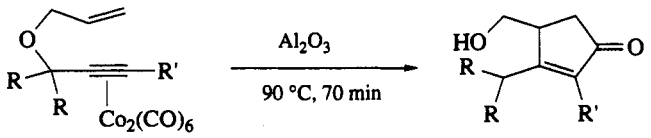
(59)



(60)

In the 'dry' Pauson–Khand reaction system oxygen is necessary in order to prevent hydrogenolysis of the allylic carbon–oxygen bond in the product. This process is presumably effected by hydridocobalt

species whose formation is facilitated by adsorption, although the details are not known. The oxygen may serve simply to scavenge adsorbed cobalt hydride species. In any event, Smit has demonstrated that the hydrogenolysis process may be selectively promoted if desired by carrying out the reaction under 'dry' conditions on alumina under an argon atmosphere. This results in 3-alkyl-4-(hydroxyalkyl)cyclopentenones directly, in yields consistently in the 70% range (equation 61).[50]

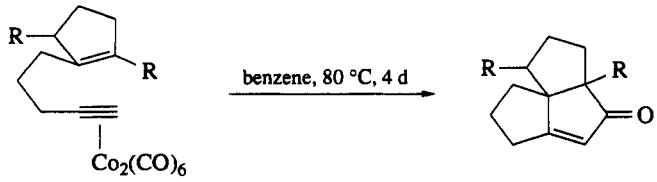


(61)

R = R' = H, 70%; R = Me, R' = H, 69%; R = H, R' = Me, 73%

9.1.4.3 Reactions involving Cyclic Enynes

As might be expected from comparable intermolecular situations, incorporation of the alkene partner in a ring of appropriate size is compatible with intramolecular Pauson–Khand reaction. However, steric and functional group considerations are essential in order to achieve acceptable results. To date work in this area has been limited to cyclopentenes containing pendant alkynes. A variety of 1-(4-pentynyl)cyclopentenes and 3-(3-butynyl)cyclopentenes have been examined by both ourselves and the Serratosa group, and a reasonably useful framework for determining the applicability of the reaction has emerged. Pauson–Khand cycloaddition of 1-(4-pentynyl)cyclopentene itself gives rise to the angularly fused triquinane (tricyclo[6.3.0.0.^{1,5}]undecane) ring system, the basis of a number of compounds of recent synthetic interest (see Section 9.1.4.4). This substrate, containing a trisubstituted alkene partner, is in fact already at the substitution limit for useful reactivity: its derivative containing additional methyl substitution and therefore a tetrasubstituted double bond gives only trace amounts of enone product (equation 62).[51]

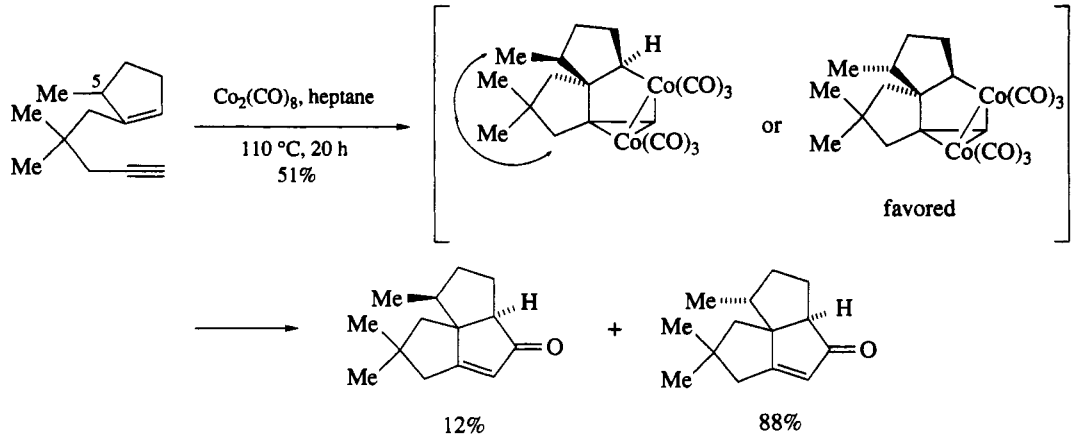


(62)

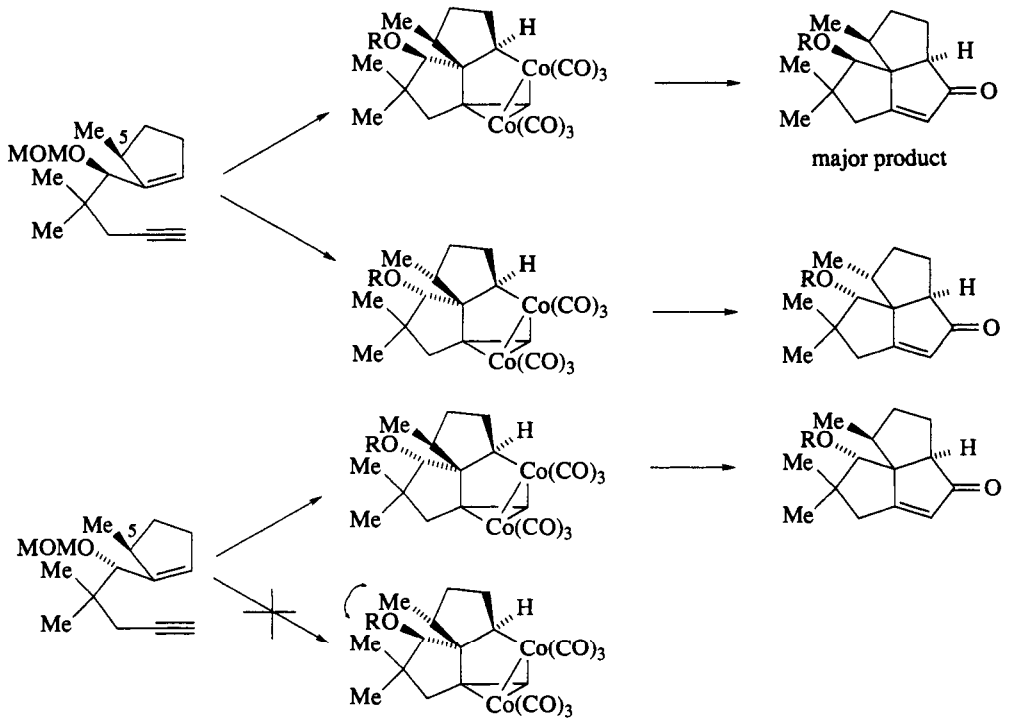
R = H, 35%; R = Me, ≈0%

The reaction has been shown to benefit from *gem*-dialkyl acceleration and to exhibit useful diastereoselectivity in the cycloaddition of an appropriately substituted analog (Scheme 14).[52] In this case the twist about the newly formed spiro center generates a 1,3-pseudodiaxial interaction between the propargyl methylene and the *endo* group at the C-5 allylic position on the cyclopentene ring, thus favoring the formation of the *exo*-methyl stereoisomer. This stereocontrol is compromised by additional substitution. The (*RS*)/(*SR*) diastereomer of an alkoxy-substituted analog gives a mixture of *endo*- and *exo*-methyl-substituted enones in which the latter no longer predominates (Scheme 15). The cause of this effect is not clear, although the alkoxy-substituted products are unstable under the reaction conditions and the observed ratio is likely not to be the kinetic one. The situation with the (*RR*)/(*SS*) diastereomer is more straightforward: the *endo*-methyl product forms exclusively. In this situation the *exo* isomer experiences a 1,3-interaction between the methyl and the methoxymethyl group that is far more severe than the *endo*-methyl–propargyl methylene interaction that controls its deoxygenated analog. In these latter systems it was found that protection of the allylic hydroxy group was essential for Pauson–Khand reactivity to be observed.

Trimethylsilyl substitution at the alkyne terminus totally eliminates cycloaddition reactivity in these systems.[53] Examination of possible structures of Pauson–Khand intermediates reveals steric interactions involving this silyl group occurring at both the alkene complexation and insertion stages. The analysis in Scheme 16 shows four possible complexation modes of the alkene. Complexation *cis* to the second cobalt appears to be disfavored by steric interactions involving the ligands on this cobalt with allylic groups (Scheme 16, structures **3** and **4**). The alternative, complexation *trans* to the second cobalt, can occur from either pseudoboat (Scheme 16, structure **5**) or pseudochair (Scheme 16, structure **6**) conformations of the side chain, and involves opposite faces of the alkene. The latter conformation, which also experiences less steric congestion involving allylic groups with the alkyne terminus, is probably the one favored in



Scheme 14

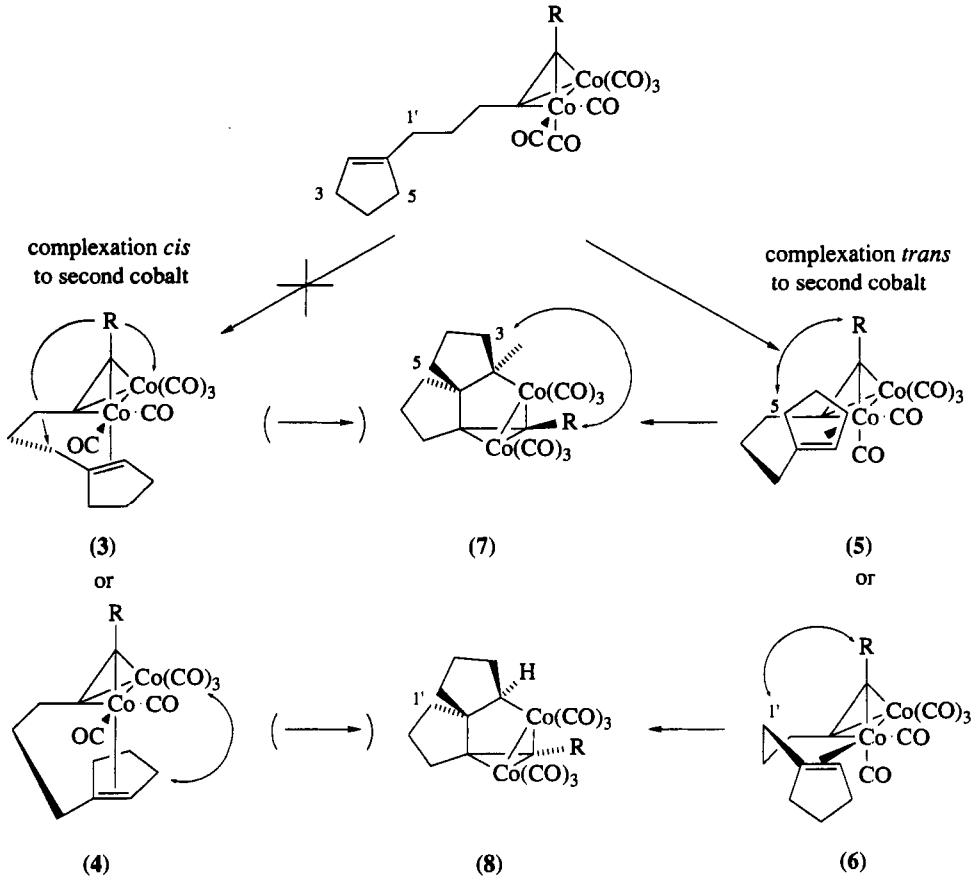


Reagent: $Co_2(CO)_8$, benzene, 80 °C, 18–22 h, 30%

Scheme 15

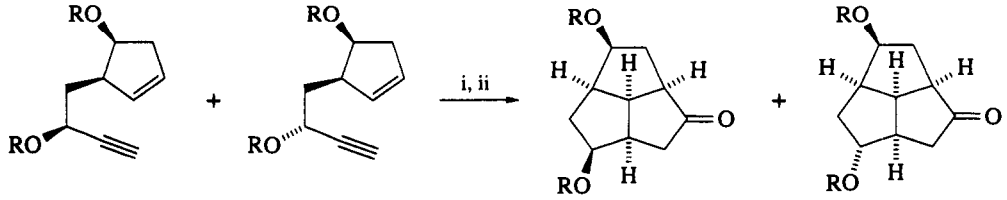
the observed cycloaddition when R = H. The structure, (**8**), shown at the bottom of the scheme, with R *cis* to the newly formed ring fusion and *trans* to the cyclopentene ring originally present, is the likely intermediate (compare Schemes 10, 11, 14 and 15). Evidently, even the relatively unimportant-looking steric interaction leading to this intermediate is sufficient to eliminate useful reactivity when R = TMS. In any event this establishes that practical intramolecular reactivity of trisubstituted alkenes is limited to terminal alkynes and, further, suggests that a similar restriction might also apply to simple acyclic hept-1-en-6-ynes containing an additional substituent at C-2. Such situations do not appear to have been examined as yet.

Similar intramolecular cycloadditions of cyclic alkenes containing alkynyl substitution have been explored by Serratosa in the 3-(3-butynyl)cyclopentene series. The product in this case is a triquinacene derivative, a tricyclo[5.2.1.$0^{4,10}$]decane. Since the targets in Serratosa's studies required functionalization of all three five-membered rings, all cycloaddition substrates utilized contained varying degrees of sub-



Scheme 16

stitution. In this class of substrate the alkene is effectively *cis*-1,2-disubstituted, and therefore it may complex to a cobalt in an orientation that avoids steric interaction with a substituent on the alkyne terminus. Substrates in which the alkyne is not terminally substituted undergo cycloaddition in variable yields.[54] The reaction also tolerates unsubstituted hydroxy functionality when carried out under 'dry' (Smit–Caple) conditions (Scheme 17).



80% 20%

R	*Total yield*		
Bn	60%	70%	30%
Bu^tMe_2Si	various	78%	22%
H	16%	–	–

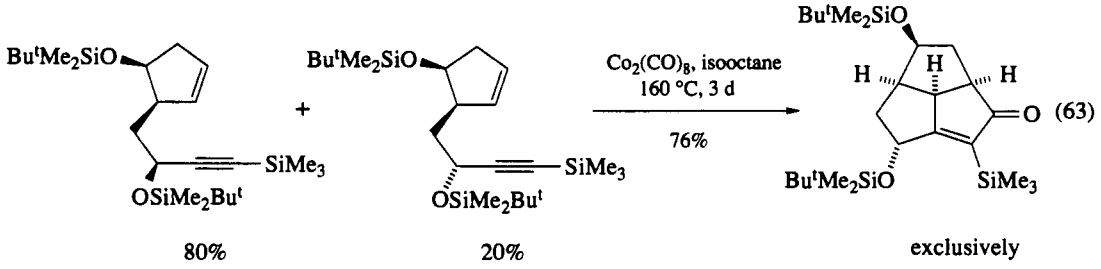
R = Bn: i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h; ii, H_2, 10% Pd/C, EtOH, Et_3N

R = Bu^tMe_2Si: i, $Co_2(CO)_8$, isooctane, 160 °C, 3 d; ii, H_2, 10% Pd/C, EtOH, Et_3N

R = H: i, $Co_2(CO)_8$, benzene, then SiO_2, remove solvent, 120 °C, 2 h; ii, H_2, 10% Pd/C, EtOH

Scheme 17

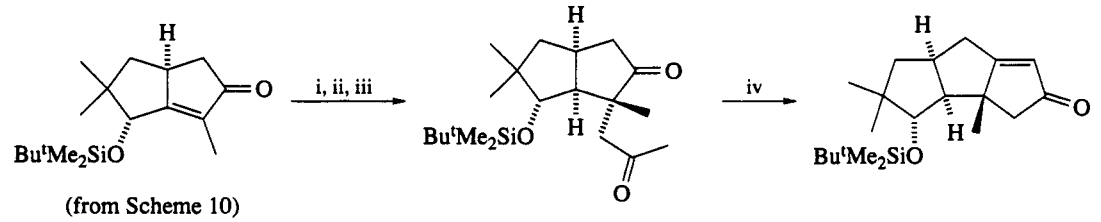
That the apparent changes in diastereomer ratio between reactants and products shown in the above examples were significant was confirmed by the results of cycloadditions of silyl-substituted alkyne analogs. In these cases only a single product, with the opposite stereochemistry to the dominant isomer in the examples above, is formed (equation 63). This result plus the high chemical yield require that a mechanism for isomerization be operative. Serratosa and coworkers proposed that the diastereomer that would lead to the unobserved *endo*-5-alkoxy isomer is rendered completely unreactive towards cycloaddition by steric interference from the silyl group. Instead, ionization of the propargylic leaving group, facilitated by the strong stabilization imparted to the propargylic cation by complexation to cobalt, allows the center to isomerize to the diastereomeric precursor to the 5-*exo* product, which then forms readily.[55] This result is of interest in the context of Magnus' earlier results (*e.g.* Scheme 10). In those systems the substrate contains only a single stereocenter and is racemic. Its isomerization merely interconverts enantiomers and therefore is an 'invisible' process. However, substrates with a second stereocenter (*e.g.* equation 59) may be worth reexamination for effects of this isomerization, and future applications of this chemistry that aim towards the preparation of optically active enones from optically pure substrates will face obvious difficulties if isomerization at a labile propargyl stereocenter cannot be prevented.



9.1.4.4 Synthetic Applications

Magnus was the first to develop extensive synthetic applications of the Pauson–Khand preparation of the bicyclo[3.3.0]oct-1-en-3-one system. His efforts amply demonstrate the degree to which the high level of functionality in the Pauson–Khand products can be directly utilized in building more complex structures. A formal synthesis of the antitumor sesquiterpene coriolin illustrates a very efficient sequence for construction of the third ring in the linearly fused triquinane series in the presence of considerable functionality (Schemes 10 and 18).[40a] A synthesis of the related triquinane hirsutic acid utilizes the observation that the proper stereochemical relationship between the substituents at C-7 and the ring-fusion carbon (C-5) of the bicyclo[3.3.0]oct-1-en-3-one system, while not controllable in the cycloaddition reaction itself, may be readily established by acid- or base-catalyzed equilibration (equation 54 and Scheme 19).[42]

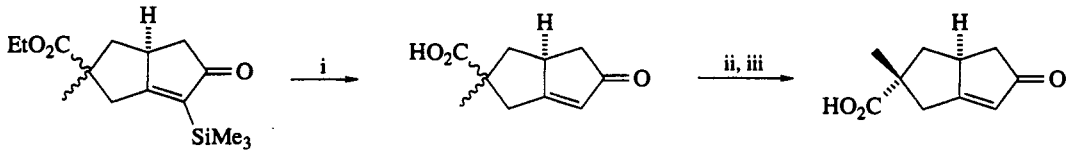
In a short and completely diastereoselective synthesis of the unusual tetracyclic natural product quadrone, Magnus was able to minimize an interfering hydrogenolysis problem involving the propargylic ether by the addition of a hindered pyridine base, which presumably scavenges highly acidic cobalt hydride species (equation 64). In contrast, addition of a phosphine oxide only exacerbated the problem.[56] Note that the three syntheses just described illustrate diastereocontrol strategies for every position around the bicyclic enone system with the exception of the saturated α-carbon (C-4). Both Magnus and Mulzer have described stereoselective synthesis of optically active carbocycline analogs.[57,58] Magnus derived



(from Scheme 10)

i, H_2, 10% Pd/C, EtOH (92%); ii, NaH, allyl bromide, DME (79%);
iii, O_2, $PdCl_2$, CuCl, DMF (64%); iv, Bu^{t}OK, Bu^{t}OH (74%)

Scheme 18

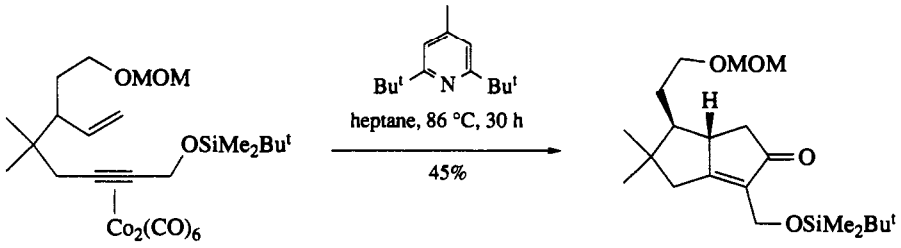


(from equation 54)

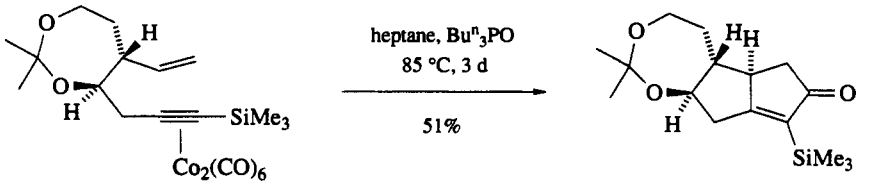
i, $MeSO_3H$, 75 °C, 135 min (96%); ii, *p*-TsOH, benzene, 80 °C, 4 h (100%); iii, separate and recycle undesired isomer three times (90% yield of isomer shown)

Scheme 19

enyne stereochemistry from D-(+)-ribonolactone, but Pauson–Khand reaction on a *trans*-disubstituted γ-butyrolactone was thwarted by excessive strain. Instead, a seven-membered ring ketal analog was used successfully (equation 65). Mulzer's stereochemistry was derived from derivatives of (+)- or (–)-glyceraldehyde.

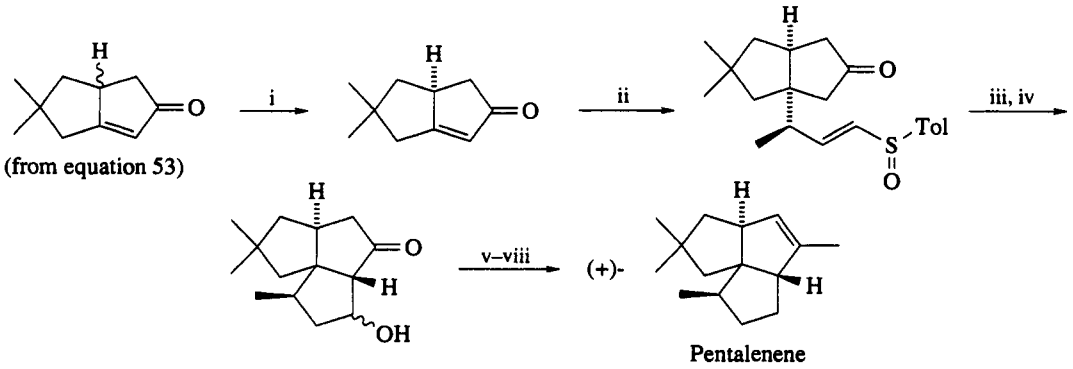


(64)



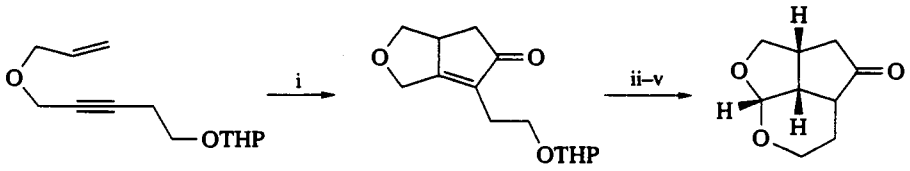
(65)

Hua has used the products of Pauson–Khand cycloadditions for syntheses of optically active pentalenene and racemic pentalenolactone E methyl ester. The racemic ketone in the first case was converted to the necessary optically active intermediate by kinetic resolution *via* 1,4-addition of an optically active allyl sulfoxide anion. These represented the first synthesis of natural products containing the angularly fused triquinane skeleton from bicyclic Pauson–Khand products (equation 53 and Scheme 20).[41]



i, 0.5 equiv. *(S)-trans-p*-$MeC_6H_4S(O)CH{=}CHCH_2Li$, THF, –78 °C, 30 min (45%); ii, 2.0 equiv. racemic *trans-p*-$MeC_6H_4S(O)CH{=}CHCH(Me)Li$, THF, –78 °C, 45 min (91%); iii, Zn, AcOH (95%); iv, HCO_2H, CF_3CO_2H, 60 °C, 24 h, then K_2CO_3, MeOH (64%); v, MeMgBr, Et_2O, 0 °C (70%); vi, $(Me_2N)_2POCl$, Et_3N, DMAP, toluene, 60 °C, 10 h (96%); vii, Li, Bu^tOH, $EtNH_2$, THF, 0 °C, 30 min (97%); viii, BF_3, Et_2O, CH_2Cl_2 (99%)

Scheme 20



i, isooctane, 60 °C, 24 h (41%); ii, H_2, Raney Ni, EtOH; iii, *p*-TsOH, MeOH; iv, $NaNO_2$, H_2SO_4, H_2O, –10 °C, 1 h; v, *hν*, benzene, 0 °C, 15 h

Scheme 21

A formal synthesis of the natural product aucubigenone by Billington has made use of a very direct route involving Pauson–Khand cycloaddition of an allyl propargyl ether (Scheme 21).[45]

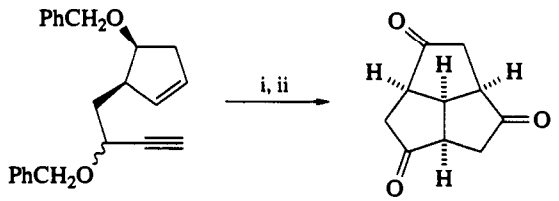
Since our direct route to angularly fused triquinanes from cycloaddition of 1-(4-pentynyl)cyclopentenes is limited to trisubstituted alkenes and simple terminal alkynes, bisnorisocomene, but not isocomene itself, could be prepared (Scheme 22).[51,53] However, this limitation is not a factor for most other compounds in this class of natural products, and the steric interactions described earlier worked to our advantage in a diastereocontrolled synthesis of pentalenene (see structure, Scheme 20). The natural product was obtained by subjecting the product of Scheme 14 to the sequence i, Li, NH_3, MeOH; ii, MeLi, Et_2O; iii, *p*-TsOH, benzene, reflux.[52]

(from equation 62)

i, Me_2CuLi, Et_2O, 0–25 °C, 2 h (89%); ii, MeLi, Et_2O, THF, –78 °C, 150 min (91%); iii, $SOCl_2$, pyridine, THF, –45 to 25 °C, 15 min (66%)

Scheme 22

Serratosa has critically evaluated the various entries to the triquinacene system available *via* Pauson–Khand chemistry, concluding that a route involving cycloaddition of the dibenzylated enyne substrate (Schemes 17 and 23) is operationally the simplest for preparation of multigram quantities of tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-trione. This in turn is a key intermediate for the study of synthetic entries to dodecahedrane and its derivatives. An optically active version of this synthesis has been developed as well.[54c,d]



(from Scheme 17)

i, $Co_2(CO)_8$, *t*-butylbenzene, 170 °C, 2–3 h (60–70%); ii, H_2, 10% Pd/C, EtOH, then PCC, Celite (63%)

Scheme 23

Finally, there have been a number of additional recent methodological advances.[59]

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9.2
Metal–Carbene Cycloadditions

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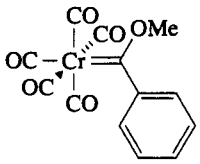
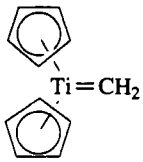
9.2.1 INTRODUCTION

The chemistry of transition metal carbene complexes has been examined with an eye to applications in organic synthesis ever since their discovery by Fischer in 1964, and the growth in the number of useful applications has been exponential with time.[1–3] There are two types of transition metal carbene complexes; those which have electrophilic carbene carbons and which are typified by the pentacarbonylchromium complex (**1**), and those which have nucleophilic carbene carbons and which are typified by the biscyclopentadienyltitanium complex (**2**). Complexes (**1**) and (**2**) are often referred to as 'carbene' and 'alkylidene' complexes, respectively. This review will be limited to the chemistry of electrophilic carbene complexes of the Fischer type. The chemistry of the nucleophilic alkylidene complexes will be covered in Chapter 9.3, this volume.[4]



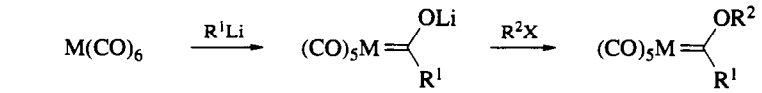
(1a)
A Fischer carbene complex



(2)
An alkylidene complex

An overview of the chemistry of the electrophilic transition metal carbene complexes will be presented, which will focus on those reactions that have established potential in organic synthesis, and on actual applications in the synthesis of organic molecules. Emphasis will be given to chemistry that has not been reviewed[1–3] and includes the literature up to the end of 1988 with a few citations from 1989. The chemo-, regio- and stereo-selectivity of the reactions of carbene complexes will be emphasized, and in Section 9.2.2 special focus will be made on the comparisons between carbene complexes and their organic analogs. The organization of this material begins with the separation of the reactions of carbene complexes into two groups: (i) those that occur at a substituent of the carbene carbon and in which the metal–carbene bond remains intact (Section 9.2.2); and (ii) those that occur at the metal center and which involve the metal–carbene bond (Section 9.2.3). Most of the reactions in this chapter involve the combining of C—C π-bonds and thus fall under the subject heading of this volume. Also included, however, are several ionic reactions of carbene complexes (Sections 9.2.2.5, 9.2.2.6 and 9.2.2.7), which are not covered in any other chapter in this work. The coverage of cyclopropanation reactions of carbene complexes will be only be briefly included for completeness, and a more extensive treatment can be found in Volume 4, Chapter 4.6.

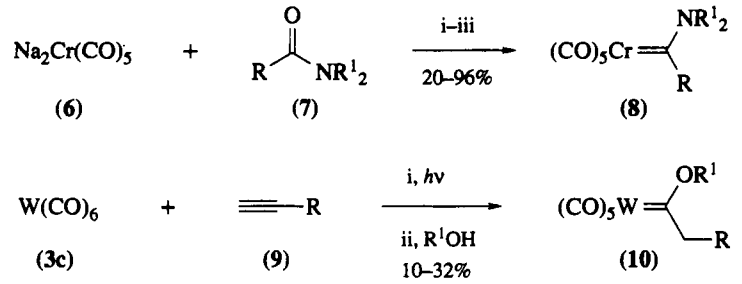
The various methods for the preparation of carbene complexes will not be presented here, as they have been extensively reviewed elsewhere.[1a,2] The syntheses of the carbene complexes from the noncarbene complex precursors presented in this review have almost all been by Fischer's original procedure (equation 1), involving the addition of an organolithium to a metal carbonyl, followed by alkylation of the resulting metal acylate. Grignard reagents are not as useful as organolithiums, and there is essentially no limit to the nature of the organolithium that may be employed. The yields of carbene complexes by the Fischer method are good to excellent and can often be prepared on an open-ended scale since most common complexes are solids and purification can be accomplished by crystallization. Most transition metal carbene complexes can be handled in the presence of air and thus alternatively can be purified on silica gel in the presence of air without noticeable losses. The sensitivity of these complexes to air increases with temperature, and for reactions carried out above room temperature, an inert atmosphere is normally employed. Finally, the cost of Group 6 metal carbonyls at 20–50 cents $mmol^{-1}$ makes them no more expensive to use in stoichiometric reactions than the typical organic reagent.



(3) M = Cr, Mo, W (4) (5) (1)

As the chemistry of Fischer carbene complexes has developed, the synthesis of new complexes by elaboration of existing complexes has naturally become increasingly important. The reactions that have become important in this regard are largely those that are discussed in Section 9.2.2. Two methods for the preparation of Fischer carbene complexes from noncarbene complex precursors, that were introduced early on but have recently been more fully developed, are mentioned here because they may find increasing utility.[5–9] The first involves preparation from Group 6 metal pentacarbonyl dianions and has been used for the preparation of carbene complexes from amides[5] and acid halides.[6] The optimal procedure in the case of amides is illustrated in Scheme 1, and is generally useful for the preparation of amino carbene complexes in very good yields.[5] This method has the advantage that amino complexes can be prepared without the intermediacy of the alkoxy complex that must of necessity be produced by the Fischer procedure. The second method involves the rearrangement of a metal–alkyne complex to a metal–alkylidene complex, which is then trapped by an alcohol. This reaction has been optimized in specific systems,[7,8] but has yet to be optimized in the more general case that is included in Scheme 1.[9] This method has the advantage that highly reactive anionic reagents need not be employed, and that the alkoxy substituent R^1

need not be limited to one that is derived from a reactive carbon electrophile as is necessary by the Fischer procedure.



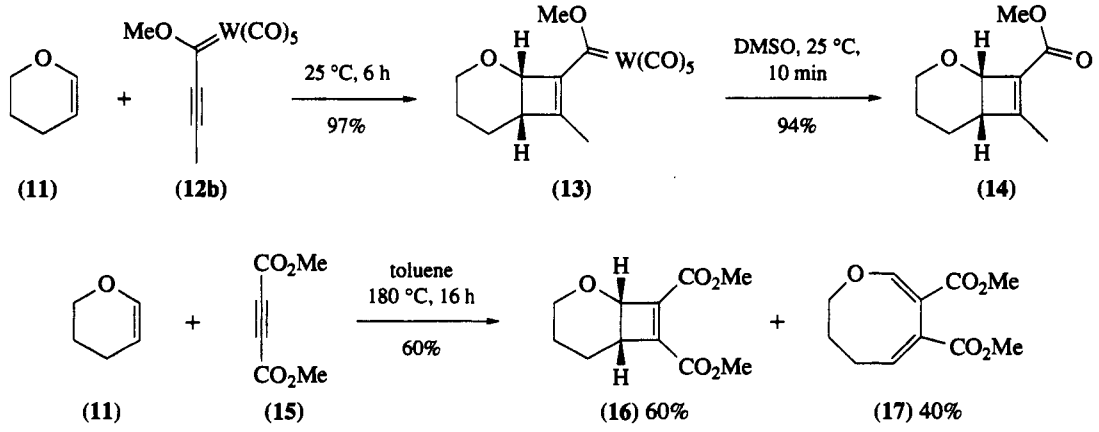
i, THF, –78 to 0 °C; ii, 3 equiv. Me_3SiCl, –78 °C; iii, Al_2O_3, –78 to 25 °C

Scheme 1

9.2.2 REACTIONS ON THE CARBENE LIGAND: THE METAL AS REACTIVITY AND SELECTIVITY AUXILIARY

9.2.2.1 [2 + 2] Cycloadditions

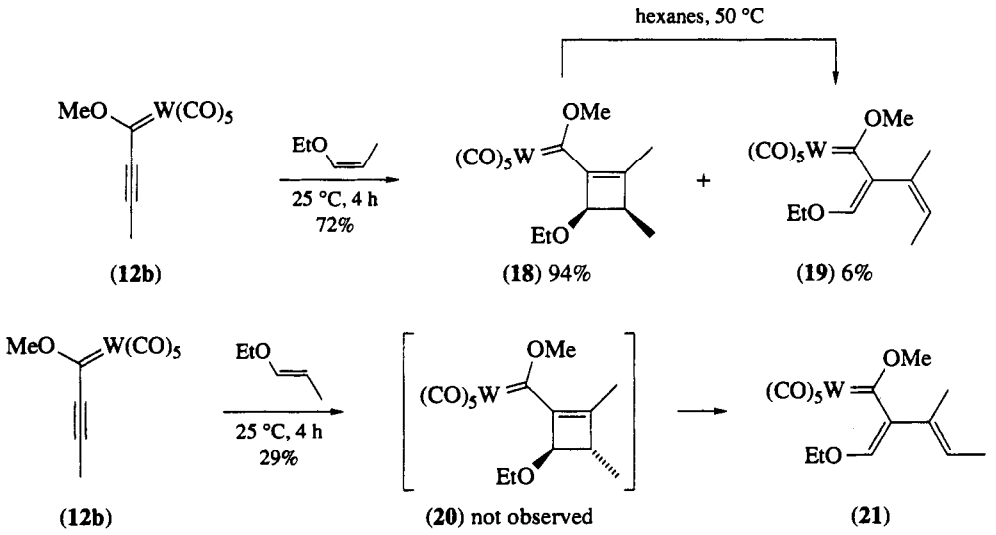
The first examples of a [2 + 2] cycloaddition at an unsaturated substituent on a carbene ligand have been recently reported.[10] In the example shown in Scheme 2 it can be seen that the cycloadditions can occur very rapidly between enol ethers and alkynic carbene complexes. Alkynic carbene complexes can serve as surrogates for alkynic esters since the cycloadducts can be very efficiently oxidized to their corresponding esters. While the [2 + 2] cycloaddition of methyl tetrolate and dihydropyran is unknown, a comparison can be made between the alkynic carbene complex (**12b**), which reacts at room temperature, and the doubly activated alkynic ester (**15**), which will only react at 180 °C with the same substrate.



Scheme 2

The [2 + 2] cycloaddition of the propynyl tungsten complex (**12b**) has been found to be stereospecific with the *cis* and *trans* isomers of ethyl propenyl ether.[11] The reaction with *cis*-propenyl ethyl ether gave rise to the cyclobutenyl complex (**18**), in addition to a minor amount of the ring-opened dienyl carbene complex (**19**). The stereochemistry about the double bonds in the dienyl complex (**19**) revealed that it was derived from a thermal electrocyclic conrotatory ring opening of the *cis*-cyclobutenyl carbene complex (**18**) and thus the stereochemistry is completely retained in this cycloaddition. In support of this analysis it was found that cyclobutenyl complex (**18**) could be thermally opened to the dienyl complex by heating in an inert solvent at 50 °C. In the cycloaddition of the propynyl complex (**12**) with *trans*-

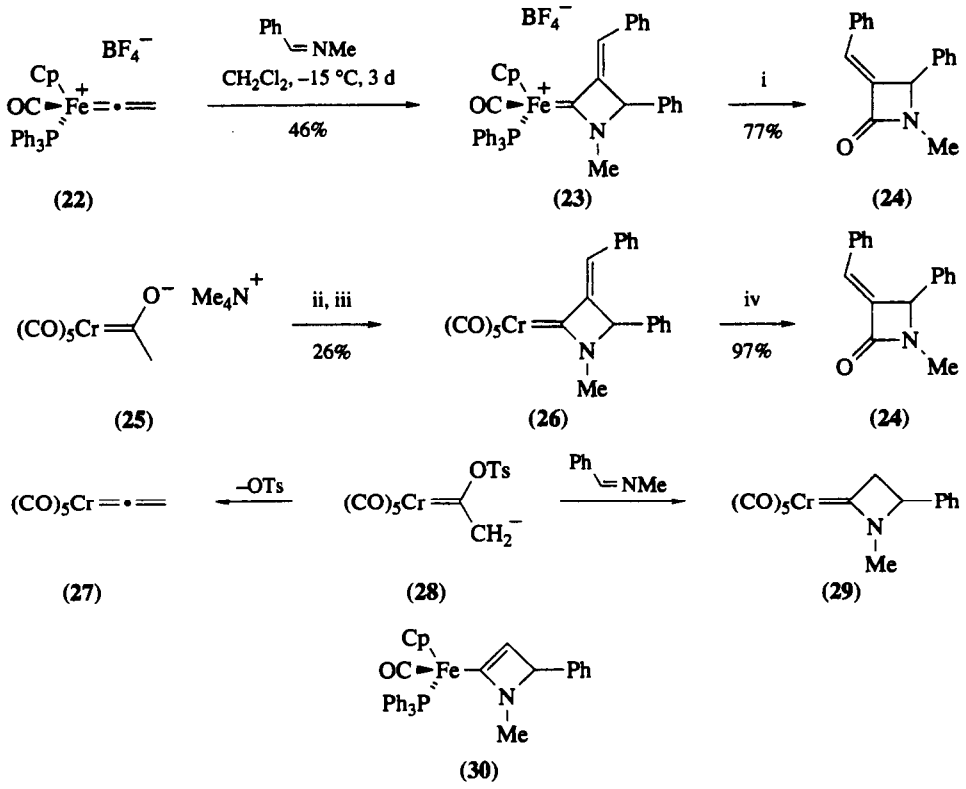
propenyl ethyl ether the expected cyclobutenyl complex (**20**) was not observed, and the only product that was isolated from this reaction was the (*Z,E*)-dienyl carbene complex (**21**). Again this stereochemistry about the diene is that expected from the ring opening of the cyclobutenyl complex that would result from the [2 + 2] cycloaddition occurring with retention of configuration about the propenyl ethyl ether. It is not unreasonable that ring opening of the *cis*-cyclobutenyl complex (**18**) should be more sluggish than for the *trans* complex (**20**), since a conrotatory opening requires that one of the substituents in (**18**) rotates inward. If there is a stepwise mechanism for this cycloaddition, then in this case the second step occurs faster than bond rotation. The reason for low mass balance for the *trans*-propenyl ether reaction has not been determined. The [2 + 2] cycloaddition of alkynyl carbene complexes with enol ethers could prove useful in the preparation of 2-substituted dienyl carbene complexes, which would be difficult to prepare with the Fischer procedure.



Scheme 3

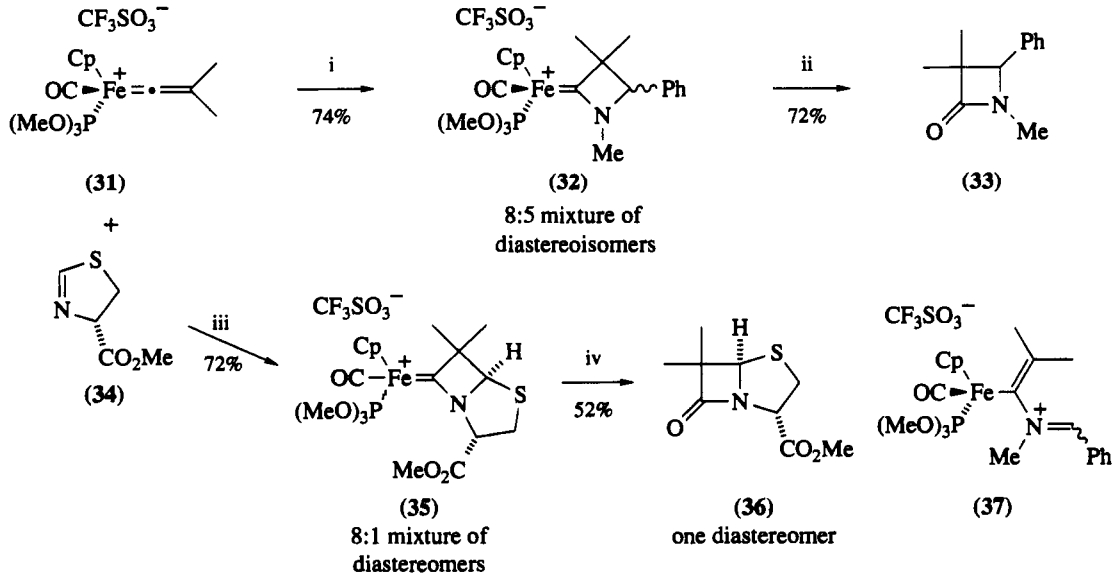
The only other examples of [2 + 2] cycloadditions come not from carbene complexes, but from vinylidene complexes.[12,13] The [2 + 2] cycloadditions of imines with vinylidene complexes was developed by Barrett and represent the first synthetic applications with this class of organometallic compounds.[14] The reaction of the vinylidene complex (**22**) with *N*-methyl benzaldehyde imine gives the cationic cyclic carbene complex (**23**) in 46% yield. The expected azacyclobutene–iron complex (**30**) was not observed and apparently very quickly reacts with a second equivalent of the imine. The β-lactam (**24**) could be obtained in good yield upon oxidation of the carbene complex (**23**) with iodosylbenzene. The same β-lactam could be obtained in a slightly different manner from the chromium metal acylate (**25**). Sequential treatment of this salt with tosyl chloride and then the same imine produced the carbene complex (**26**), which was oxidized in 97% yield to (**24**). There are two possible pathways for the sequence of events in the chromium case. Deprotonation of the product from the tosylation of (**25**) would give the anionic carbene complex (**28**), which can undergo β-elimination to the vinylidene complex (**27**) or condense with the imine followed by subsequent ring closure to give the cyclic carbene complex (**29**). Preliminary experiments indicate that the latter is most likely. In either event, the chromium complex (**29**), like the iron analog (**30**), is apparently not stable with respect to reaction with a second equivalent of imine.

The incorporation of the second equivalent of imine can be prevented in these reactions if a vinylidene complex, such as (**31**), is employed which is β,β-disubstituted. Under the optimized conditions indicated, the reaction of (**31**) with *N*-methyl benzaldehyde imine will provide the cycloadduct (**32**) in quite good yield. A rather unorthodox oxidation procedure (Bu_4NNO_2, 6.5 kbar; 1 bar = 10^5 Pa) is required for the effective cleavage of the cationic complex (**32**) to the β-lactam (**33**). This reaction was shown to involve a two-step process, since the salt (**37**) could be isolated in 80% yield by column chromatography if the reaction was stopped shortly after the reaction mixture was brought to room temperature. The reaction with the cyclic thioimidate (**34**) indicates that vinylidene complexes can be useful in the synthesis of functionalized β-lactams in good yields with high stereoselectivity.



i, PhIO, CH_2Cl_2, 25 °C, 2 d; ii, TsCl, CH_2Cl_2, 25 °C, 10 min; iii, PhCH=NMe, 25 °C, 8 h; iv, PhIO, CH_2Cl_2, 25 °C, 4 d

Scheme 4

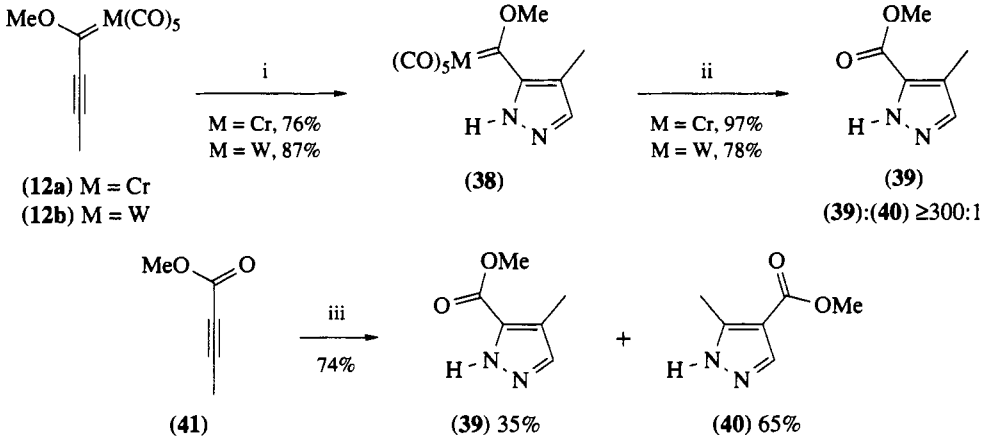


i, PhCH=NMe, $ClCH_2CH_2Cl$, Amberlyst A21 resin, 25 °C, 1 h, reflux 2 h; ii, Bu_4NNO_2, CH_2Cl_2, 6.5 kbar, 60 h; iii, (**34**), conditions in i; iv, PhIO, EtOH, 25 °C, 4 d

Scheme 5

9.2.2.2 [3 + 2] Cycloadditions

The only examples of [3 + 2] cycloadditions of carbene complexes are of diazoalkanes with alkynyl complexes.[15,16] The reactions of the chromium and tungsten propynyl complexes, (**12a**) and (**12b**), with trimethylsilyldiazomethane give high yields of the pyrazole carbene complexes (**38**).[15] The reaction of alkynyl complexes with diazomethane was first reported by Fischer, but with diazomethane the pyrazole complex (**38**) was not isolated. The carbene ligand was cleaved to give a nonorganometallic product with the less sterically hindered diazoalkane.[16] The pyrazole complexes of the type (**38**) can be isolated from the reaction with diazomethane if conditions are carefully controlled but the yields are low, since carbene ligand cleavage can not be completely suppressed. The cycloaddition of a number of alkynyl carbene complexes with trimethylsilyldiazomethane and 3-diazopropene give good to excellent yields of pyrazole complexes. Of particular advantage in these cycloadditions is the regioselectivity. The reaction of methyl tetrolate (**41**) with trimethylsilyldiazomethane gives approximately a 2:1 mixture of the two possible cycloadducts, whereas both the chromium and tungsten complexes, (**12a**) and (**12b**), give a greater than 300:1 selectivity for the cycloadduct (**38**). It was demonstrated that the pyrazole carbene complex (**38**) can be oxidized in high yield to the ester (**39**). From the point of view of regioselectivity and the relative rates of the reactions, alkynyl carbene complexes should prove to be useful as synthons for alkynyl esters in [3 + 2] cycloadditions. The reactions of other carbene complexes and other 1,3-dipoles have yet to be investigated.



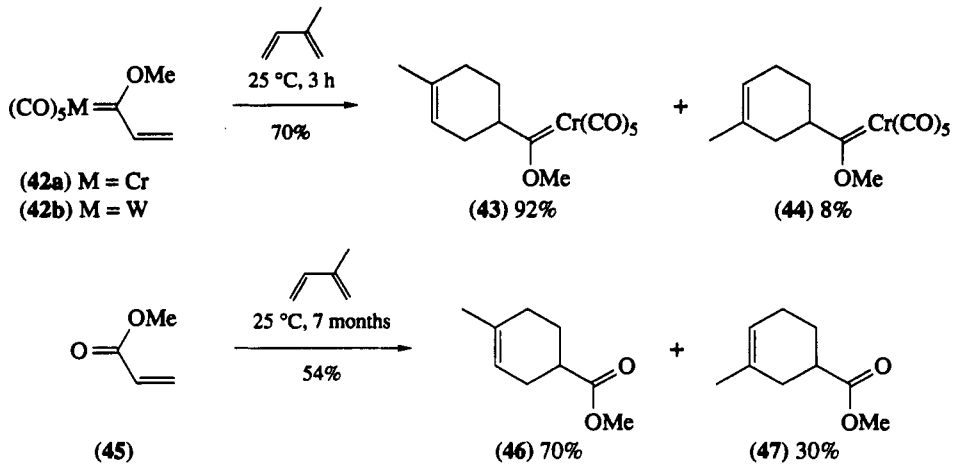
i, Me_3SiCHN_2 , hexane, 25 °C, 2–4 h; ii, $Ce(NH_3)_6(NO_3)_2$, Et_2O, 25 °C, 30 min;
iii, Me_3SiCHN_2, hexane, 69 °C, 5 d

Scheme 6

9.2.2.3 [4 + 2] Cycloadditions

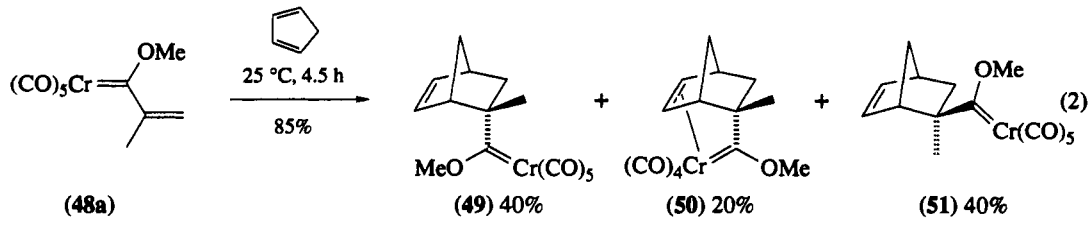
The most thoroughly studied pericyclic reaction of carbene complexes is the Diels–Alder reaction of α,β-unsaturated complexes. The first examples were published in 1983 and since that time a number of other reports have appeared which together demonstrate that this reaction is a useful tool for the preparation of highly functionalized carbene complexes and should have significant utility in organic synthesis.[17–29] In the first study a comparison was made between the Diels–Alder reactions of the vinyl carbene complexes (**42**) and methyl acrylate with several 1,3-dienes.[17] The reaction of the vinyl chromium carbene complex (**42a**) with isoprene occurs at room temperature in three hours, whereas its ester analog, methyl acrylate (**45**), has been reported to react in seven months at this temperature. The rate enhancement for the reaction of the carbene complex (**42a**) over methyl acrylate is 2×10^4 and associated with this rate enhancement is a significant increase in the regioselectivity. These enhanced rates and regioselectivities are comparable to those observed for the aluminum trichloride mediated Diels–Alder reaction of methyl acrylate and isoprene. Since carbene complexes can be easily oxidized to esters, this initial report pointed to the potential that vinyl carbene complexes could have as synthons for esters in the Diels–Alder reaction.

The earliest studies examining the stereoselectivity of these reactions involved cyclopentadiene[17,18,20] and among the examples in the literature is the reaction of the isopropenyl chromium complex (**48a**).[18] The reaction is rapid and gives the *endo* and *exo* adducts (**49**) and (**51**), as well as the chelated complex

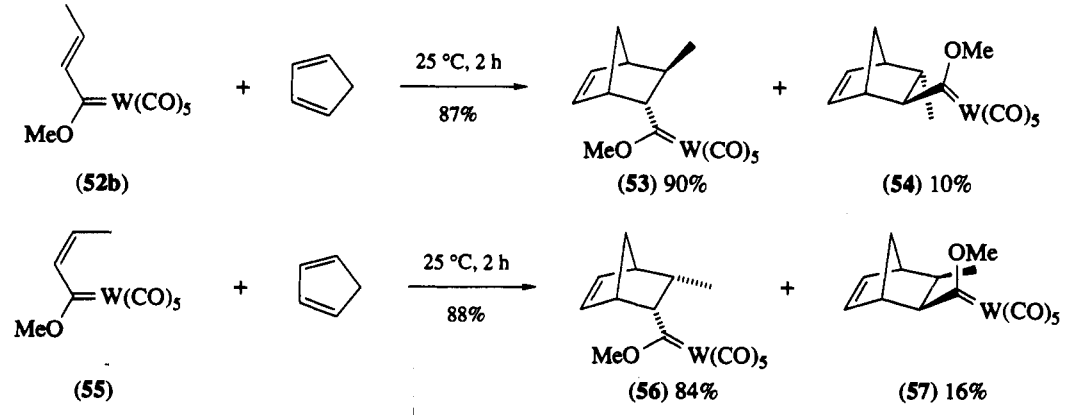


Scheme 7

(**50**) derived from the *endo* adduct. The assignment of stereochemistry was made on the basis of the observation that the *endo* adduct (**49**) could be converted upon heating to the chelated complex (**50**), which in turn was characterized by X-ray diffraction. The stereoselectivity of this reaction thus is in favor of the *endo* adduct, but only by a small amount (60:40).[19] The reaction of methyl methacrylate with cyclopentadiene is also not stereoselective and in fact gives a small preference for the *exo* adduct. The Lewis acid mediated reaction of methyl methacrylate with cyclopentadiene, interestingly, also gives a 60:40 mixture of *endo* to *exo*.

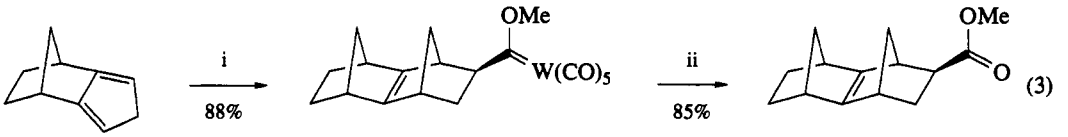


The stereospecificity of the reactions of the *trans*- and *cis*-propenyl complexes (**52b**) and (**55**) with cyclopentadiene has been investigated.[20] The *trans*-propenyl complex (**52b**) affords the *endo* and *exo* adducts as a 90:10 mixture, in which the *trans* stereochemistry present in the carbene complex is completely retained in both cycloadducts. As a point of comparison, the reaction of *trans*-methyl crotonate with cyclopentadiene gives a 54:46 *endo:exo* ratio in the thermal reaction and a 93:7 ratio in the aluminum chloride mediated reaction. The stereospecificity of these reactions was established when it was found that the *cis*-propenyl carbene complex (**55**) was found to give the *cis*-derived *endo* and *exo* adducts (**56**) and (**57**) in an 84:16 ratio. Thus, no evidence for stereochemical crossover could be found in the reactions of (**52b**) or (**55**) in their reactions with cyclopentadiene.



Scheme 8

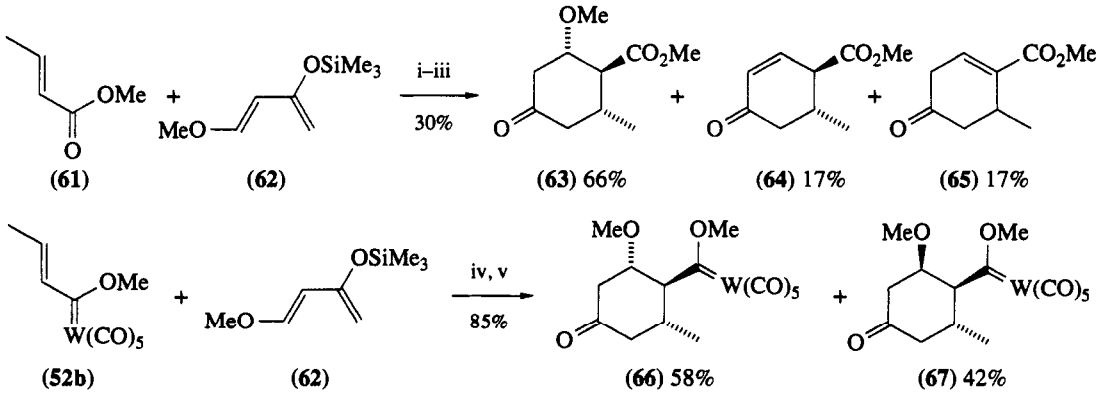
The reaction of the unsubstituted vinyl tungsten complex (**42b**) was found to be completely *exo* selective in its cycloaddition with the diene (**58**).[21] The reaction of this same diene with methyl acrylate also occurred with exclusive *exo* addition giving the adduct (**60**), but at a significantly lower rate. The stereochemistry of the carbene complex cycloadduct (**59**) was confirmed by oxidation with DMSO, which gave the ester (**60**) which was identical with the adduct obtained from the reaction of diene (**58**) with methyl acrylate. It was interesting to observe that, despite the much greater reactivity of the carbene complex (**42b**) compared to methyl acrylate, the *exo* adduct was the only isomer isolated in each reaction. This is especially interesting in light of the increased *endo* selectivities observed for the carbene complexes over their ester analogs in cycloaddition with the parent cyclopentadiene.



(**58**) (**59**) (**60**)

i, (**42b**) M = W, PhH, 20 °C, 15 min; ii, DMSO, 25 °C, 58 h

In the Diels–Alder reaction, the typical dienophile will display lower stereoselectivity with acyclic dienes than with cyclic dienes. This is the case for the reactions of both methyl crotonate and the propenyl tungsten complex (**52b**) with Danishefsky's diene (Scheme 9).[20] Carbene complex (**52b**) gives a 58:42 selectivity in favor of the *exo* adduct (**66**), while methyl crotonate gives a similar selectivity of 66:34 in favor of the *exo* adduct (**63**) (**64** and **65** are both derived from elimination of methanol from the *endo* adduct). This example reveals that the Diels–Alder reactions of carbene complexes are viable with functionalized and highly electron rich dienes. Furthermore, although the reaction of the carbene complex (**52b**) with Danishefsky's diene is not stereoselective, it does occur with a much greater rate and efficiency than that for the organic ester for which it can serve as synthon.



(**61**) (**62**) (**63**) 66% (**64**) 17% (**65**) 17%

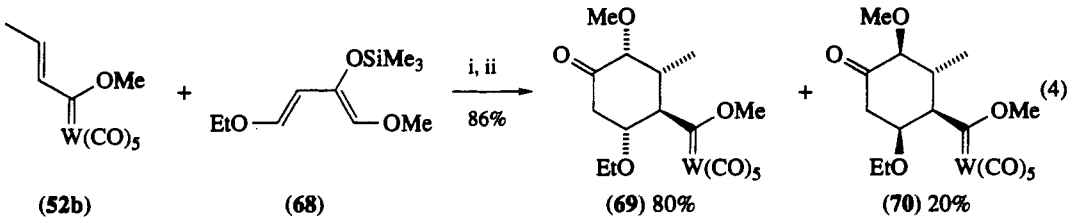
(**52b**) (**62**) (**66**) 58% (**67**) 42%

i, toluene, 110 °C, 2 d; ii, 0.005 M HCl, THF, 25 °C, 1 h; iii, silica gel; iv, 25 °C, 2 min; v, silica gel, ether/hexane/CH_2Cl_2, 25 °C, 3.5 h

Scheme 9

The reaction of the propenyl tungsten complex (**52b**) with the trisubstituted *trans,trans*-diene (**68**) occurs with retention of the stereochemistry of both the diene and the dienophile.[20] In this reaction the facial selection at the 1,3-diene favors the formation of the *exo* adduct (**69**) by a factor of 4:1. The reaction of the relatively unhindered tungsten complex (**52b**) gives high yields of Diels–Alder adducts with both of the electron rich dienes (**68**) and (**62**; Scheme 9) with no cyclopropane side products, which is to be contrasted with more highly substituted alkenyl chromium carbene complexes (Section 9.2.3.1.1).[22,23]

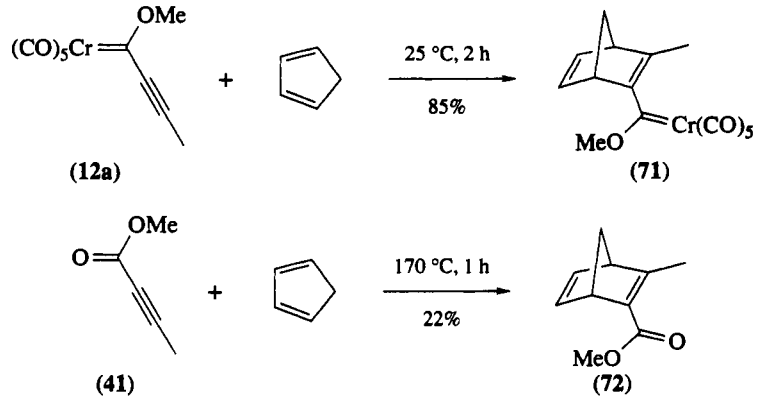
The [4 + 2] cycloadditions of alkynyl carbene complexes with 1,3-dienes have also been examined and, as illustrated by the examples in Scheme 10, they occur with the same increased rates that are observed for alkenyl complexes over their organic ester analogs.[24–26] The reaction of the propynyl chromium complex with cyclopentadiene occurs in 2 h at room temperature to give the cycloadduct (**71**) in 85% yield after purification by silica gel chromatography.[24] On the other hand, the reaction of methyl tetrolate only gives a low yield of the cycloadduct (**72**) under relatively forcing conditions. A good yield



(52b) (68) (69) 80% (70) 20%

i, PhH, 25 °C, 68 h; ii, silica gel, hexane/ether, 25 °C, 2.5 h

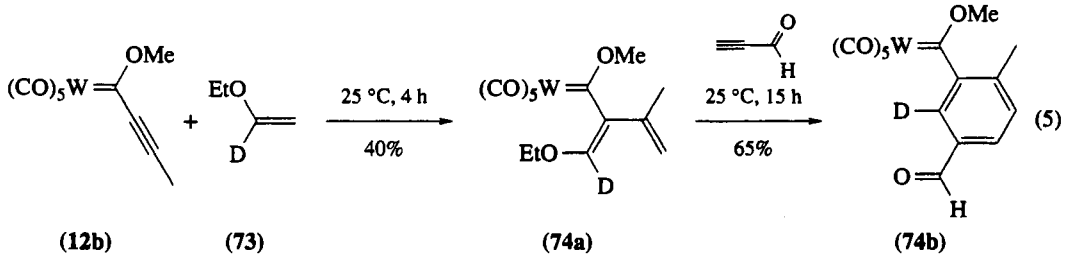
of the analogous cycloadduct can be obtained with the more reactive tetrolyl chloride; however, the reaction is significantly slower than the reaction of the carbene complex (**12a**) and the cycloadduct is not stable to chromatography. There is clearly potential for alkynyl carbene complexes to serve as synthons for alkynyl esters in the Diels–Alder reaction. Additionally, as will be seen in Section 9.2.3.2.4, the cycloadducts from alkynyl carbene complexes and 1,3-dienes can be employed in various annulation reactions.



(12a) (71) (41) (72)

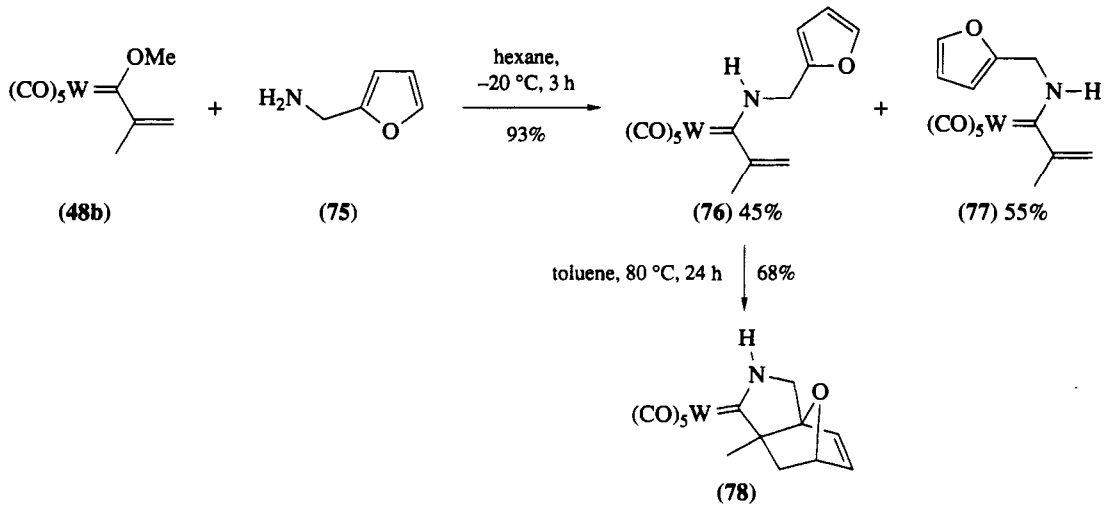
Scheme 10

There are only two reports in the literature concerning the Diels–Alder reactions of carbene complexes where the diene is part of the carbene complex.[10,27] The example in equation (5) illustrates the utility of the [2 + 2] cycloadditions discussed in Section 9.2.2.1. The [2 + 2] cycloaddition of the propynyl tungsten complex (**12b**) and ethyl vinyl ether proceeds at room temperature; however, the subsequent electrocyclic ring opening of the resulting cyclobutenyl carbene complexes occurs at a similar rate, and the initial cycloadduct is isolated in only a low yield (6%).[10] The major product is the dienyl carbene complex (**74a**), which can be obtained in 40% yield, and this will react with a number of reactive dienophiles in Diels–Alder reactions. In the case of propargyl aldehyde, the initial cycloadduct eliminated ethanol and gave the aryl carbene complex (**74b**). Such an aryl complex bearing an aldehyde group would be rather difficult to prepare by the standard procedures. It is apparent that the ethoxy group in (**74b**), and not the electron-withdrawing carbene complex functionality, is controlling the regiochemistry. A possible explanation involves the preference for a conformer about the carbene-carbon to the carbon of the 2-position of the diene in which the electronic influence of the carbene complex functionality is not felt in the diene.



(12b) (73) (74a) (74b)

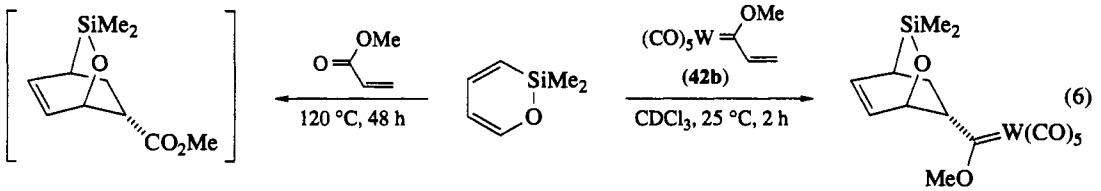
Both of the examples of intramolecular Diels–Alder reactions of carbene complexes involve the 1,3-diene tethered through the heteroatom ancilliary substituent of the carbene carbon.[25,28] The example shown in Scheme 11 is the only example of a Diels–Alder reaction of an amino carbene complex.[28] Alkenylamino and alkynylamino complexes are inert to reaction under intermolecular conditions with very reactive dienophiles, such as cyclopentadiene and Danishefsky's diene.[28,29] The aminolysis of the methoxy complex (**48b**) with the amine (**75**) represents the most common method for the preparation of amino carbene complexes.[1,2] It is typical that two isomeric amino carbene complexes are obtained by this procedure, and, as is the case for the complexes (**76**) and (**77**), it is also typical that these isomers about the carbene–nitrogen bond are not interconvertable, even at elevated temperatures. The (*E*)-isomer (**76**) was separated and was found to undergo an intramolecular Diels–Alder reaction at 80 °C to give the interesting tricyclic carbene complex (**78**).



(**48b**) (**75**) (**76**) 45% (**77**) 55% (**78**)

Scheme 11

The final example is illustrative of another advantage that the Diels–Alder reactions of carbene complexes can offer. The Diels–Alder reaction of the α-silapyran (**79**) with methyl acrylate requires heating to 120 °C before a reaction ensues.[17,20] The expected cycloadduct (**80**) was not observed and it is likely that this is due to a subsequent retro-Diels–Alder reaction involving extrusion of a silicon–oxygen double bond. This thermal limitation to this reaction can not be overcome by the typical approach to this kind of problem in conventional Diels–Alder technologies, that is the use of Lewis acids. The silapyran (**79**) is relatively sensitive and all attempts to effect its reaction with standard Lewis acids ($AlCl_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$) failed. Alkenyl carbene complexes, such as (**42b**), are relatively tolerant of sensitive organic functionalities and, at least in this case, tolerant of pathways that would be competitive to the Diels–Alder reaction, which then occurs at room temperature to give clean formation of the cycloadduct (**81**).



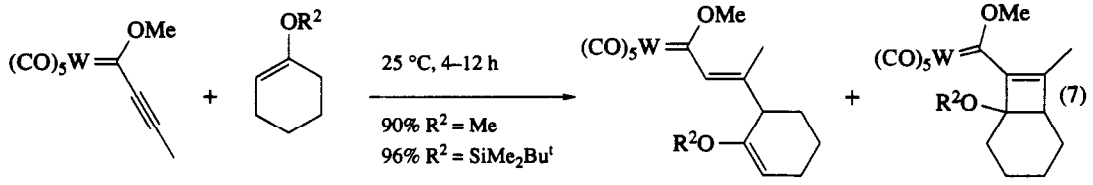
(6)

(**80**) not observed (**79**) (**81**)

The Diels–Alder reactions have been examined for a number of alkenyl and alkynyl complexes with a dozen or so different dienes and the general observation is that they occur with rates, regio- and stereoselectivities that are normally only associated with the Lewis acid mediated reactions of their corresponding organic esters. The Diels–Alder reaction of carbene complexes has been introduced more recently than other reactions of carbene complexes that have found applications in syntheses of various organic targets. Although the Diels–Alder reaction of carbene complexes has yet to be employed in natural product synthesis, the special advantages that they offer suggests that this situation may change.

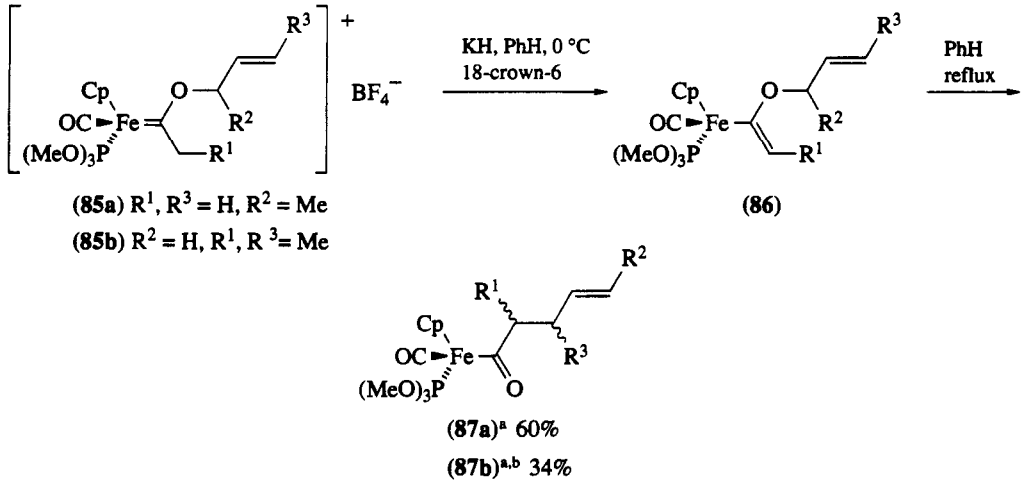
9.2.2.4 Ene Reactions and Sigmatropic Rearrangements

Very few pericyclic reactions of carbene complexes have been studied that are not in the cycloaddition class. The two examples that are known involve ene reactions and Claisen rearrangements. Both of these reactions have been recently studied and thus future developments in this area are anticipated. Ene reactions have been observed in the the reactions of alkynyl carbene complexes and enol ethers, where a competition can exist with [2 + 2] cycloadditions.[11] Ene products are the major components from the reaction of silyl enol ethers and [2 + 2] cycloadducts are normally the exclusive products with alkyl enol ethers (Section 9.2.2.1). As indicated in equation (7), methyl cyclohexenyl ether gives the [2 + 2] adduct (**84a**) as the major product along with a minor amount of the ene product (**83a**). The *t*-butyldimethylsilyl enol ether of cyclohexanone gives the ene product 9:1 over the [2 + 2] cycloadduct. The reason for this effect of silicon is not known at this time but if the reaction is stepwise, this result is one that would be expected on the basis of the silicon-stabilizing effect on the β-oxonium ion.



(**12b**) (**82a**) R^2 = Me; (**82b**) R^2 = $SiMe_2Bu^t$ (**83a**) 23% (**83b**) 90% (**84a**) 77% (**84b**) 10%

Cationic iron–carbene complexes were used as precursors in the Claisen rearrangement of the iron-substituted allyl vinyl ethers (**86**).[30] The carbene complexes were generated *in situ* from the corresponding iron–acyl complexes by deoxygenation to cationic vinylidene complexes, which were trapped by an allyl alcohol. The cationic iron–carbene complexes were not isolated, but were deprotonated directly to give the allyl vinyl ether complexes (**86**). The Claisen rearrangement of these complexes occurred in refluxing benzene to give the iron–acyl complexes (**87**). The yields were only modest, but they were determined for the overall process involving four steps from the iron–acyl complexes that were the precursors to the carbene complexes (**85**). These Claisen rearrangements were found not to proceed with useful stereoselectivities. The complex (**87b**) was obtained as a complex mixture of diastereomers. These first examples of ene reactions and Claisen rearrangements of carbene complexes should stimulate further study of pericyclic reactions of the noncycloaddition type.



(**85a**) R^1, R^3 = H, R^2 = Me
(**85b**) R^2 = H, R^1, R^3 = Me

(**86**)

(**87a**)[a] 60%
(**87b**)[a,b] 34%

(8)

[a]Yield from the iron acyl precursor of (**85**). [b]Complex mixture of diastereomers.

9.2.2.5 Coupling of Anions of the Carbene Ligand with C—X σ-Bonds

The alkylation of carbene complexes is one of the potentially most useful methods for the preparation of highly substituted and/or highly functionalized carbene complexes *via* the elaboration of more simple

and readily available carbene complexes. The high acidity of protons on a carbon α to the carbene was first recognized by Kreiter in 1968.[31] In the years to follow, it was the work of Casey that revealed the scope of the reactions of anions generated from alkyl carbene complexes with electrophiles.[33,34] The pK_a of the methyl complex (**88a**)[33,34] was found to be nearly equal to that of *p*-cyanophenol ($pK_a \approx 8$) and it thus might be expected that the conjugate base (**89**) is a relatively stable and unreactive anion. The alkylation of the anion (**89**) with methyl iodide is successful but is not synthetically useful, due to the low yield.[33] Alkylation of (**89**) with other simple alkyl halides has not been reported. The reactions of the 'enolates' of carbene complexes with epoxides is one that has found use in the preparation of substituted 2-oxacyclopentylidene complexes of the type (**93**).[35] These complexes can be oxidatively cleaved to γ-butyrolactones and have been employed in the synthesis of α-methylene-γ-butyrolactones.[36] The anions generated from the cyclic carbene complexes (**93**) are more reactive towards alkylating reagents than noncyclic alkyl complexes and this may be for stereoelectronic reasons. In the stoichiometric additions of carbene enolates to enones, the cyclic complex (**93a**) gives a 41% yield of the adduct (**96**), whereas the methyl complex (**88a**) is alkylated in only 22% yield.[37] It is interesting that, in the presence of a catalytic amount of base, the reaction of (**93a**) with methyl vinyl ketone gives the bis adduct (**97**). As indicated by the reaction of 3-penten-2-one, the complex (**93a**) can be alkylated in good yield by a number of substituted enones. The efficiency of these alkylations is greatly increased with more active alkylating agents, but as illustrated for complex (**88a**) and methyl bromoacetate, dialkylation is usually a serious side reaction.[38]

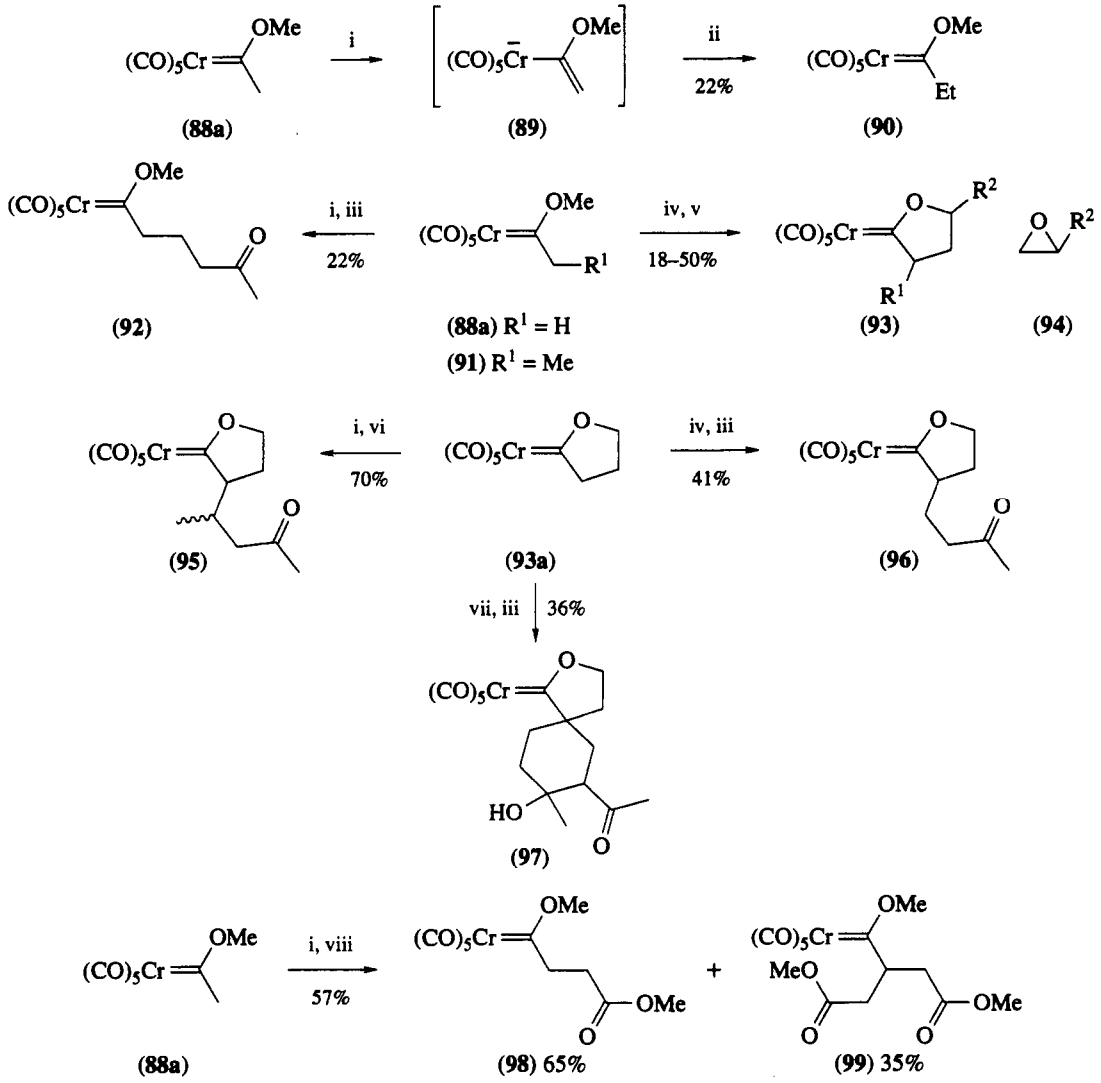
The cyclic carbene complex (**93a**) can be alkylated in good yield with allyl bromide, but again, significant dialkylation was reported.[39] The tungsten complex, however, was reported to be alkylated with allyl bromide in good yield, and no dialkylation product was reported.[40] The alkylation product (**104**) was used to prepare the complex (**105**) *via* a metathesis reaction with $WOCl_4$, and it was surprising to find that this could be carried out to any extent without affecting the tungsten–carbene bond. The dialkyation problem can often be avoided for chromium complexes using inverse addition of the reagents. The methyl chromium complex (**88a**) can be monoalkylated in good yield (72%) with allyl bromide if anion (**89**) is added to a solution of allyl bromide.[41] The alkyations of alkyl(alkoxy) pentacarbonyl carbene complexes are not useful with simple alkyl halides and this is illustrated in the fact that even the more reactive anion derived from complex (**93a**) can only be alkylated with ethyl bromide in 20% yield.[42]

The anions generated from tetracarbonyl(phosphine) carbene complexes are more reactive in their reactions with organic electrophiles.[43] This is consistent with the observation that the pK_a of the methyl pentacarbonyl complex (**88a**) is increased by six orders of magnitude when one of the carbon monoxide ligands is replaced with tributylphosphine. The anion generated from (**106**) will give good yields of alkylated products with simple alkyl halides such as ethyl bromide; however, dialkylation is still a serious side reaction. It has been reported that both pentacarbonyl and tetracarbonyl(phosphine) complexes can be efficiently monoalkylated with alkyl triflates (primary and secondary). The anion (**89**) for example, can be monoalkyated with the 3-butenyl triflate in 80% yield.[43]

The anions generated from alkylamino carbene complexes can be alkylated in high yields with simple alkyl halides without any detectable amount of dialkylation.[44] This is illustrated for the methyl pyrrolidine complex (**109**), which can be alkylated cleanly with ethyl bromide to give the monoalkylated product (**110**) in 87% yield. The methyl pyrrolidine complex (**109**) can be prepared in nearly quantitative yield quite simply by treating an ether solution of the methyl methoxy complex (**88a**) with pyrrolidine at room temperature for a few minutes. A few examples of diastereoselective alkylations are known. The *O*-alkylimidate carbene complex (**112**) can be alkylated with methyl triflate to give a 93:7 mixture of (**113**) and (**114**), which are diastereomers as a result of the chiral axis about the aza–allenyl linkage.[45] Other examples of diastereoselective alkylations will be presented in Section 9.2.2.7.

9.2.2.6 Coupling of Anions of the Carbene Ligand with C—X π-Bonds

The condensation of the anions generated from alkyl alkoxy pentacarbonyl carbene complexes with carbonyl compounds occurs with the formation of α,β-unsaturated carbene complexes of the type (**117**). This reaction was first explored by Casey and it was found that this reaction was limited to nonenolizable aldehydes.[32] The reaction of the anion (**89**) with benzaldehyde gave the styryl complex (**117**) in 48% yield, and with pivaldehyde the corresponding unsaturated carbene complex was obtained in 26% yield. No reaction was observed with several ketones, including acetone, acetophenone, benzophenone and cyclopentanone.[46] Reactions with enolizable aldehydes, including butanal, diphenylacetaldehye and acetaldehyde, also failed.[46] Recently a modification of this reaction was reported that does not require the stoichiometric generation of the anion (**89**).[47] The complex (**88c**) was observed to give the unsaturated

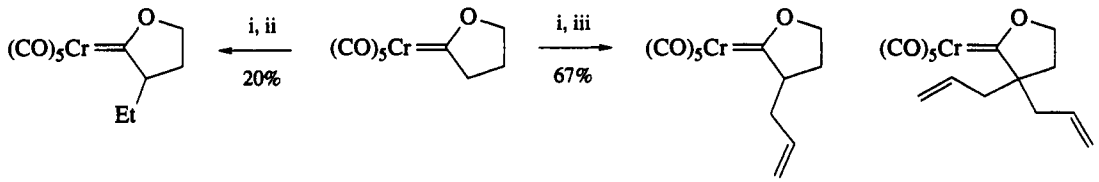


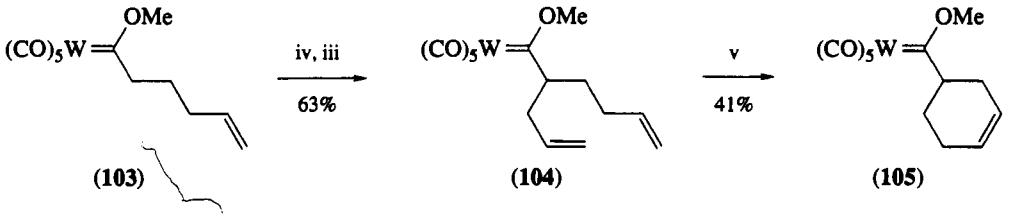
i, Bu^nLi (1.0 equiv.), THF, –78 °C; ii, MeI (1.0 equiv.), –78 to 0 °C, 30 min;
iii, methyl vinyl ketone (1.5 equiv.), 0 °C, 2 h; iv, Bu^nLi (1.0 equiv.), THF, –78 to 0 °C;
v, (**94**) (1.5 equiv.), 0 °C, 0.5–2 h; vi, *trans*-3-penten-2-one, 25 °C, 2 h;
vii, Bu^nLi (0.1 equiv.), THF, –78 °C; viii, methyl bromoacetate (1.0 equiv.), 0 °C, 1 h

Scheme 12

complexes (**117**) with the aldehyde (**115**) in the presence of triethylamine and trimethylsilyl chloride. The reaction was reported only for nonenolizable aldehydes. The aldol adducts are not isolable from these reactions and, apparently, the initial adduct (**116**) undergoes proton transfer from the more acidic methylene group α to the carbene carbon, and the resulting anion suffers rapid β-elmination of the hydroxy group.

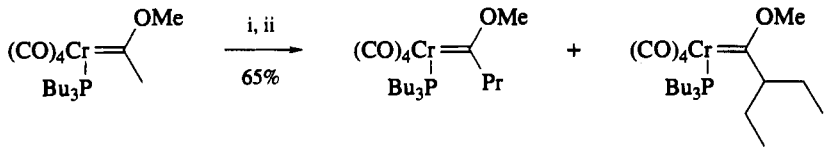
The isolation of the initial aldol products from the condensation of the 'enolates' of carbene complexes and carbonyl compounds is possible if the carbonyl compound is pretreated with a Lewis acid.[48] As indicated in equation (9), the scope of the aldol reaction can also be extended to ketones and enolizable aldehydes by this procedure. The condensations with ketones were most successful when boron trifluoride etherate was employed, and for aldehydes, the Lewis acid of choice is titanium tetrachloride. The carbonyl compound is pretreated with a stoichiometric amount of the Lewis acid and to this is added a solution of the anion generated from the carbene complex. An excess of the carbonyl–Lewis acid complex (2–10 equiv.) is employed; however, above 2 equiv. only small improvements in the overall yield are realized.

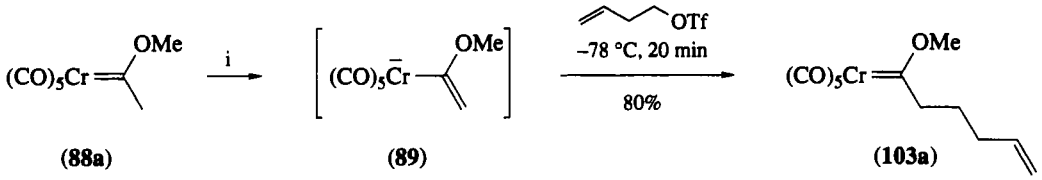




i, Bu^nLi (1.0 equiv.), THF, –78 °C; ii, EtBr (1.3 equiv.) 67 °C, 45 min;
iii, allyl bromide (1.0 equiv.), 0 °C, 12 h; iv, Bu^nLi (1.0 equiv.), THF, –60 °C;
v, $WOCl_4$ (1 equiv.), Ph_2SiH_2 (2 equiv.), hexane, 60 °C, 2 h

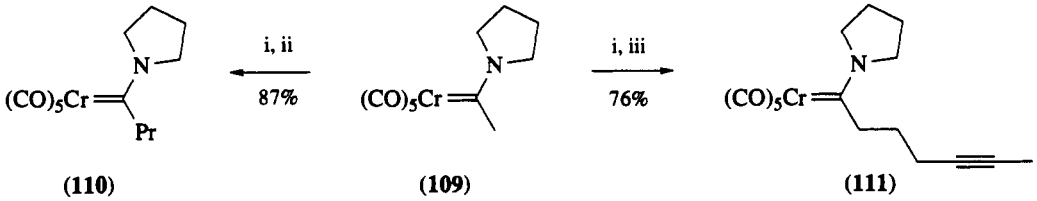
Scheme 13

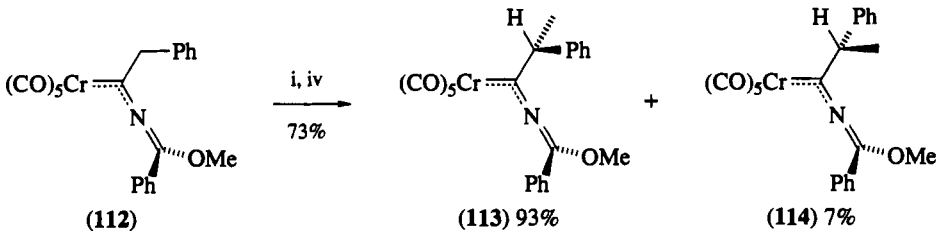




i, Bu^nLi (1.0 equiv.), THF, –78 °C; ii, EtBr (3 equiv.), 22 °C, 10 h

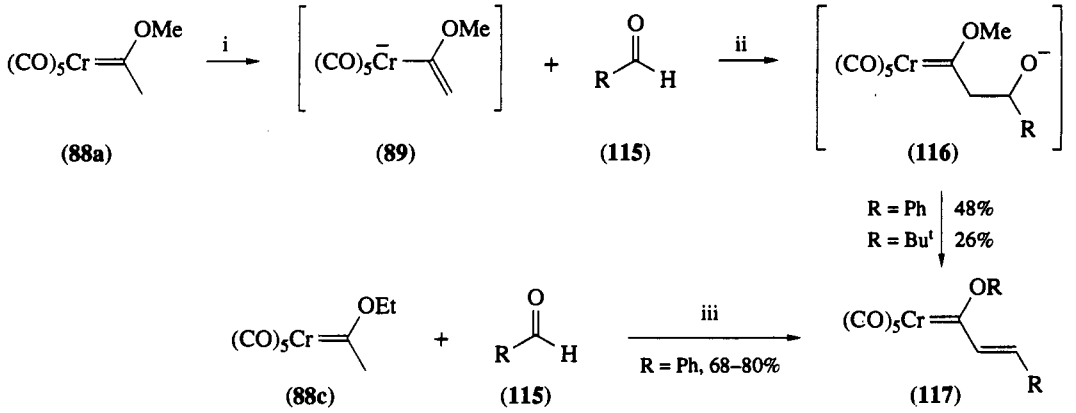
Scheme 14





i, Bu^nLi (1.0 equiv.), THF, –78 °C; ii, EtBr (2.0 equiv.), 0 °C, 40 min;
iii, 1-iodo-3-pentyne (2.0 equiv.), 0 °C, 1 h; iv, methyl triflate, 0 °C, 40 min

Scheme 15

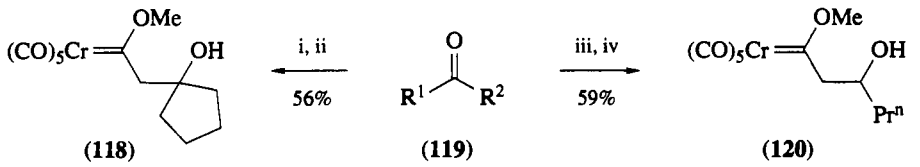


(88a) (89) (115) (116) (88c) (115) (117)

i, Bu^nLi, Et_2O, –78 °C; ii, –78 to 25 °C, 2 h;
iii, (**115**) (1.0 equiv.), Et_3N (4 equiv.), Me_3SiCl (3.0 equiv.) 25 °C, 1–14 d

Scheme 16

The aldol adduct (**120**) is obtained in 59% yield with 2 equiv. of the carbonyl–Lewis acid complex and in 67% with 10 equiv.

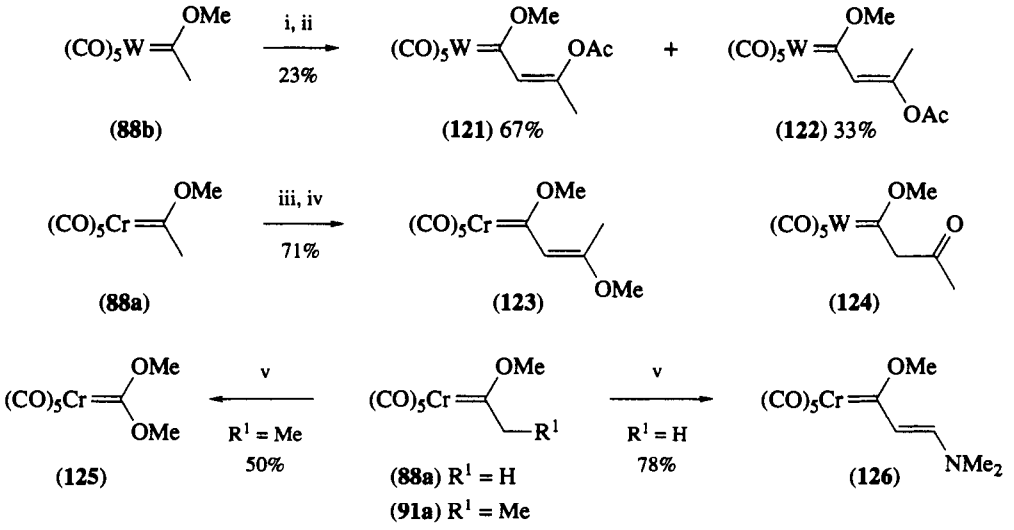


(118) (119) (120) (9)

i, $BF_3{\cdot}Et_2O$ (1.0 equiv.), Et_2O, 0 °C; ii, (**89**) (0.1 equiv.), 0–25 °C, 20–30 min;
iii, $TiCl_4$ (1.0 equiv.), CH_2Cl_2, –78 °C; iv, (**89**) (0.5 equiv.), –78 °C, 1 h

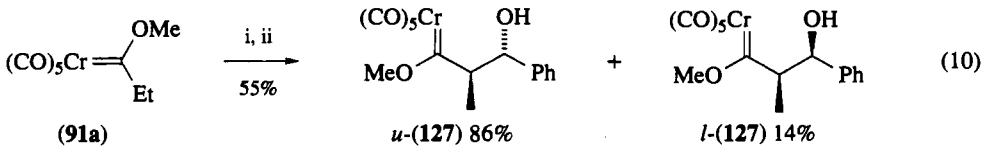
The condensation of the α-anions of carbene complexes with acid halides cannot be stopped at the monoacylated product.[49] The reaction of the anion generated from the tungsten complex (**88b**) with acetyl chloride gives a 2:1 mixture of the enol acetate complexes (**121**) and (**122**) along with recovered (**88b**). The initially formed β-keto carbene complex (**124**) was not isolated, and apparently acetyl chloride more rapidly *O*-acylates (**124**) than *C*-acylates the enolate of (**88b**); the reason for this may be due to rapid proton transfer from (**124**) to the anion of (**88b**). The related complexes of the type (**123**) can be prepared in high yield from the reaction of the anion of (**88a**) with electrophiles generated from the treatment of orthoesters with Lewis acids.[48] This type of product can also be obtained from acetals that have been pretreated with Lewis acids[48] and from alkyl enol ethers in the presence of trifluoroacetic acid.[50] The reaction of carbene complexes with *N,N*-dimethylformamide dialkyl acetals has recently been reported to give β-aminoalkenyl complexes of the type (**126**).[51] Complexes of the type (**126**) can only be prepared from the methyl complex (**88a**), and unexplainedly, the ethyl complex (**91a**) gives the dimethoxy complex (**125**).

The stereochemistry of the aldol reaction has been examined with regard to simple diastereoselective induction.[48] The anion generated from the ethyl carbene complex (**91a**) was added to a solution of benzaldehyde that had been pretreated with titanium tetrachloride and the resulting aldol adduct was obtained as an 86:14 mixture of diastereomers in favor of the *u*-isomer. This example demonstrates that carbene complexes could have value as synthons for esters in the aldol reaction since the corresponding aldol reaction of methyl propionate with benzaldehyde is nonselective and gives a 62:38 mixture (in favor of the *l*-isomer) of the β-hydroxy esters (**128**). That carbene complexes could be synthons for esters was established by the fact that the purified *u*-isomer of the carbene complex (**127**) could be oxidized in 73% yield to the ester (**128**), in which the stereochemistry was completely retained (>99.4% diastereomeric purity).[48] That the stereochemistry could have been lost during this oxidation was of some prior concern given the high acidity of carbene complexes. The origin of the stereoselectivity in the reaction in equation (10) is not known, since the stereochemistry of the 'enolate' generated from (**91a**) is not known under the reaction conditions.



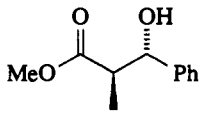
i, Bu^nLi, THF, –20 °C; ii, AcCl (2.2 equiv), 5 min; iii, Bu^nLi, Et_2O, –78 °C;
iv, addition to a CH_2Cl_2 solution of $MeC(OMe)_3$–$TiCl_4$ complex (10 equiv.), –78 to 0 °C;
v, $(MeO)_2CHNMe_2$ (1.0 equiv.), DMF, 20 °C, 30 min

Scheme 17



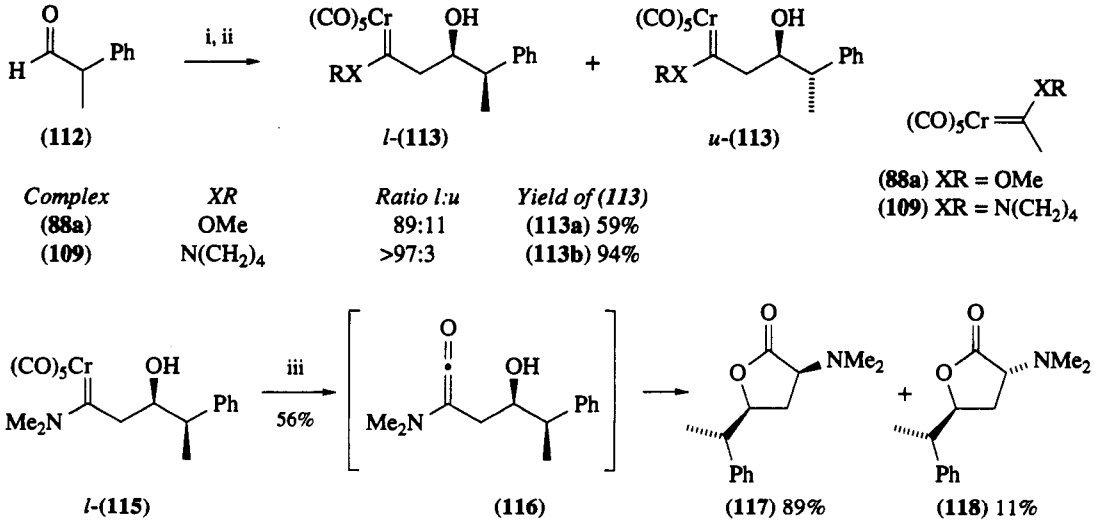
(10)

i, Bu^nLi, Et_2O, –78 °C;
ii, addition to a CH_2Cl_2 solution of benzaldehyde–$TiCl_4$ complex (2.0 equiv.), –78 °C, 1 h



u-(128)

The aldol reactions of amino carbene complexes are superior to the aldol reactions of alkoxy carbene complexes in several respects.[52] First, the condensations of the anions generated from alkyl amino carbene complexes can be carried out with both aldehydes and ketones without the need to precoordinate the carbonyl compound with a Lewis acid. Second, high yields of the aldol adducts can be obtained even with stoichiometric amounts of the carbonyl compound. Third, as illustrated in Scheme 18, it has been found that aldol reactions of amino carbene complexes display much higher diastereofacial selective addition to chiral aldehydes than do alkoxy complexes. The anion of the methyl pyrrolidine complex (**109**) will add to 2-phenylpropanal to give the Cram product *l*-(**113**) with greater than 97:3 stereoselectivity. This is the highest facial selection ever observed for the addition of an enolate of a carbonyl compound to this aldehyde. Employing the carbonylative demetallation procedure developed by Hegedus (Section 9.2.2.8),[53] the aldol adduct *l*-(**115**) can be converted to the 2-amino-γ-butyrolactone (**117**) with reasonable stereoselectivity. These results should prompt further examination of the utility of carbene complexes in stereoselective aldol reactions.



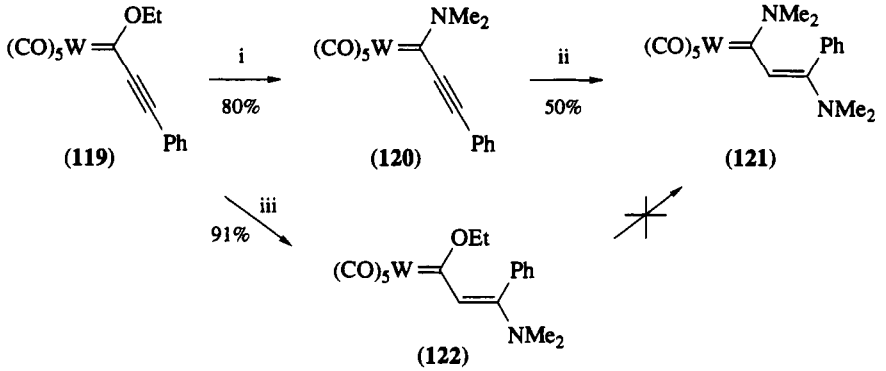
Complex	*XR*	*Ratio l:u*	*Yield of (113)*
(**88a**)	OMe	89:11	(**113a**) 59%
(**109**)	$N(CH_2)_4$	>97:3	(**113b**) 94%

i, for (**88a**) the anion of (**88a**) is added to a CH_2Cl_2 solution of a $TiCl_4$ complex with (**112**) (2.0 equiv.), –78 °C, 1 h; ii, for (**109**), (**112**) (2.0 equiv.) is added to a THF solution of the anion of (**109**), –78 °C, 10 min; iii, MeCN, *hν*, 4 h

Scheme 18

9.2.2.7 Michael Additions to α,β-Unsaturated Carbene Complexes

Conjugate additions to α,β-unsaturated carbene complexes have not been extensively studied; however, from the few reports that have appeared in the literature one can get a brief sense of the scope, limitations and special features of these reactions that may ultimately find application in synthetic organic chemistry. One of the earliest examples involves the addition of amines to alkynyl carbene complexes.[54] The example in Scheme 19 is particularly interesting because complete control between 1,4- *versus* 1,2-addition can be exercised simply by proper choice of reaction temperature. The complex (**119**) suffers exclusive 1,2-addition with dimethylamine at –90 °C and exclusive 1,4-addition at –20 °C. The 1,2-adduct (**120**) will further react with dimethylamine, but the 1,4-adduct (**122**) will not. This example demonstrates the importance of being attentive to reaction conditions when preparing amino carbene complexes, such as the alkynyl complex (**120**), or the alkenyl complex (**76**) in Scheme 11.

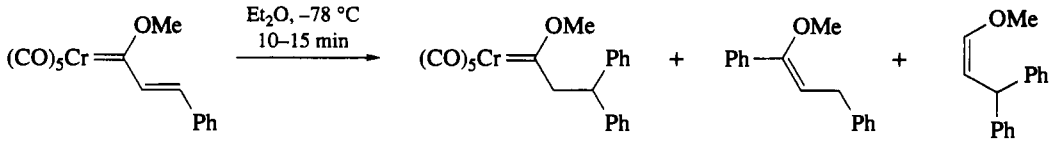


i, $HNMe_2$ (8 equiv.), Et_2O, –80 °C, 1 h; ii, $HNMe_2$ (8 equiv.), Et_2O, 20 °C, 1 h; iii, $HNMe_2$ (10 equiv.), Et_2O, –20 °C, 1 h

Scheme 19

One of the first studies directed to carbon–carbon bond formation *via* Michael addition to α,β-unsaturated carbene complexes involved the examination of the traditional reagent for this purpose in organic systems. The reactions of the styryl complex (**123**) with phenyllithium and diphenyl cuprate were com-

pared as indicated in Scheme 20, but neither were particularly efficient.[55] As would be the case in organic systems, the cuprate gave higher proportions of 1,4-addition than the organolithium reagent. In addition to the expected 1,4-adduct (**124**), two nonorganometallic products were also formed. The enol ether (**125**) most likely results from γ-protonation of the initial 1,2-adduct (**128**). The enol ether (**126**) is likely a 1,4-addition derived product resulting from the protonation of 'enolate' (**127**) on the metal rather than on carbon, and subsequent reductive elimination from the resulting metal hydride intermediate.



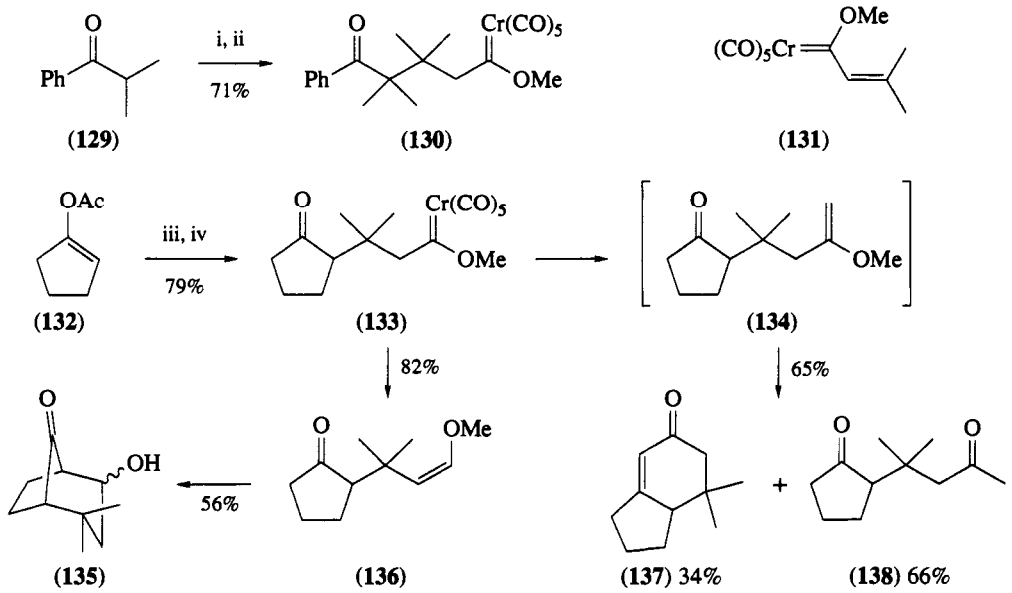
(**123**) (**124**) (**125**) (**126**)

Reagent	*Total yield (%)*			
PhLi	26	35%	65%	0%
Ph_2CuLi-PBu_3	44	65%	13%	22%

(**127**) (**128**)

Scheme 20

Greater success in Michael additions with carbon nucleophiles was achieved with ketone enolates.[56] The enolate of isobutyrophenone will undergo 1,4-addition to the isobutenyl carbene complex (**131**) in 71% yield and the enolate of cyclopentanone will react with the same carbene complex to give the Michael adduct (**133**) in 82% yield. Cleavage of the carbene ligand in (**133**) with diazomethane generates the homologated enol ether (**134**), which upon purification on silica gel gives rise to the diketone (**138**) and the aldol closed product (**137**) in a total of 65% yield. Alternatively, base-induced cleavage of the metal from the Michael adduct (**133**) with pyridine gives the (*Z*)-enol ether (**136**) in 82% yield. Hydrol-



(**129**) (**130**) (**131**)

(**132**) (**133**) (**134**)

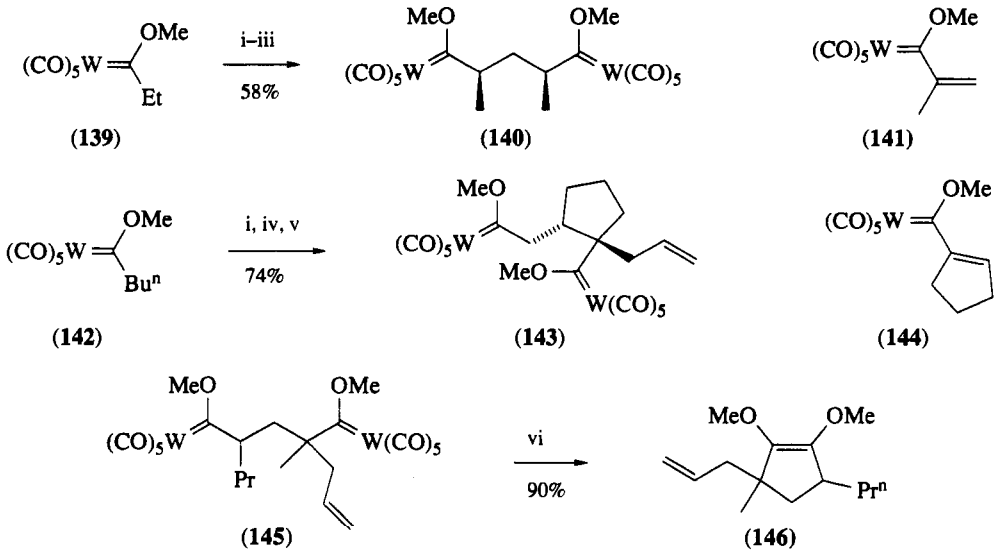
(**135**) (**136**) (**137**) 34% (**138**) 66%

i, $KOBu^t$ (1.0 equiv.), THF, 0 °C, 15 min; ii, addition to (**131**) (1.0 equiv.), THF, –78 °C, 40 min; iii, MeLi, THF, 15 min, –78 °C; iv, addition to (**131**), (0.88 equiv.), –78 °C, 5 min; v, CH_2N_2 (excess), PhH, 25 °C, 30 min; vi, silica gel; vii, pyridine (12 equiv.), heptane, 100 °C, 14 h; viii, 2M HCl

Scheme 21

ysis of (**136**) gives the intramolecular aldol product as a mixture of diastereomers. In addition to the high efficiency of the Michael addition of ketone enolates to α,β-unsaturated carbene complexes is the degree of steric congestion tolerated by these condensations as illustrated in the formation of (**130**). The addition of an enolate to an α,β-unsaturated carbonyl compound with the generation of two adjacent quaternary centers has not been accomplished in the all-carbon case.

In line with the observed greater propensity of softer nucleophiles to Michael add to α,β-unsaturated carbene complexes, the 'enolates' of carbene complexes undergo very facile conjugate additions to α,β-unsaturated carbene complexes. This type of reaction was observed early on,[36] but a recent report more clearly defines its potential. Two of the twelve examples from the work of Macomber are included in Scheme 22.[57] The condensation of the 'enolate' of the ethyl complex (**139**) with the isopropenyl complex (**141**) occurs in a highly stereoselective fashion to give only the *meso* adduct (**140**) in 58% yield. The formation of the adduct (**143**) illustrates that the Michael addition can be coupled with alkyation of the enolate resulting from the conjugate addition. The alkylation step with allyl bromide in the formation of (**143**) occurs stereoselectively with approach of the alkylating agent from the least-hindered side of the enolate. The adducts in these reactions are bis-carbene complexes and a unique opportunity provided by these complexes is an approach to five-membered ring synthesis. Thermolysis of adduct (**145**) gives the 1,2-dimethoxycyclopentene (**146**) in 90% yield. The parent 1,2-dimethoxycyclopentene is apparently an unknown compound and the Michael additions of carbene complexes clearly provides a facile entry to functionalized systems of this class. The dimerization of carbene complexes to give alkenes has long been known for intermolecular reactions,[1,2] but they occur with lower yields than that observed from the thermolysis of (**145**), which is the first example of an intramolecular dimerization.



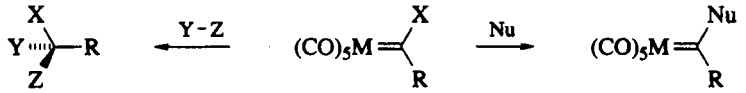
i, Bu^nLi, THF, –78 °C; ii, (**141**) (1.0 equiv.), –78 °C, 1 h; iii, Me_3SiCl (1.0 equiv.), –78 to 25 °C; iv, (**144**) (1.0 equiv.), –78 °C, 1 h; v, allyl bromide (1.0 equiv.), –78 to 25 °C; vi, PhH, 75 °C, 3 h

Scheme 22

9.2.2.8 Nucleophilic Substitutions at and Cleavage of the Carbene Ligand

There is a very large number of reactions of carbene complexes that result in cleavage of the carbene ligand from the metal. These reactions are too numerous to include in this review and have been thoroughly treated in other reviews on the chemistry of carbene complexes.[1,2] Nucleophilic substitution reactions are an important class of reactions for the preparation of carbene complexes. This general reaction is indicated in equation (11) by the transformation of (**147**) to (**149**) and is most important for heteroatom nucleophiles, most typical being nitrogen, sulfur and oxygen. Examples of substitution of an alkoxy group for an amino group can be found in Schemes 11 and 19. Other nucleophiles of synthetic importance in substitution reactions include hydride and aryllithiums.

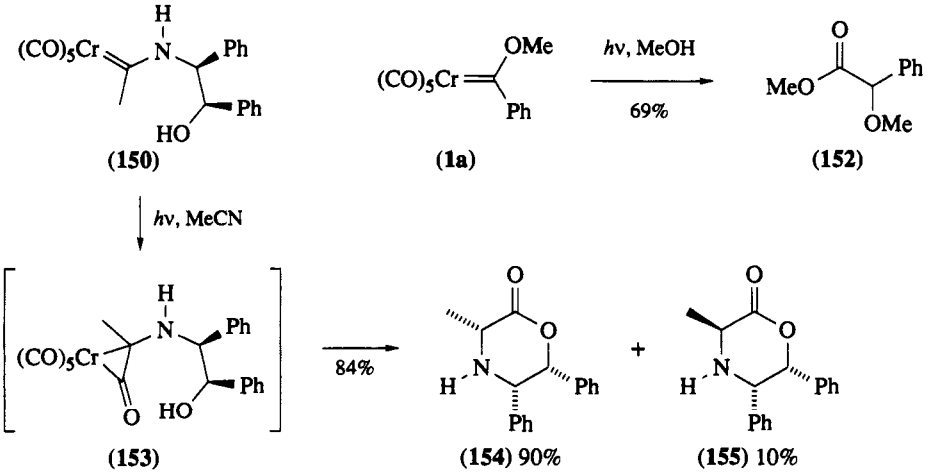
In most reactions involving addition of a reagent to the carbene carbon the outcome is liberation of the carbene ligand in the general process indicated by (**147**) to (**148**) in equation (11). Reactions of this type



(148) (147) (149) (11)

are of course of key importance in the use of carbene complexes as surrogates for organic functional groups in the reactions described in this section (Section 9.2.2), where the advantages of the metal as reactivity and selectivity auxilliary can be exploited. Examples of this type will not be included here, but can be found in the oxidative cleavages in Schemes 2, 4–6 and equation (3), in the diazomethane cleavage in Scheme 21, and in the pyridine cleavage in Scheme 21. Depending on the nature of the cleavage reaction, carbene complexes not only can serve as synthons for organic esters (their closest organic analogs), but also for a variety of other organic functional groups, including ketones, aldehydes, enol ethers, alkyl ethers, allenes and 1,3-dienes.[1,2,58]

One new method that has been reported recently will be mentioned since it has significant potential in organic synthesis. Hegedus has reported that the carbene ligand can be carbonylatively liberated upon photolysis with UV radiation.[53] Irradiation of the methoxy complex (**1a**) in the presence of methanol generated the α-methoxy ester (**152**) in 69% yield. With the development of this new method for ligand liberation, carbene complexes can serve as alkoxy- and amino-ketene synthons. This reaction most likely involves the generation of either a free or coordinated ketene and, as illustrated in the photolysis of the optically active complex (**150**), the ketene intermediate can also be trapped in an intramolecular fashion. Significant asymmetric induction in this intramolecular trapping was observed since the lactone (**154**) was produced 9:1 over its diastereomer (**155**). Since lactones of the type (**154**) can be cleaved to amino acids, this should have potential in the synthesis of optically active α-amino acids. An additional example of the utility of this method for removing the metal can be found in Scheme 18.



Scheme 23

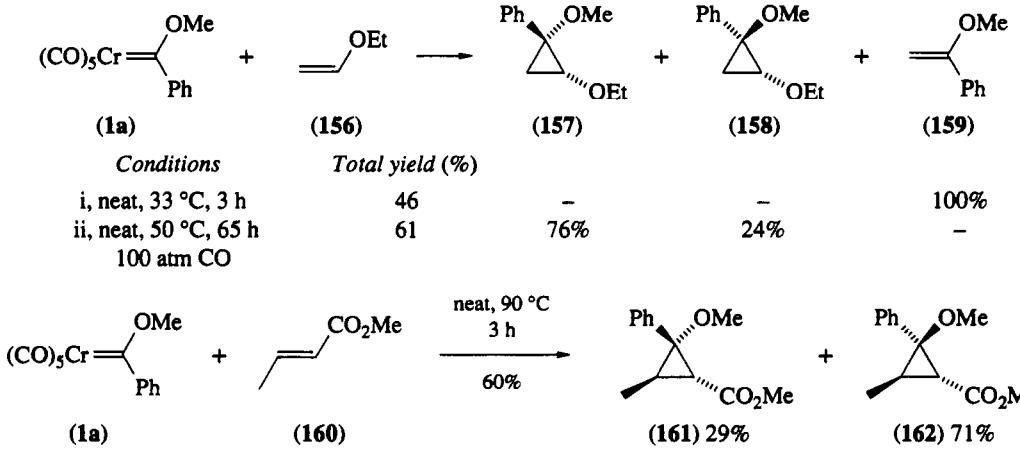
9.2.3 REACTIONS AT THE METAL CENTER: CYCLOADDITIONS IN THE COORDINATION SPHERE

9.2.3.1 Coupling of the Carbene Ligand with Alkenes and 1,3-Dienes

9.2.3.1.1 Three-membered rings via *[2 + 1] cycloadditions: cyclopropanes*

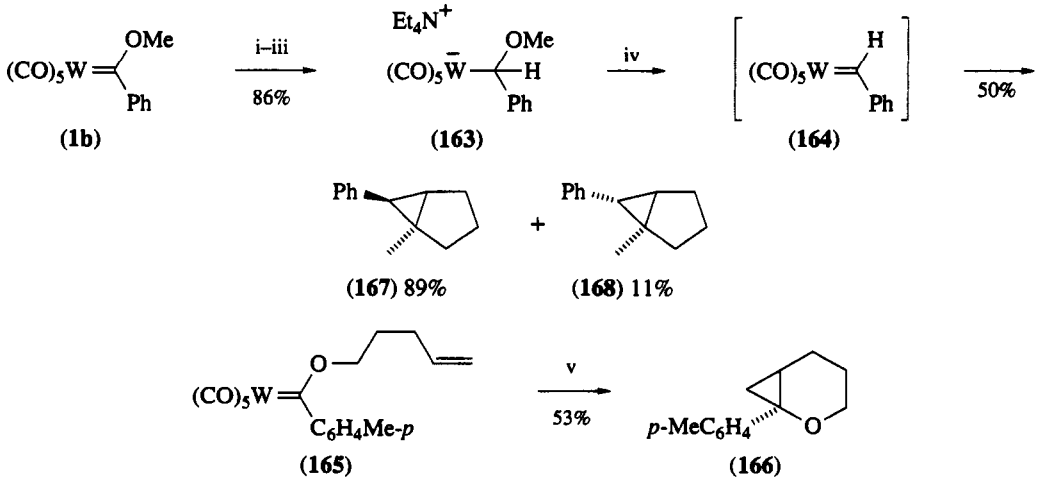
One of the first reactions of carbene complexes to be investigated after their discovery was the cyclopropanation of alkenes. This reaction has been extensively studied and will only be briefly surveyed here. Two excellent reviews of this subject have appeared,[59,60] and the cyclopropanation of alkenes with

carbene complexes is covered in Volume 4, Chapter 4.8 of this work. The investigation of this reaction has been driven not only by potential synthetic applications, but also due to the relationship of this reaction to alkene metathesis. The first examples, reported by Fischer and Dötz, showed that good to moderate yields of cyclopropanes could be obtained from the reaction of aryl carbene complexes with both electon-rich[61] and electron-deficient alkenes.[62] In the case of the former, good yields of cyclopropanes could be obtained only if the reaction was carried out under pressure of carbon monoxide. The reactions were not particularly stereoselective as illustrated by the formation of (**157**) and (**158**) in a 3:1 ratio under 100 atm (1 atm = 101 kPa) of carbon monoxide in a total of 61% yield. Recently, it has been reported that higher yields and stereoselectivities could be achieved with silyl enol ethers.[63] An unactivated alkene such as tetramethylethylene could not be cyclopropanated even under forcing conditions.[64] The fact that good yields of cyclopropanes could be obtained with both electron-rich and electron-deficient alkenes, but not simple alkenes, suggests that the two reactions in Scheme 24 operate with different mechanisms.



Scheme 24

Unactivated alkenes can be cyclopropanated if more electrophilic carbene complexes are employed or if the cyclopropanation is carried out in an intramolecular fashion. As an example of the former approach, Casey prepared the highly reactive benzylidene complex (**164**) *in situ* and found that it will efficiently cyclopropanate most unactivated alkenes. This is illustrated in Scheme 25 by its reaction with 1-methylcyclopentene.[65] It has since been found that the complex (**164**) could be isolated and can be

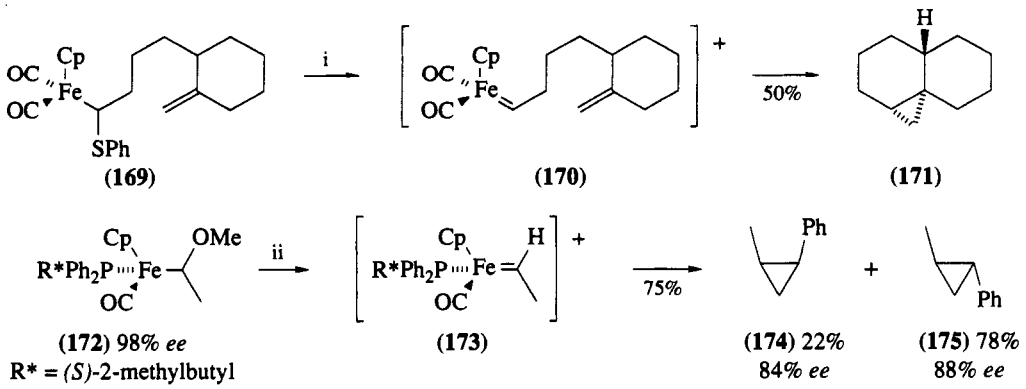


i, $HB(OPr^i)_3$, THF, (1.5–2.2 equiv.), 0 °C; ii, 1 M NaOH; iii, Et_4NBr (3 equiv.); iv, 1-methylcyclopentene (excess), CF_3CO_2H (3 equiv.), CH_2Cl_2, –78 °C, 40 min, –78 to 25 °C; v, PhH, 70 °C, 13 h

Scheme 25

handled in the solid form.[66] A number of intramolecular cyclopropanations related to the example shown in Scheme 25 have been examined, mainly as a probe for mechanistic issues, nonetheless, given the ease of preparation of compounds of the type (**165**) this could be a useful synthetic method.[67–69]

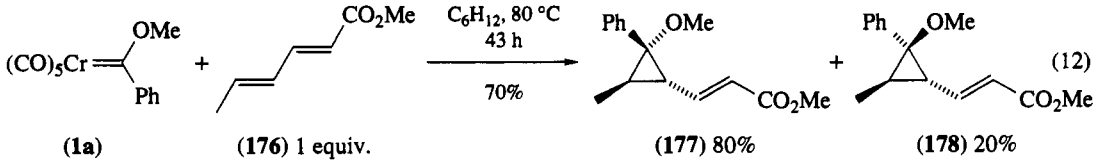
Efficient cyclopropanations of unactivated alkenes can also be achieved with cationic cyclopentadienyliron–carbene complexes and this area has been developed by Brookhart,[70] Casey[71] and Helquist.[72] Alkylation of the α-thioalkyl iron complex (**169**) generates the cationic carbene complex (**170**), which is not observed, but presumably very rapidly cyclopropanates the unactivated alkene to give the tricyclic compound (**171**) as a single diastereomer.[73] Optically active cyclopropanes can be obtained by asymmetric induction from the iron center by employing carbene complex precursors of the type (**172**), in which the iron center was resolved with the aid of a chiral phosphine ligand in place of one of the two carbon monoxide ligands.[74] The carbene complex (**173**) was generated in the presence of styrene and very rapidly led to the formation of the cyclopropanes (**174**) and (**175**). This reaction was not particularly selective with regard to the formation of diastereomers, but each was formed with reasonably high optical purity.



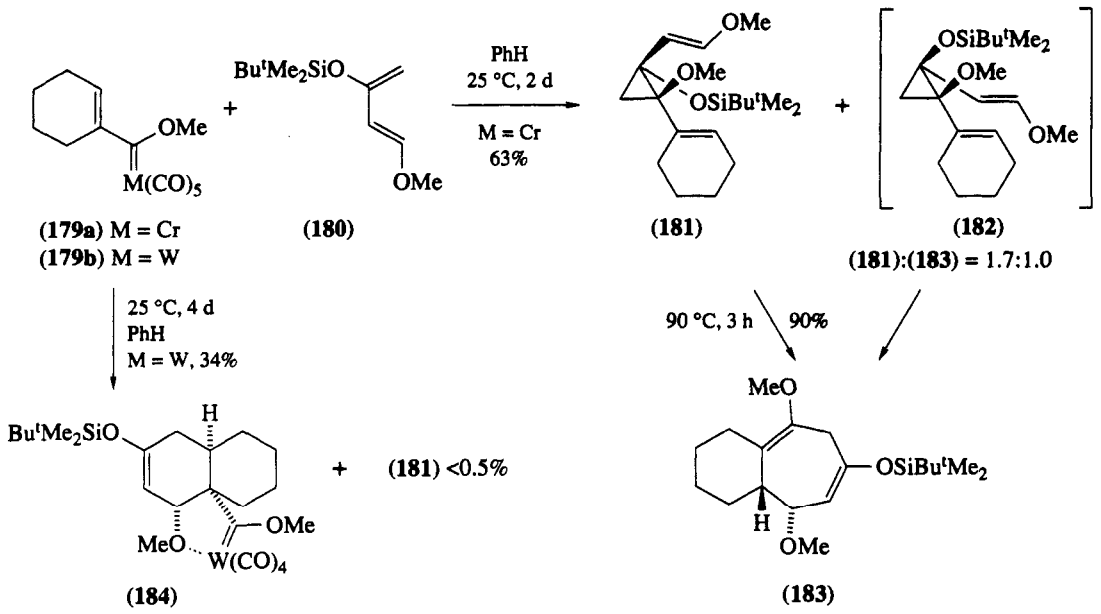
i, $(MeO)_3CBF_4$ (1.25 equiv.), CH_2Cl_2, 25 °C, 12 h;
ii, styrene (8 equiv.), Me_3SiOTf (1 equiv.), Et_3N (0.05 equiv.), CH_2Cl_2, −78 to 25 °C

Scheme 26

In a recent development, it has been found that the cyclopropanations of electron-deficient alkenes with heteroatom-stabilized complexes, such as (**1a**), need not be carried out with the alkene as solvent (as are the reactions in Scheme 24), but in fact better yields are obtained if the reaction is performed stoichiometrically in cyclohexane.[75,76] A variety of different electron-deficient alkenes were examined including the dienyl ester (**176**) which gave a 4:1 mixture of diastereomers in 70% total yield. This report should stimulate a reconsideration of the potential of these reactions for synthetic organic applications.



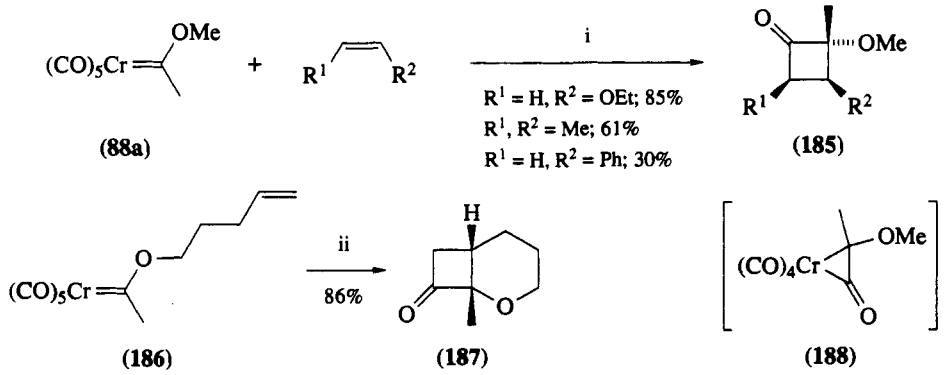
The cyclopropanation reaction has been extended to electron-rich dienes with the recent report of the reactions shown in Scheme 27.[22] The carbene complex in this reaction was the cyclohexenyl chromium complex (**179a**) and the resulting products from its reaction with the diene (**180**) were found to be the *trans*-divinylcyclopropane (**181**) and the seven-membered dienol ether (**183**). The latter presumably results from the Cope rearrangement of the initially formed *cis*-divinylcyclopropane (**182**) and the stereoselectivity of the cyclopropanation is 1.7:1.0. The *trans*-divinylcyclopropane (**181**) can thermally be converted to the same diastereomer (**183**) and thus this tandem cyclopropanation–Cope sequence should have potential for the construction of highly functionalized seven-membered rings. Although the reasons for it are unknown at this time, it was observed that the analogous reaction of the tungsten complex (**179b**) did not give cyclopropanation products, but rather the Diels–Alder adduct (**184**).



Scheme 27

9.2.3.1.2 Four-membered rings via *[2 + 1 + 1] cycloadditions: cyclobutanones*

In a recent publication in 1989, Sierra and Hegedus reported that cyclobutanones can be obtained from the photolysis of Fischer carbene complexes in the presence of alkenes.[77] The cyclobutanones are produced as a single diastereomer and a single regioisomer in high yields. A few of the examples from this report are presented in Scheme 28. Electron-rich alkenes give high yields of cyclobutanones as a single regioisomer, unactivated alkenes also work well and react with retention of stereochemistry, as illustrated in the case of *cis*-2-butene. The yield with styrene falls off, and electron-deficient alkenes such as methyl acrylate and acrylonitrile fail. The intramolecular reaction of the carbene complex (**186**) is most successful if the reaction is carried out under an atmosphere of carbon monoxide. The first step of this reaction is thought to involve a photo-induced insertion of carbon monoxide to give the ketene complex (**188**). It is suspected that the cyclobutanones are a result of the reaction of the ketene complex (**188**) with the alkenes rather than the result of a [2 + 2] cycloaddition of the alkene with a metal-free ketene, but at this time this issue cannot be resolved. This method for the generation of cyclobutanones is clearly superior in terms of yields and reaction conditions to the traditional [2 + 2] cycloaddition of alkenes and alkoxyketenes generated from acid halides.

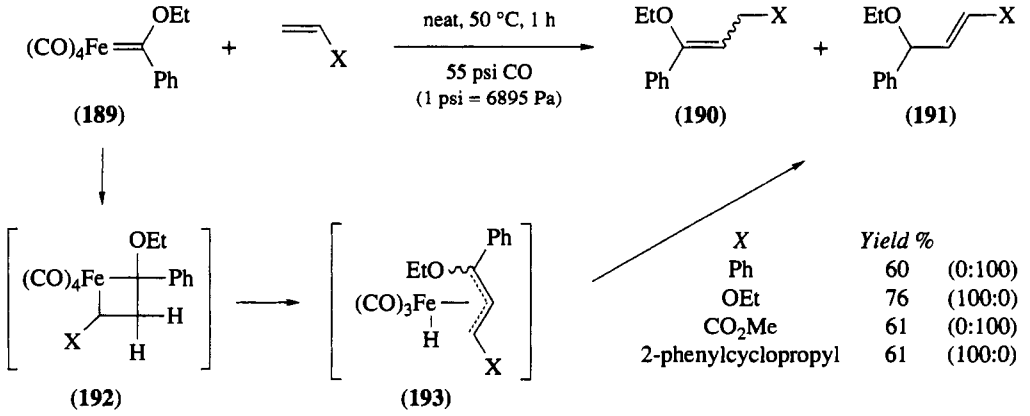


i, *hν*, MeCN, 15 h, 25 °C; ii, same as i except the reaction was carried out under CO

Scheme 28

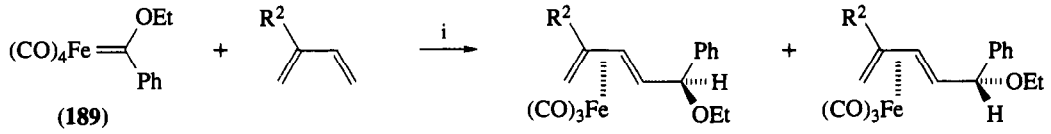
9.2.3.1.3 Coupling leading to acyclic products

The reaction of carbene complexes with alkenes generally leads to cyclopropane formation or to metathesis; however, in the reactions of the iron carbene complexes (**189**) with alkenes a new mode of reactivity was uncovered.[78] The reactions of (**189**) with a variety of alkenes lead to the acyclic coupling products (**190**) and (**191**). These products are thought to arise from a β-hydride elimination in the ferracyclobutane intermediate (**192**) and a subsequent reductive elimination from the allyl complex (**193**), which can occur in either of two directions to give (**190**) or (**191**). The regiochemistry of the incorporation of the alkene into the ferracyclobutane is independent of the nature of the alkene. The regioselectivity in the formation of (**192**) is consistent with a steric consideration or with a two-step mechanism involving a diradical intermediate, but not a two-step mechanism involving a zwitterionic intermediate. The present view is that steric effects lead to the stereoselective formation of (**192**), since an alkene with a cyclopropyl substituent is converted to the coupling products (**190**) with the cyclopropyl ring intact.

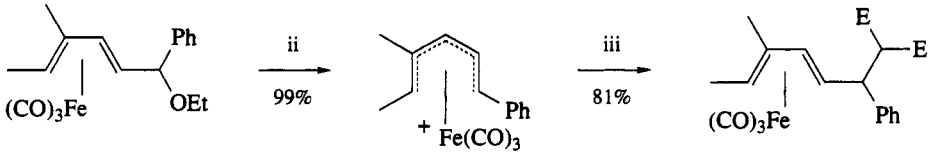


Scheme 29

A similar type of reaction has been observed in the reactions of iron–carbene complexes with 1,3-dienes.[79] In this case the direction of reductive elimination in the metal hydride intermediate corresponding to (**193**) is constrained to that which generates a conjugated 1,3-diene; however, two isomeric products are also obtained from this reaction which are epimers about the face of the diene to which the iron tricarbonyl group is attached. This reaction produces highly functionalized 1,3-dienyl complexes of iron in high yield under relatively mild conditions and will likely play a role in the development of the



R^2	Yield (%)	(194) *endo*	(195) *exo*
H	68	75	25
Me	90	67	33
OMe	87	75	25



i, hexane, 25 °C, 0.5–10 h; ii, $HClO_4$, Ac_2O, 0 °C; iii, diethyl sodiomalonate, 25 °C

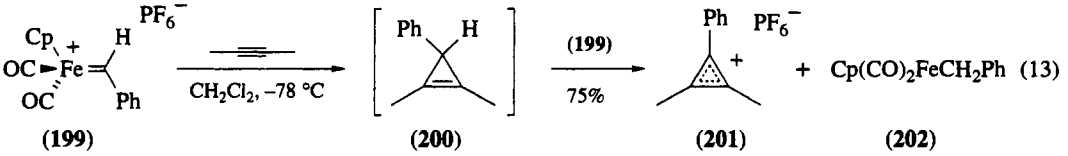
Scheme 30

chemistry of 1,3-dienyl complexes of iron. This is illustrated in Scheme 30 with the generation of the cationic η^5-dienyl complex (**197**) by the treatment of (**196**) with acid. Although the chemistry of cyclic η^5-dienyl complexes of iron has been explored by a number of groups for two decades, the chemistry of acyclic complexes of the type (**197**) is essentially undeveloped. In one of the few examples of nucleophilic addition to such complexes, the 1,3-dienyl complex (**198**) can be obtained in 81% yield from the addition of diethyl sodiomalonate to (**197**).

9.2.3.2 Coupling of the Carbene Ligand with Alkynes

9.2.3.2.1 Three-membered rings via *[2 + 1] cycloadditions: cyclopropenes*

The reaction of alkenes with Fischer carbene complexes most typically leads to cyclopropane products; however, the formation of a three-membered ring product from a reaction with an alkyne has been observed on only one occasion.[80] The reaction of the cationic iron–carbene complex (**199**) with 2-butyne presumably leads to the formation of the cyclopropene (**200**), which was unstable with respect to hydride abstraction by the starting carbene complex and the ultimate product isolated from this reaction was the cyclopropenium salt (**201**) and the benzyl–iron complex (**202**). Cyclopropene products have never been observed from Group 6 carbene complexes despite the extensive investigations of these complexes with alkynes that have been carried out since the mid 1970s.

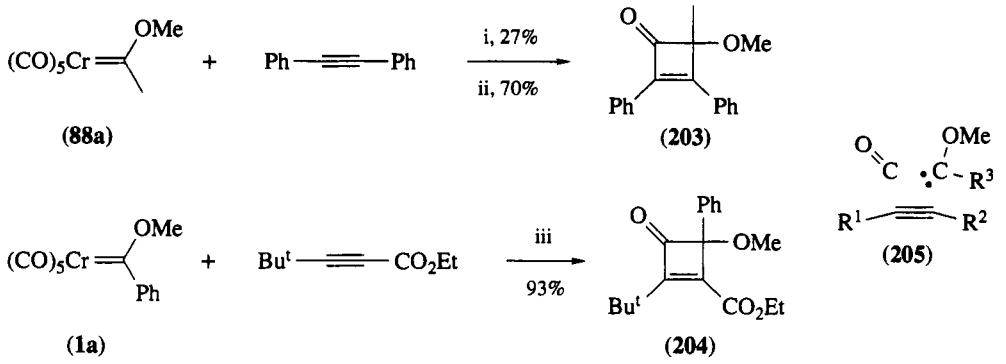


(**199**) (**200**) (**201**) (**202**)

9.2.3.2.2 Four-membered rings via *[2 + 1 + 1] cycloadditions: cyclobutenones*

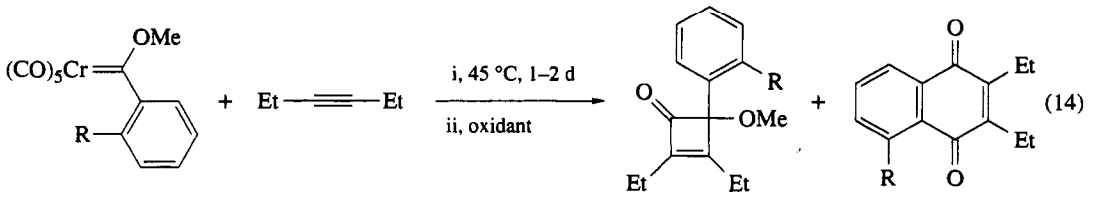
The reactions of Group 6 carbene complexes with alkynes has been studied extensively since the mid 1970s, and normally these reactions produce six-membered ring products, but in a dozen or so instances cyclobutenone products have been observed.[81,82] In most cases cyclobutenones were minor products from these reactions, but in a few cases where circumstances were favorable they were the major products of the reaction. Cyclobutenone formation is the result of the assembly of the pieces indicated diagramatically in (**205**). A mechanistic discussion of their formation will be deferred until Section 9.2.3.2.4 The first report of a cyclobutenone was by Dötz who found that the reaction of the methyl complex (**88a**) with diphenylacetylene produced cyclobutenone (**203**) as an aryl chromium tricarbonyl complex (coordinated to one of the phenyl groups) in 27% yield.[83] It was later found that the yield of (**203**) (as the metal-free cyclobutenone) could be increased to 70% if the reaction was carried out in the presence of 1 equiv. of triphenylphosphine.[84] This reaction is not general, as it was found that cyclobutenones are not produced in this reaction with terminal alkynes or with internal alkynes, such as 3-hexyne, that are not as sterically encumbered as diphenylacetylene.[84] That sterically bulky substituents on the alkyne favor cyclobutenone formation can be seen in the example from the work of Yamashita of the reaction of complex (**1a**) with ethyl *t*-butylpropynate, which gives (**204**) in 93% yield, whereas the same reaction with ethyl phenylpropynate does not give any cyclobutenone.[85]

The formation of cyclobutenones is also affected by solvent and internal chelating groups, as indicated by the reactions in equation (14).[86,87] As indicated by the first two reactions, cyclobutenone formation is favored in the more polar solvent. The third and fourth reactions indicate that cyclobutenone formation is also favored by the presence of an oxygen substituent that can chelate to the metal center during the reaction. These observations, however, are not general. For example, the quinone products (to be discussed in Section 9.2.3.2.4i) are formed in high yield from the reaction of complexes of the type (**206**, R = H and R = OMe) with terminal alkynes in both THF and acetonitrile. Although dependence of cyclobutenone formation on chelation in complexes of the type (**206**) is consistent with the observed effect of triphenylphosphine on the reaction of complex (**1a**), the reaction of the (**206**, R = H) is unaffected by the presence of triphenylphosphine. At this point in time, the reactions of carbene complexes with alkynes cannot be employed as a general approach to the synthesis of cyclobutenones.



i, Bu^n_2O, 70 °C, 1 h; ii, THF, 1 equiv. Ph_3P, 80 °C, 24 h; iii, THF, 65 °C, 6 h

Scheme 31



R	*Solvent*	*Oxidant*	*Yield* (%)	*Yield* (%)
H	THF	Ce^{IV}	<2	88
H	MeCN	Fe^{III}	23	38
o-OMe	MeCN	air	43	<2
o-OBu^t	MeCN	Fe^{III}	23	24

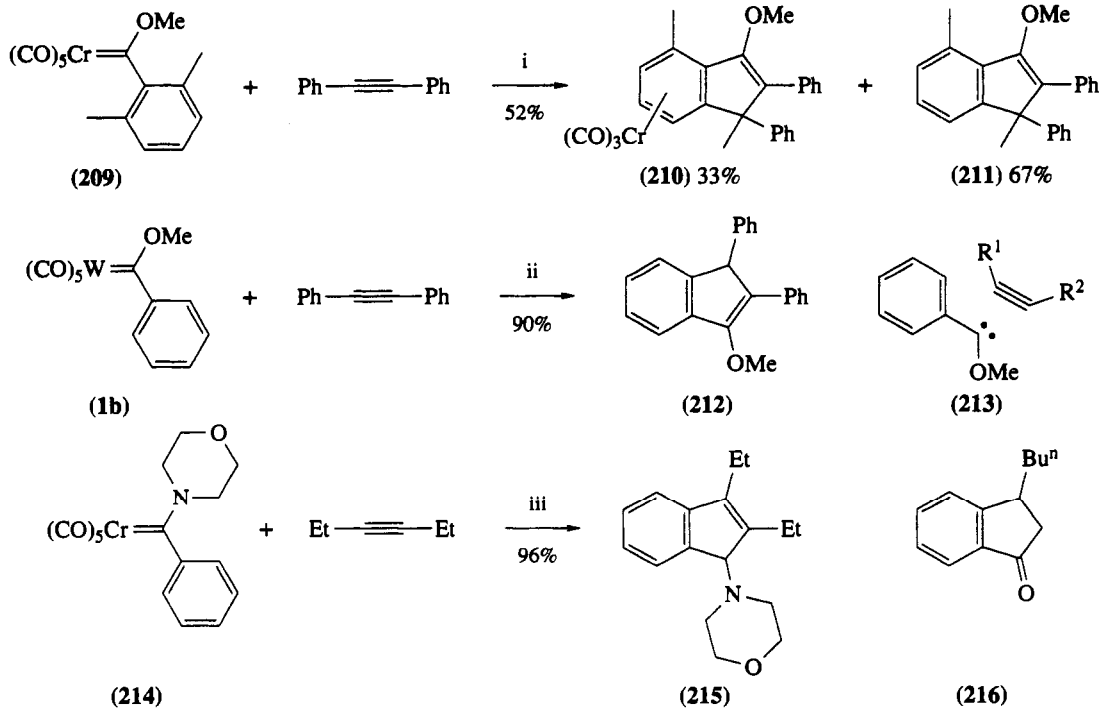
9.2.3.2.3 Five-membered rings

(i) [3 + 2] Cycloadditions—cyclopentadienes and indenes

In almost all situations the reactions of Fischer carbene complexes of chromium with alkynes lead to the formation of six-membered ring products, but on several occasions five-membered ring annulated products have been observed as minor products or as major products if the formation of six-membered rings is blocked.[81] In an early report by Dötz, the reaction of the 2,6-dimethylphenyl complex (**209**) was observed to react with diphenylacetylene to give the complexed and uncomplexed indenes (**210**) and (**211**).[88] This reaction is not general; if one or two of the methyl groups are removed from complex (**209**) only six-membered ring products are observed and these reactions will be discussed in Section 9.2.3.2.4i. These annulations occur with cyclization to the aryl substituent of the carbene carbon, the overall transformation is represented by the assembly of the pieces indicated diagramatically by structure (**213**), and a mechanistic consideration of this reaction will be presented in Section 9.2.3.2.4.

While unsubstituted aryl complexes of chromium react with alkynes to give six-membered ring products, the tungsten carbene complex (**1b**) was reported to react with diphenylacetylene to give the indene (**212**) in 90% yield.[89] This reaction with tungsten complexes was reported to fail with terminal alkynes and sterically less encumbered disubstituted alkynes. This was attributed to competing polymerization of the alkyne, although this can be offset in many cases if the reactions are carried out at low concentrations.[90] It was reported that five-membered annulation is favored by polar coordinating solvents,[86,87] and Yamashita found that carbene complexes bearing an amino ancilliary substituent, such as (**214**), undergo reactions with alkynes in DMF to exclusively give five-membered ring annulated products.[91] This reaction is general for aryl complexes with both disubstituted and terminal alkynes; (**216**) is obtained from the reaction of (**214**) and 1-hexyne in 95% yield.

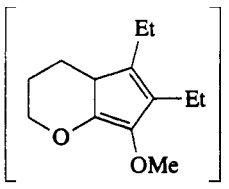
The five-membered annulation of amino complexes appears not to be general for alkenyl complexes. The reaction of the morpholino complex analogous to (**217**) with 3-hexyne in DMF gives a low yield



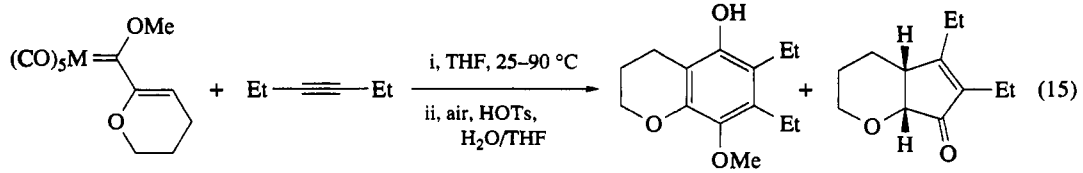
i, *n*-butyl ether, 100 °C, 2 h; ii, toluene, 100 °C, 3 h; iii, DMF, 125 °C, 5 h

Scheme 32

(<10%) of a mixture of compounds that has not yet been identified.[90] The reactions comparing the three Group 6 metals indicated in equation (15) include the first examples of the annulation of a molybdenum–carbene complex.[90] In contrast to the aryl tungsten complex (**1b**), the alkenyl tungsten complex (**219**) (as well as the chromium complex **217**) gives only the six-membered ring annulated product (**220**) with 3-hexyne. The molybdenum complex (**218**), however, gives the five-membered ring annulated product (**221**) as the major product of the reaction. The enone (**221**) is the result of the acid hydrolysis of the primary product of the reaction, which is presumably the cyclopentadiene (**222**) or isomers thereof. This is the first example of the formation of a five-membered ring annulated product from the reaction of an alkenyl carbene complex and should stimulate further investigations of the chemistry of molybdenum–carbene complexes.



(**222**)

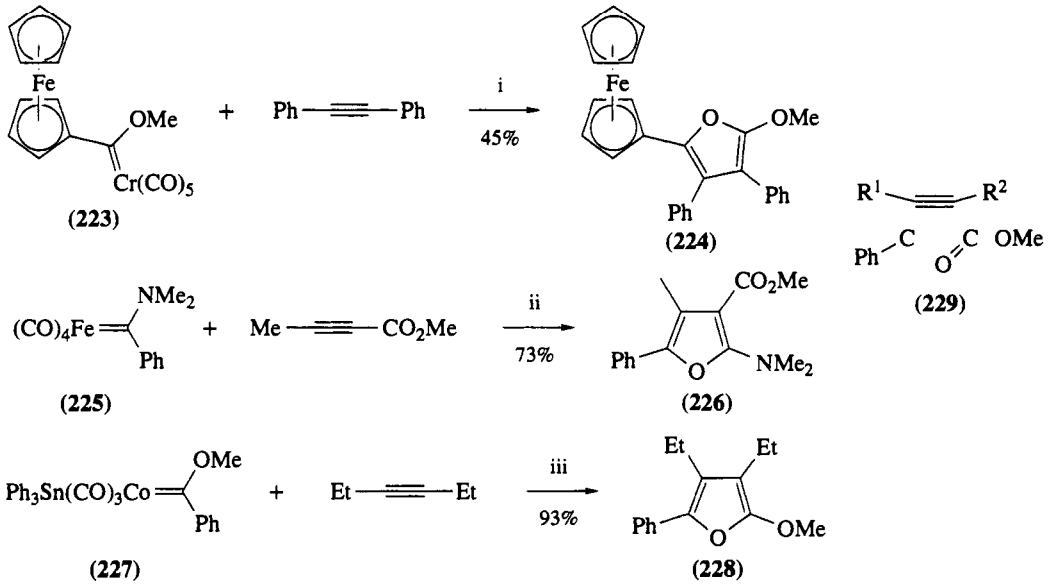


(15)

Complex	*M*	*Yield* (%)	(**220**)	(**221**)
(**217**)	Cr	73	>99%	<1%
(**218**)	Mo	67	12%	88%
(**219**)	W	77	>98%	<2%

(ii) [2 + 2 + 1] Cycloadditions: furans

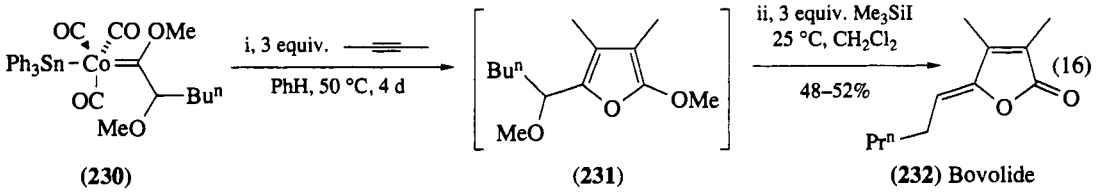
As is the case with cyclobutenones and five-membered annulation products, furans are usually only observed as minor products in the reaction of chromium–carbene complexes and alkynes, and have only been observed in a few instances.[81] One exception is the reaction of the ferrocenyl carbene complex (**223**) with diphenylacetylene for which the furan (**224**) was reported as the only product.[92] The reactions of carbene complexes of other metals with alkynes have been more recently found to display higher selectivity for the formation of furan products. Iron amino carbene complexes of the type (**225**) will react with a variety of alkynes to give furans as either the major or exclusive product.[93] The reaction of (**225**) with methyl tetrolate gives exclusively the aminofuran (**226**) as a single regioisomer. Other alkynes give varying amounts of pyrone and two-alkyne annulation products along with the furans. Cobalt–carbene complexes of the type (**227**) give exclusively furan products with all of the alkynes that were examined.[94] The furan nucleus is constructed from the pieces indicated diagramatically in (**229**) and the mechanism will be briefly presented in Section 9.2.3.2.4i. The connectivity indicated in the assembly (**229**) was determined by two labeling experiments, and the reader is referred to the original report for a discussion of these experiments.[82]



i, Bu^n_2O, 80 °C, 4 h; ii, $ClCH_2CH_2Cl$, 60 °C, 1 h; iii, PhH, 50 °C, 6 h

Scheme 33

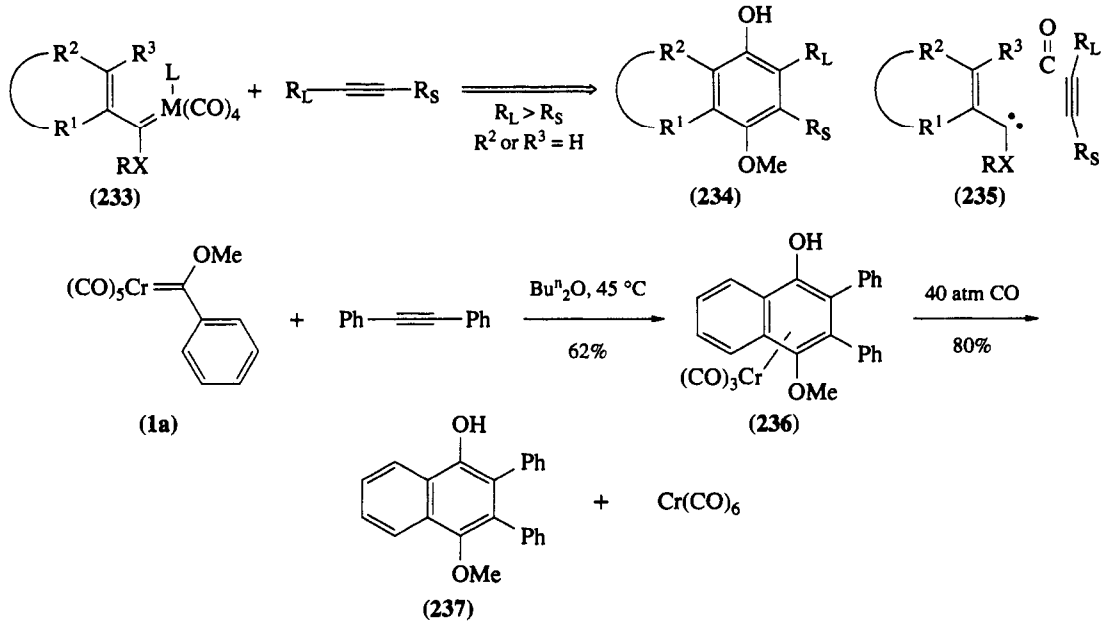
The high selectivity of the reaction of cobalt–carbene complexes with alkynes for furan products was taken advantage of in the synthesis of bovolide, a natural flavor constituent of butter.[94] The carbene complex (**230**) was prepared in two steps from *n*-pentanal and was treated with 3 equiv. of 2-butyne. The crude reaction mixture, which presumably contained the furan (**231**), was treated directly with 3 equiv. of trimethylsilyl iodide to give bovolide in ~ 50% yield from carbene complex (**230**).



9.2.3.2.4 Six-membered rings

(i) [3 + 2 + 1] Cycloadditions; benzannulation and cyclohexadienone annulation

With the possible exception of the cyclopropanation of alkenes, the most thoroughly examined reaction of Fischer carbene complexes is that with alkynes.[1–3] The reactions in this class that have been of most interest to date are those that lead to six-membered ring 4-alkoxyphenols of the general type (**234**). This reaction is a benzannulation, in which the newly formed benzene ring is generated in the coordination sphere of the metal under neutral conditions at near ambient temperatures from the pieces indicated diagramatically in (**235**). This benzannulation reaction produces new benzene rings that have a 1,4-dioxygen substitution pattern and it is for perhaps this reason that it is the most extensively applied reaction of carbene complexes in organic synthesis.

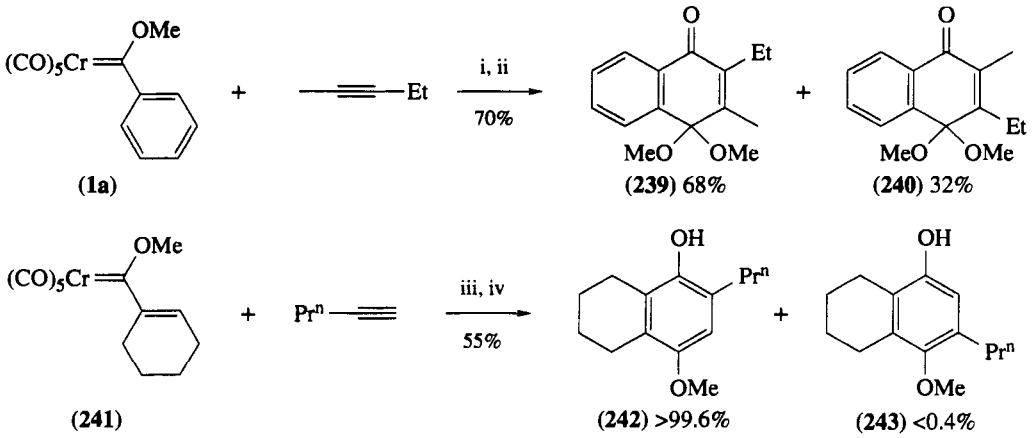


Scheme 34

A comprehensive treatment of the benzannulation of Fischer carbene complexes with alkynes is not possible in this review, and thus instead the material presented here will hopefully serve to give the reader an overview of its scope and limitations. The first report of this reaction was in 1975 by Dötz in which he describes the formation of the naphthol chromium tricarbonyl complex (**236**) from the reaction of the phenyl chromium complex (**1a**) with diphenylacetylene.[95] In the intervening years over 100 papers have been published describing various aspects of this reaction.[1–3] The reaction of the generic carbene complex (**233**; Scheme 34) with alkynes will serve to focus the organization of the scope and limitations of the benzannulation reaction. The issues to be considered are: (i) the regioselectivity with unsymmetrical alkynes; (ii) possible mechanisms; (iii) applications in natural product syntheses; (iv) the effect of substitution on the aryl or alkenyl substituent of the carbene carbon; (v) functionality on the alkyne; (vi) effects of the solvent and the concentration of the alkyne; (vii) tandem applications with other reactions of carbene complexes; (viii) reactions where aromatization is blocked (cyclohexadienone annulation); (ix) annulation of aryl *versus* alkenyl carbene complexes; (x) the effect of the ligands L on the metal; (xi) the effect of the ancilliary substituent RX; and (xii) reactions with —C≡X functionality.

(a) Regiochemistry of alkyne incorporation. All of the studies in the literature suggest that the regioselectivity of the incorporation of an unsymmetrical alkyne is determined by the steric differences of the alkyne substituents and not by their electronic differences.[3,96] The regioselectivity with unsymmetrical disubstituted alkynes is low for alkenyl complexes as well as for aryl complexes, as indicated by the the reaction of complex (**1a**) with 2-pentyne.[97] The major isomer is always that in which the sterically larger group is incorporated adjacent to the phenol functionality. This lack of regiocontrol for unsymmetrical disubstituted alkynes can be overcome in intramolecular annulations in which the alkyne is tethered to

the ancillary substituent RX (**233**; Scheme 34) and in this manner regioselective syntheses of deoxyfrenolicin (**263**),[98,115] nanaomycin (**264**),[98,115] angelicin (**271**)[99] and sphondin (**272**)[99] were possible (Scheme 37). The benzannulations of both aryl and alkenyl complexes are highly regioselective with terminal alkynes and in the case of the reaction of (**241**) with 1-pentyne this was greater than 250:1.[3]



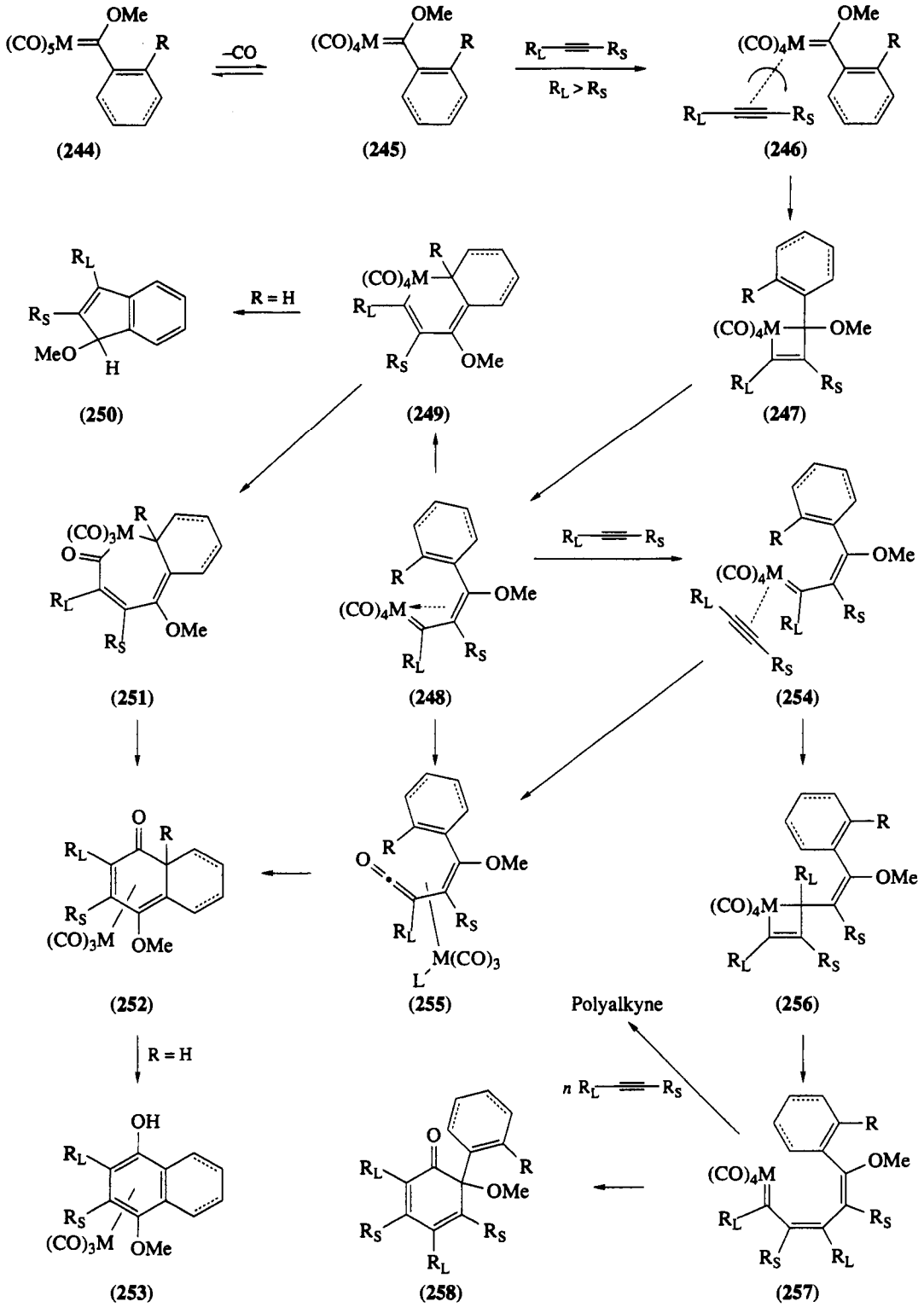
i, Bu^n_2O, 45 °C, 24 h; ii, $Ce(NO_3)_6(NH_4)_2$, methanol, 25 °C, 30 min;
iii, THF, 45 °C, 24 h; iv, $FeCl_3$–DMF, THF, 25 °C, 30 min

Scheme 35

(b) Mechanistic considerations. A consideration of all of the mechanistic possibilities for all of the nine known structural types[81] from the reactions of Fischer carbene complexes with alkynes is not possible in this review.[1d,3,82,87,100] The mechanistic possibilities presented in Scheme 36 are for the formation of the five-membered ring annulated product (**250**),[101] the benzannulated product (**253**), the two-alkyne-annulated product (**258**)[102] and polyalkyne.[103] With regard to the mechanism for the formation of the six-membered benzannulated product (**253**) there are two mechanisms that have been proposed, neither of which can be ruled out on the basis of existing data. The kinetics of the reaction suggest that the first step is the dissociation of a carbon monoxide ligand to generate the unsaturated intermediate (**245**).[100a] This step is thought to be the rate-limiting step in most situations and all subsequent steps are then fast, which is consistent with the fact that none of the intermediates indicated in Scheme 36 have been isolated from these reactions where M is chromium. The vinyl ketene complex (**255**) has been isolated when M is cobalt[94] and vinyl ketenes have been trapped[81] or isolated where the metal is displaced from the vinyl ketene functionality.[81]

The second step is proposed to involve the addition of the alkyne to give the alkyne complex (**246**). The next step involves carbon–carbon bond formation between the carbene carbon and one of the alkyne carbons and it is this step which may determine the regioselectivity of the reaction. The regioselectivity can be accounted for by a consideration of the most stable conformer of the alkyne complex (**246**) on the basis of steric interactions; this should be that which has the smallest substituent adjacent to the carbene ligand and the largest substituent adjacent to the *trans* carbon monoxide ligand. Electrocyclic ring opening of (**247**) would generate the vinyl carbene complex intermediate (**248**), which is the branch point between the two mechanisms that have been proposed for the formation of the benzannulated product (**253**).[1d,100]

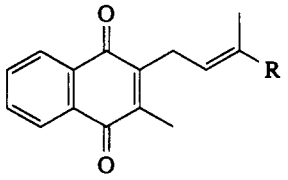
The mechanism proposed by Dötz involves the insertion of a carbon monoxide into the vinyl carbene complex intermediate with the formation of the vinyl ketene complex (**255**).[100a] Electrocyclic ring closure of (**255**) leads to the cyclohexadienone complex (**252**), which is related to the final benzannulation product by a tautomerization when R is hydrogen. The mechanism proposed by Casey differs from that of Dötz in that the order of the steps involving carbon monoxide insertion and cyclization to the aryl or alkenyl substituent is reversed.[1d] Specifically, the vinyl carbene complex intermediate (**248**) first undergoes cyclization to the metallacyclohexadiene (**249**), followed by carbon monoxide insertion to give the intermediate (**251**), and finally reductive elimination to give cyclohexadienone intermediate (**252**). At this time the circumstantial evidence favors the intermediacy of vinyl ketene intermediates since they can be trapped from these reactions[81] and isolated where the metal is dispaced from the vinyl ketene functionality;[81] however, there is not any evidence which can rule out the alternative mechanism.



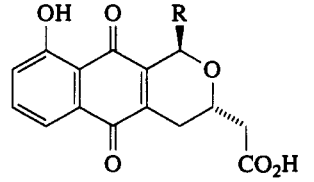
Scheme 36

(c) Applications in natural product synthesis. The applications of the benzannulation of Fischer carbene complexes to natural product synthesis is too extensive to review comprehensively here. Those targets which have been realized in either formal or total synthesis are listed in Scheme 37 and they include the total syntheses of vitamins $K_{1(20)}$, $K_{2(5)}$, $K_{2(10)}$ and $K_{2(15)}$,[104] the total synthesis of vitamin E,[105] the

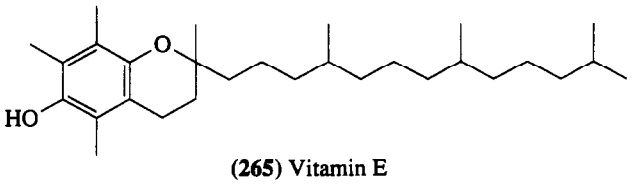
total syntheses of deoxyfrenolicin and nanaomycin,[98] the total synthesis of 7-ethoxyprecocene,[106] the total synthesis of khellin,[107] the total syntheses of angelicin, sphondin, heratomin and thiosphondin,[99] and formal syntheses of 4-demethoxydaunomycinone, daunomycinone and 11-deoxydaunomycinone.[3,108,109]



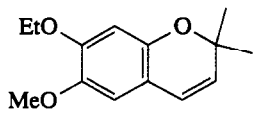
(**259**) $K_{1(20)}$ R = $(CH_2CH_2CH_2CHMe)_3Me$
(**260**) $K_{2(5)}$ R = Me
(**261**) $K_{2(10)}$ R = $CH_2CH_2CHCMe_2$
(**262**) $K_{2(15)}$ R = $(CH_2CH_2CHMe)_2Me$



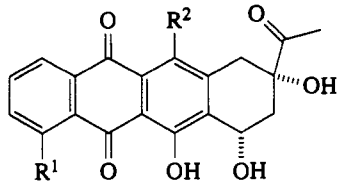
(**263**) Deoxyfrenolicin; R = Pr^n
(**264**) Nanaomycin; R = Me



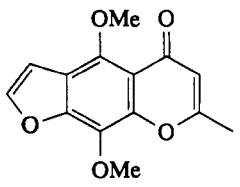
(**265**) Vitamin E



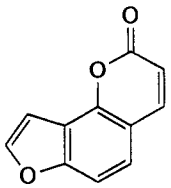
(**266**) 7-Ethoxyprecocene



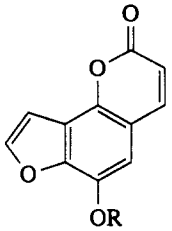
(**267**) 4-Demethoxydaunomycinone; R^1 = H, R^2 = OH
(**268**) Daunomycinone; R^1 = OMe, R^2 = OH
(**269**) 11-Deoxydaunomycinone; R^1 = OMe, R^2 = H



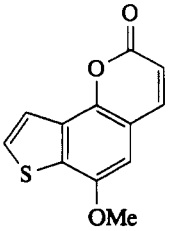
(**270**) Khellin



(**271**) Angelicin



(**272**) Sphondin; R = Me
(**273**) Heratomin; R = CH_2CHMe_2

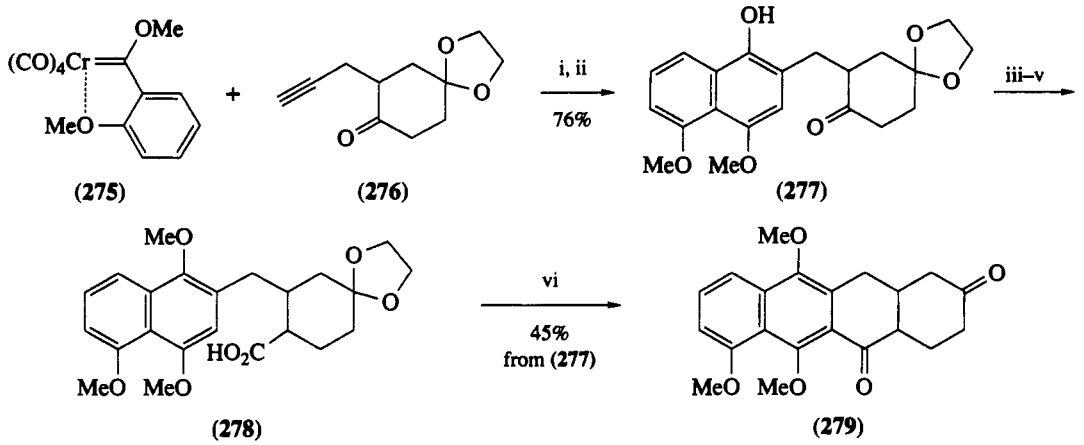


(**274**) Thiosphondin

Scheme 37

The two syntheses of 11-deoxydaunomycinone are summarized in Schemes 38 and 39 as they are illustrative of the viability of carbene complexes as intermediates in organic synthesis. The synthesis by Dötz and Popall begins with the chelated *o*-methoxyphenyl carbene complex (**275**)[124,127] and the alkyne (**276**).[109d,e] A single regioisomer of the phenol (**277**) was obtained in 76% yield in the benzannulation. After protection of the phenol and carbon homologation of the ketone to the acid, an intramolecular Friedel–Crafts reaction gave the tetracyclic dione (**279**) in 45% overall yield from (**277**). This represents a formal synthesis of 11-deoxydaunomycinone (**269**) since it has been reported that (**279**) can be converted to (**269**) by the procedures of Sih[110] and Johnson.[111]

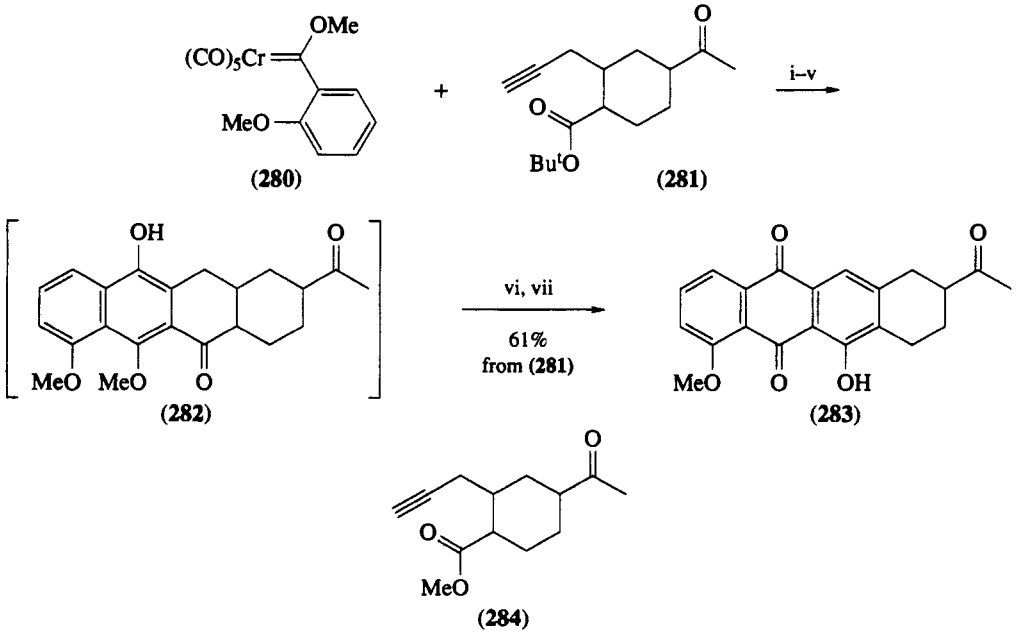
The synthesis of 11-deoxydaunomycinone by Wulff and Xu is presented in Scheme 39 and involves the benzannulation of the non-chelated *o*-methoxyphenyl complex (**280**) with the alkyne (**281**).[108c] The utilization of a *t*-butyl ester in the alkyne (**281**) makes possible a one-pot construction of the tetracyclic dione (**282**) *via* a tandem benzannulation–Friedel–Crafts cyclization. After the reaction between the



i, Bu^{t}OMe, 40 °C, 1 h; ii, CH_2Cl_2, 75 bar CO (1 bar = 100 kPa), 70 °C, 72 h; iii, CH_2N_2 (excess); iv, $TosCH_2NC$, KOBu^t, THF, –10 °C; v, HOAc; vi, TFA, TFAA, 0 °C

Scheme 38

complex (**280**) and alkyne (**281**) is complete, the reaction is opened to air for 10 min to allow for the oxidative removal of the chromium tricarbonyl group, and then is diluted with trifluoroacetic anhydride containing a small of amount of sodium acetate to protect the phenol. After 10 min, the mixture is again diluted with trifluoroacetic acid to effect cleavage of the *t*-butyl ester and the Friedel–Crafts cyclization which yields, after base work-up to deprotect the phenol, the tetracyclic dione (**282**) in 56% yield. If (**282**) is not purified, but oxidized directly, the anthracyclinone (**283**) can be obtained to 61% overall yield from alkyne (**281**). A slightly higher overall yield of (**283**) can be obtained if the reaction is carried out with the alkyne (**284**) containing a methyl ester (since **281** is prepared from **284**); however, the convenience of a one-pot reaction is lost since it is not possible to cleave the methyl ester and simultaneously effect the Friedel–Crafts closure. No difference in the yield for the benzannulation step was noted between the reactions of (**284**) and either (**280**) or (**275**).

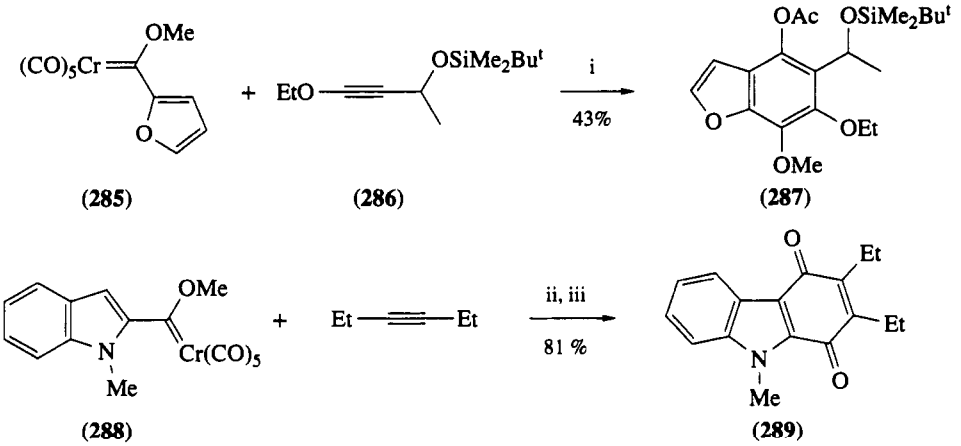


i, PhH, 75 °C, 12 h; ii, air, 10 min, 25 °C; iii, $(CF_3CO)_2O$, NaOAc, 10 min; iv, CF_3CO_2H, 1.5 h, 25 °C; v, aq. NaOH; vi, AgO, HNO_3, acetone, 25 °C; vii, O_2, DMF, 100 °C, 3 h

Scheme 39

An appreciation of the value of carbene complexes in anthracycline synthesis can be obtained by comparing the two syntheses of 11-deoxydaunomycinone shown in Scheme 38 and 39 with the 20 other syntheses that do not involve transition metal reagents.[112–114] The overall yields for the 22 reported syntheses of 11-deoxydaunomycinone range from 0.05% to 9.7%. The overall yield for the synthesis of (**269**) according to Scheme 38 can be calculated to be 2.8% starting from cyclohexan-1,4-dione monoethylene acetal and including the five steps by Sih[110] and three steps by Johnson.[111] The overall yield for the synthesis of (**269**) according to Scheme 39 can be calculated to be 8.5% starting from methyl vinyl ketone and, including four steps by Johnson.[111] By this criteria, the synthesis in Scheme 39 ranks second out of 22 and clearly demonstrates the efficacy of carbene complexes as intermediates in organic synthesis.

(d) Functionality on the aryl and alkenyl substituent. Although not yet completely defined, the range of functionality on the aryl complex (**1a**) and the alkenyl complex (**233**; Scheme 34) that can be tolerated in the benzannulation reaction is beginning to be established. Benzannulations of aryl complexes of the type (**1a**) have been examined and found to be successful with *o*-methoxy,[87,96a,98,108c,d,109c,d,e] *m*-methoxy,[96a] *p*-methoxy,[87] *o*-*t*-butoxy,[87] *m*-methyl,[96a] *p*-methyl,[82,121,125] *m*-trifluoromethyl,[96a] *p*-trifluoromethyl[121] and *p*-chromium carbene complex[131] substituents. The annulations of diaryl complexes have been examined but the yields are not generally useful.[120] The annulations of naphthyl complexes have been examined[121,125] and have been employed in the synthesis of daunomycinone and 4-demethoxydaunomycinone.[109] The annulations of a number of heteroaryl complexes have been reported by Dötz, Yamashita and Wulff. These include complexes derived from furans,[128] thiophenes,[99,121,132] pyrroles,[118,119] pyrazoles[15] and indoles[117] and an example of the annulation of the latter is shown in Scheme 40. The annulation of the furyl complex (**285**) indicated in Scheme 40 was employed in the synthesis of khellin.[107]



i, THF, Ac_2O, NEt_3, 65 °C, 10 h; ii, THF, 50 °C, 24 h; iii, $Ce(NO_3)_6(NH_4)_2$, 25 °C, 30 min

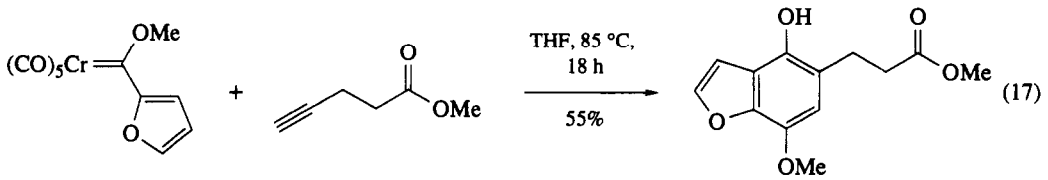
Scheme 40

The annulations of alkenyl complexes of the type (**233**; Scheme 34) have been examined mainly with alkyl substituents and in a few cases with oxygen[87,106,126] and silicon[108b,c] substituents in a variety of cyclic and noncyclic systems.[129] It is notable that the benzannulations of the parent vinyl complex of (**233**) (**42a**; Scheme 7) fail, which is apparently due to competing polymerization of (**42a**).[106] Annulations of complexes of the type (**233**) are successful if at least one of the three substituents is nonhydrogen. Benzannulations of alkenyl complexes have been employed in the synthesis of 7-ethoxyprecocene,[106] vitamin E[105,123] and daunomycinone.[108a–c]

(e) Functionality on the alkyne. Considerable progress has been made towards identifying the scope and nature of the functionality that can be present on the alkyne and tolerate the benzannulation reaction. The benzannulation reaction can give good yields with silyl groups[134] directly substituted on the alkyne carbon and gives lower yields with oxygen[135] and carbonyl groups[136] directly attached to the alkyne carbon. The reaction can give good to excellent yields with functionalized arylalkynes[96b,100a] and alkylalkynes bearing esters,[137] alkenes,[122,138] amides,[139] α-ethers,[140] lactones,[108a–c] sulfides,[99,130] enol

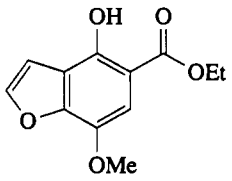
ethers,[106,108c] tosylates,[117] ketones,[108d,109c–e] nitriles[108c] and acetal groups[96c,107,109c,d] on the alkyl chain. Alkylalkynes bearing remote alcohol groups do give benzannulated products, but usually in competition with ketene trapping products.[82,125]

The benzannulation reaction has the advantage that a great range of functionality can be tolerated by the reaction. One major limitation involves alkynes with leaving groups alpha to the alkyne function (α-ethers[140]), where a competing pathway is *o*-quinone methide formation.[119] The competing pathway can often be overcome by carrying out the benzannulation reaction in the presence of triethylamine and acetic anhydride, such that the phenol functionality of the benzannulated product is trapped *in situ*.[118] Another major limitation involves the presence of carbonyl groups conjugated with the alkyne.[136] Benzannulation products can often be obtained from reactions of alkynes of this type, but the yields are usually reduced. The example in equation (17) is presented since the reactions of conjugated and non-conjugated esters have been carried out on the same complex. The reaction of (**285**) with methyl-4-pentynoate gives the phenol (**291**) in 55% yield and has been employed in the synthesis of sphondin and angelicin.[99] The reaction of the same complex with methyl propiolate only gives the annulated product (**292**) in 21% yield.[107]



(17)

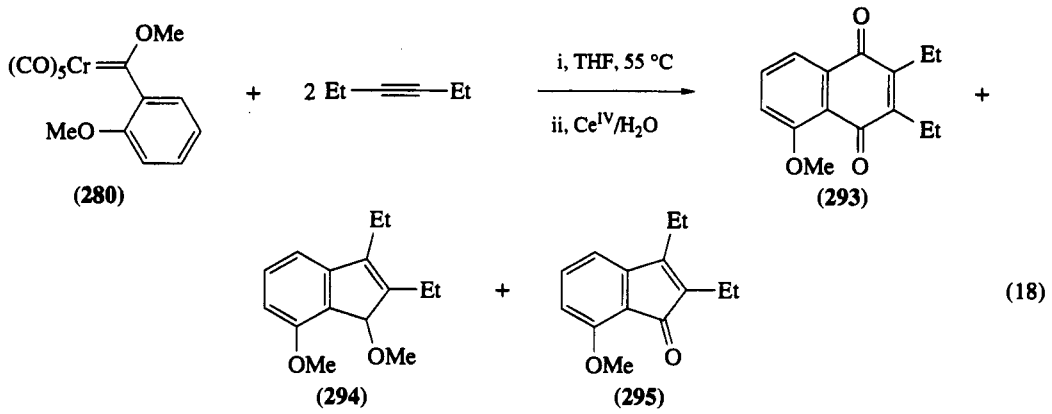
(**285**) (**290**) (**291**)



(**292**) 21%

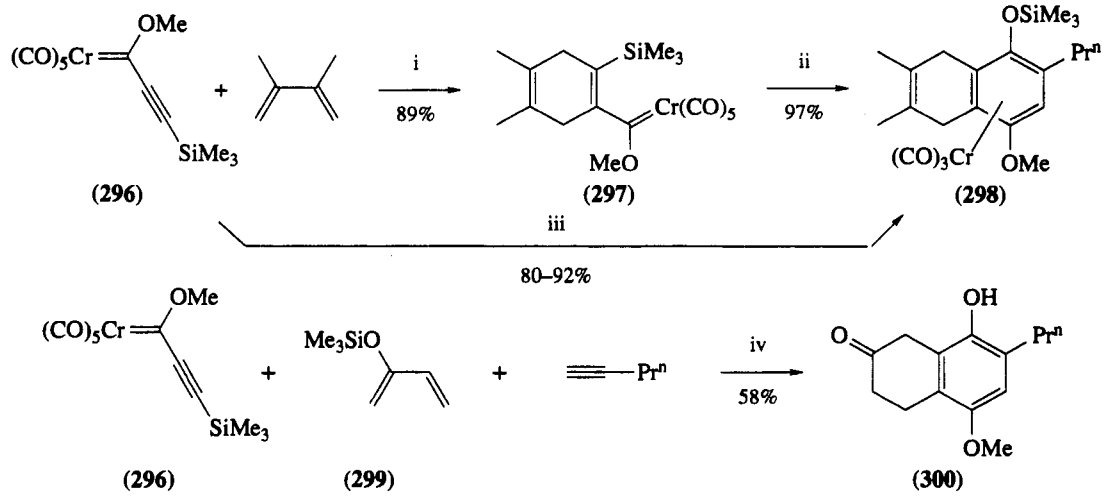
(f) Effects of the solvent and the concentration of the alkyne. The role of the solvent can be extremely important in determining the product distribution from the reaction of Fischer carbene complexes with alkynes. Early on it was thought that the reaction displayed its highest selectivity for benzannulated products in more polar solvents,[141] but subsequent studies have shown that it is highest in nonpolar solvents.[87] This is illustrated by the reaction in equation (18) for the reaction of the complex (**280**) with 3-hexyne in hexane and THF (see also equation 14 and Scheme 32).[87] The product distribution has also been found to depend in some cases on the concentration of the alkyne, as is illustrated for the reaction of (**280**) with 3-hexyne, where at 0.01 M in alkyne (0.005 M in **280**) the five-membered ring annulated products are the major products. An explanation for this phenomenon, termed the allochemical effect, is illustrated in Scheme 36 and has been proposed to be due to an increased rate of CO insertion as a result of the coordinated alkyne in intermediate (**254**).[87,90]

(g) Tandem Diels–Alder–benzannulation. The potential of the benzannulation reaction in organic synthesis can be enhanced when it is coupled with other reactions of carbene complexes and the tandem Diels–Alder–benzannulation sequence is particularly attractive in this regard.[3,15,24] The Diels–Alder reaction of the alkynyl carbene complex (**296**) with 2,3-dimethylbutadiene gives the alkenyl complex (**297**) in 89% yield after chromatography.[24] The benzannulation of (**297**) with 1-pentyne gives the trimethylsilyl-protected phenol–metal complex (**298**) in essentially quantitative yield. This tandem cycloaddition–annulation sequence can also be carried out concurrently. In the presence of both the diene and the alkyne, the carbene complex (**296**) chemoselectively reacts with the diene and the *in situ* generated Diels–Alder adduct (**297**) chemoselectively reacts with the alkyne. The tandem Diels–Alder–benzannulation sequence has been used in the preparation of an intermediate employed in the synthesis of daunomycinone (**268**; Scheme 37).[24]



(18)

Solvent	*[Alkyne]*	*Yield (%)*	*(293)*	*(294) + (295)*
hexane	0.3	83	100%	not determined
THF	1.0	84	73%	27%
THF	0.01	80	6%	94%

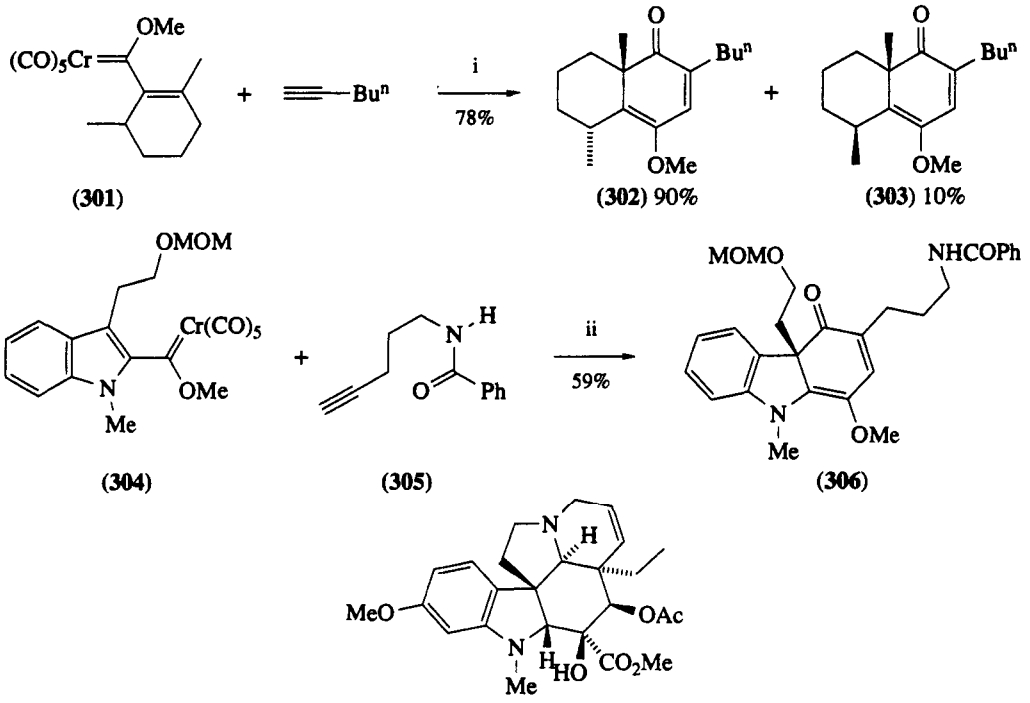


i, neat, 50 °C, 4 h; ii, 1-pentyne (1.5 equiv.), THF, 45 °C, 24 h; iii, 2,3-dimethyl-1,3-butadiene (excess), 1-pentyne (2 equiv.), THF, 50 °C, 60 h; iv, a) THF, 50 °C, 36 h; b) silica gel, air

Scheme 41

(h) Benzannulation where aromatization is blocked: cyclohexadienone annulation. Alkenyl carbene complexes in which the β-vinyl carbon is disubstituted produce cyclohexadienone products from reactions with alkynes.[142] In the case of the complex (**301**) which contains a chiral center there is significant asymmetric induction in the selective formation of the *trans*-decaladienone (**302**), which was greater than 90% for alkynes that were examined.[116] The formation of cyclohexadienone products occurs because the final step of the mechanism is thwarted: tautomerization of (**252**) in Scheme 36 is prevented when R is a group of low migratory ability. An additional example of the cyclohexadienone annulation is included in Scheme 42, which was recently reported as a potential new route for the synthesis of the *Aspidosperma* alkaloids.[117]

(i) Benzannulation of aryl versus *alkenyl complexes.* The reactions of alkynes with aryl (**1a**) or alkenyl complexes (**233**; Scheme 34) generally produce good to excellent yields of benzannulated products. There appears to be no significant difference in the type of functional groups they can tolerate. The annulations of alkenyl complexes seem to be less sensitive to the nature of the solvent.[87] With the excep-



i, THF, 45 °C, 24 h; ii, PhH, 50 °C, 17 h

Scheme 42

tion of the molybdenum complex[90] shown in equation (15) the formation of five-membered ring products and cyclobutenones has not been observed from the reaction of an alkyne and an alkenyl carbene complex. The cyclohexadienone annulation is also useful mainly for alkenyl complexes, the reactions of *ortho*-blocked aryl complexes generally give five-membered ring annulated products (Scheme 32), with the only known exception being the reactions of *ortho*-blocked indole carbene complexes (Scheme 42).[117]

(j) The effect of the ligand complement on the metal. Only two reports have appeared which describe the benzannulation of carbene complexes of the type (**233**) (alkenyl or aryl), in which the ligand complement is not pentacarbonyl.[43,120] In both reports it was observed that if one of the carbon monoxides is replaced by a phosphine that the reaction gives the same products but generally in lower yields. Further investigations are warranted in this area.

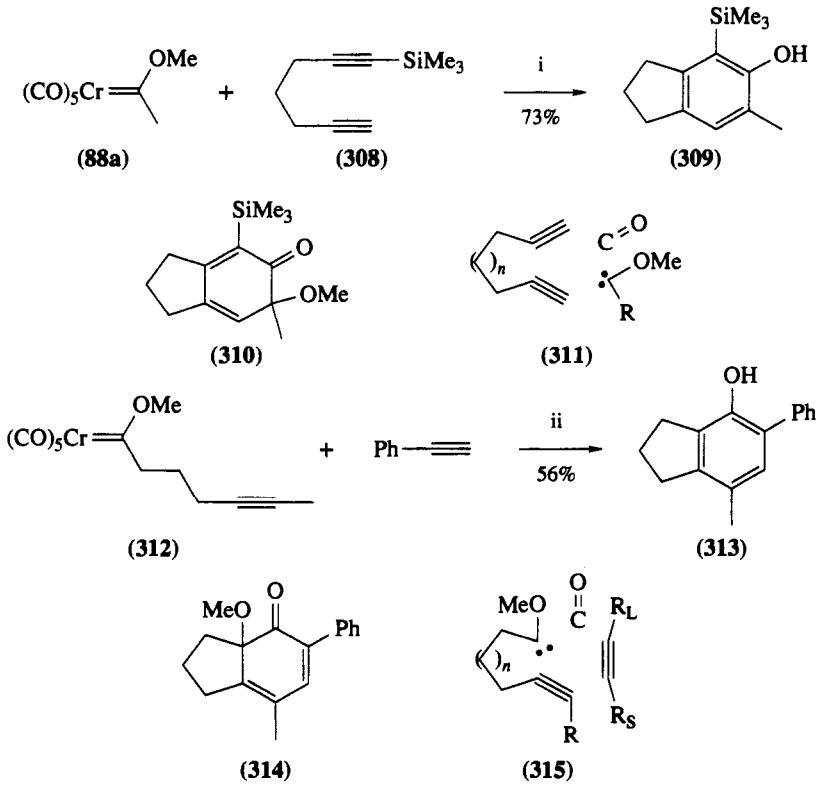
(k) The effect of the ancilliary substituent RX. Up to now, the benzannulation reaction has been almost exclusively limited to alkoxy functional groups as the ancilliary substituent RX in (**233**; Scheme 34) for both alkenyl and aryl complexes. As indicated in Section 9.2.3.2.3i nitrogen substituents lead to five-membered ring annulation products,[87,91,133] and six-membered ring benzannulation products (Scheme 32) have yet to observed from the reaction of amino complexes. Only one example of the benzannulation of a complex bearing a thiol group has been reported, and although it gave the six-membered ring benzannulated product, the yield was lower than for its methoxy analog.[3] Control of the group RX has the potential to allow for further fine tuning of the benzannulation reaction.

(l) Reactions with other carbon triple bonded functional groups. The substitution of nitrile for alkynes does not lead to pyridines or quinolines in the benzannulation reaction.[143,144] Instead noncyclic products are obtained that are the result of insertion of the carbon–nitrogen triple bond into the metal–carbene bond. On the other hand, in a very recent report it was found that λ^3-phosphaalkynes will undergo the benzannulation reaction to produce phosphaarene chromium tricarbonyl complexes.[145]

(ii) [2 + 2 + 1 + 1] Cycloadditions: two-alkyne annulations and pyrone formation

The reactions of Fischer carbene complexes with alkynes can under certain conditions lead to products that result from the incorporation of two alkynes, the carbene ligand and a carbon monoxide. In intermolecular reactions, this is most commonly observed for acetylene itself or for sterically unhindered alkynes.[3,102] As can be anticipated by the mechanism in Scheme 36, two-alkyne incorporated products of the type (**258**) are also favored for high alkyne concentration. Synthetically, the two-alkyne reactions are most useful in intramolecular reactions, two of which have been reported and are exemplified by the reactions in Scheme 43. The typical product from the reaction of a Fischer carbene complex with a diyne, such as (**308**), is a bicyclic phenol of the type (**309**).[3,43,102] These products are apparently the result of the assembly of pieces indicated by (**311**). Under some conditions, dienones of the type (**310**) and (**314**) can be isolated, and it is thought they are the immediate precursors of the phenol products *via* an *in situ* reduction by a chromium(0) species. This reaction is completely regioselective with diyne (**308**) and the phenol (**309**) results from incorporation of the terminal alkyne of (**308**) before the disubstituted alkyne.[102] Phenols of the type (**309**) have also been observed from the reaction of diynes with carbyne complexes.[146a]

A less efficient mode of the two-alkyne annulation is the intra-intermolecular reaction of an alkyne-containing carbene complex of the type (**312**) with a second alkyne.[146b] Under optimal conditions, these reactions will lead to moderate yields of bicyclic phenols of the type (**313**), which result from the assembly of pieces indicated by (**315**). The precursor dienones (**314**) can be isolated as minor products from these reactions.[147] Applications of the two-alkyne annulations in organic synthesis have not yet been reported.

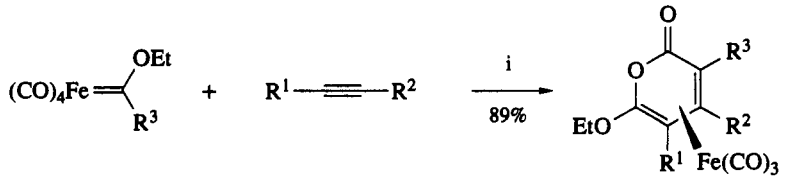


i, THF, 70 °C, 6 h; ii, MeCN, 50 °C, 36 h

Scheme 43

Alkoxy iron complexes of the type (**316**) will also react with alkynes to give six-membered ring products that, like the two-alkyne annulation, are formally the result of a [2 + 2 + 1 + 1] cycloaddition. The formation of these pyrone complexes (**317**) have only been reported from the reactions of alkynes with iron–carbene complexes.[93,148] These pyrones are also the only product from the reaction of an alkyne with any carbene complex which incorporates one alkyne, two carbon monoxides and the carbene ligand.

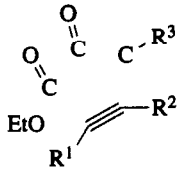
Pyrone formation by this reaction appears to be general (eight examples) and quite efficient (33–93%) and for a discussion of mechanistic possibilities the reader is referred to the primary literature.[148] With terminal alkynes, pyrone formation occurs with the same regioselectivity as is observed in the benzannulation reaction of chromium complexes (R^1 = Ph, R^2 = H).



(19)

(316) R^3 = Ph, $R^1 = R^2$ = Me (317)

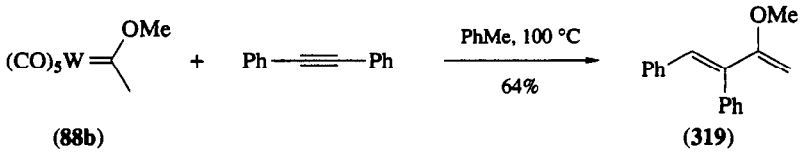
i, CH_2Cl_2, 70 °C, 1 h, 55 psi carbon monoxide



(318)

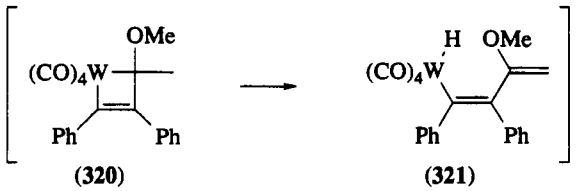
9.2.3.2.5 Coupling leading to acyclic products

The reaction of alkyl-substituted tungsten–carbene complexes of the type (**88b**) have been reported by Macomber to react with alkynes to give dienes of the type (**319**).[149] One mechanism that has been proposed to account for this product is a β-hydride elimination from the metallacyclobutene intermediate (**320**) and subsequent reductive elimination in the metal hydride species (**321**). An additional example of this type of reaction has been reported by Rudler, also for an alkyl tungsten carbene complex.[150] Chromium complexes have not been observed to give diene products of this type; the reaction of the analogous chromium complex (**88a**) with diphenylacetylene gives a cyclobutenone as the only reported product (see Scheme 31).[83] Acyclic products are observed for both tungsten and chromium complexes in their reactions with ynamines. These reactions produce amino-stablized carbene complexes that are the result of the formal insertion of the ynamine into the metal–carbene bond.[151–153]



(20)

(88b) (319)



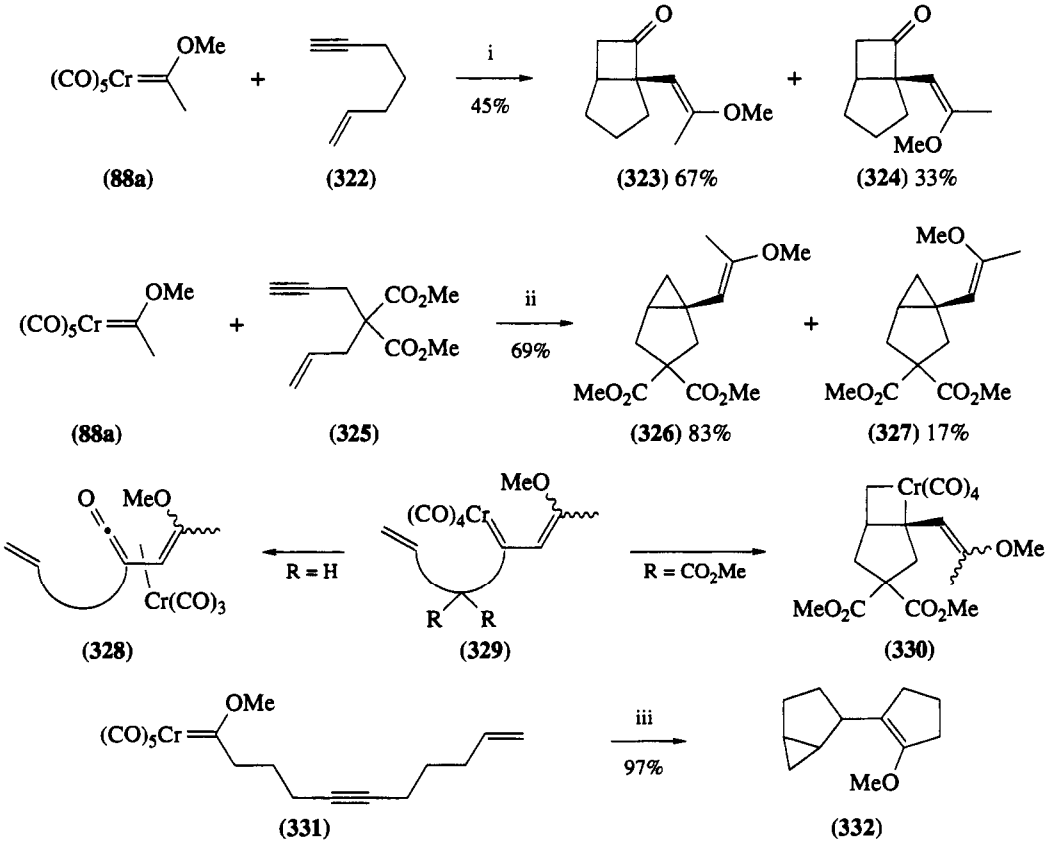
(320) (321)

9.2.3.2.6 Coupling leading to intercepted products

The two-alkyne annuation reactions shown in Scheme 43 are actually reactions of this class since mechanistically they can be viewed as the interception of vinyl carbene complex intermediate (**248**) in Scheme 36 by an alkyne. In addition to alkynes, intermediates from the reactions of Fischer complexes

and alkynes have also been intercepted with alcohols and amines.[154,155] In all of the known examples these trapping reactions produce β,γ-unsaturated esters and amides that apparently result from the trapping of vinyl ketene complexed intermediates of the type (**255**; Scheme 36) by alcohols or amines.

The first examples of the interception of intermediates from these reactions by alkenes were reported in 1985 by Wulff,[156] Katz[157] and Rudler.[158] Wulff reported that enynes of the type (**322**) would react with Fischer carbene complexes to give bicycloheptanones of the type (**323**) and (**324**). In contrast to these results, Hoye has recently observed that enynes derived from dimethyl malonate will react with the same carbene complex to give bicyclohexane products of the type (**326**) and (**327**).[160] It is possible that the difference between these two observations can be accounted for on the basis of the Thorpe–Ingold effect on the two possible pathways for the vinyl carbene complexed intermediate (**329**). When the substituents R in (**329**) are not hydrogen, the intramolecular formation of the metallacyclobutane (**330**) would be favored relative to the CO insertion that generates the vinyl ketene complex (**328**). Reductive elimination from (**330**) would give the bicyclohexane products, and an intramolecular [2 + 2] cycloaddition of the alkene and the ketene in (**328**) would lead to the bicycloheptanone products. Another possible outcome for the metallacyclobutane intermediate (**330**) is a metathesis reaction leading to cycloalkene products and these have been observed.[157,160] The Thorpe–Ingold effect does not account for the formation of cyclopropane products from the double intramolecular reaction of the complex (**331**), which gives the tricyclic product (**332**) in high yield.[160] Much yet needs to be learned before the outcome of reactions of this type can be predicted.

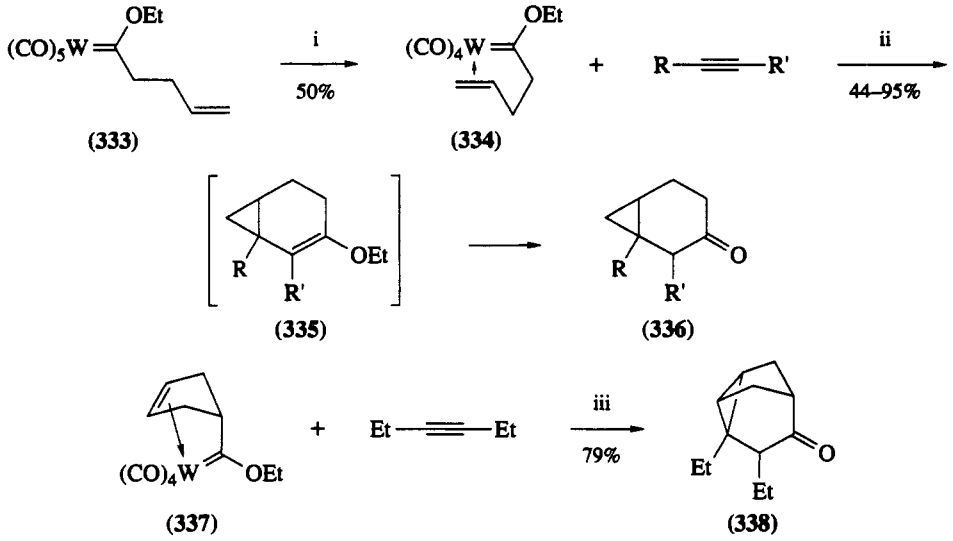


i, MeCN, 70 °C, 3 h; ii, PhH, 80 °C, 2 h; iii, PhH, 80 °C, 5 h

Scheme 44

In a variation of the reactions in Scheme 44, Rudler has reported that the alkene which intercepts the vinyl carbene complex leading to cyclopropane products can be tethered onto the starting carbene complex.[158] This was extensively studied for the reaction of the carbene complex (**334**) with a number of alkynes leading to bicycloheptanones of the type (**336**).[150] This reaction is quite general (14 examples, 44–95%) and is regioselective with terminal alkynes, *i.e.* it occurs in the same sense that has been observed for the benzannulation reaction (R′ = H in **336**). Acetylene fails and cyclooctyne gives a reduced

yield (31%) of (**336**). The intermediate (**335**) was not observed in these reactions and apparently suffers hydrolysis upon purification on silica gel. The interesting tricyclic product (**338**) can be obtained from the reaction of the cyclopentenyl complex (**337**) with 3-hexyne. Products similar to (**336**) can be obtained from the reactions of amino complexes in which the alkene is tethered through the nitrogen.[159]

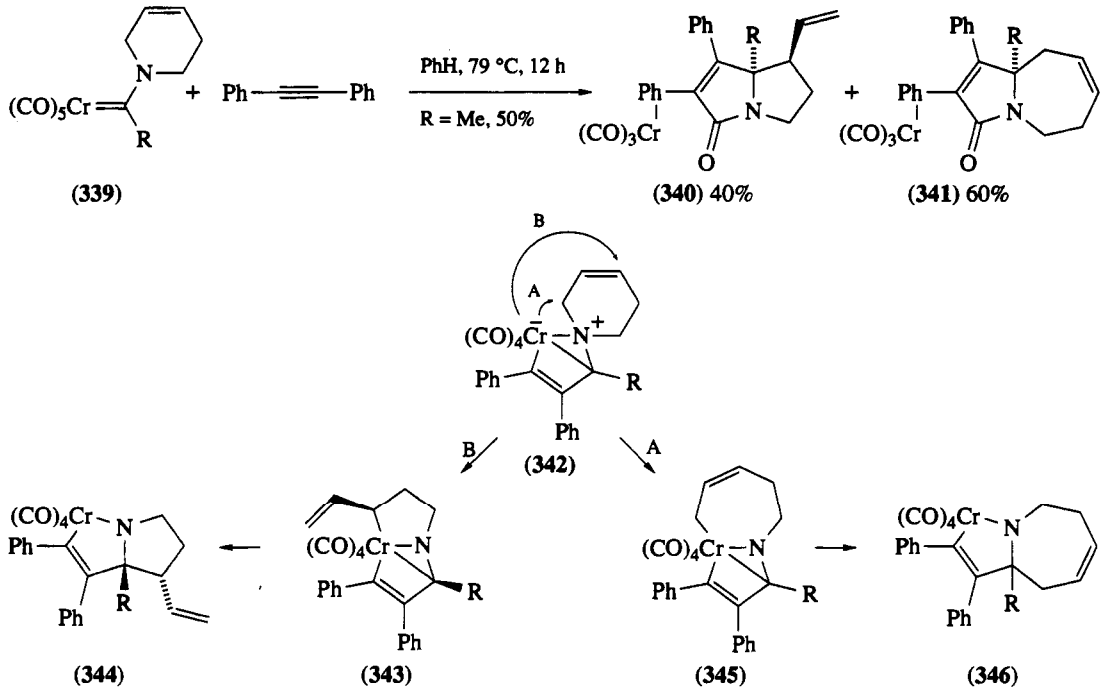


i, PhH, 78 °C, 12 h; ii, CH_2Cl_2, 10 °C, 12 h; iii, hexane, 25 °C, 48 h

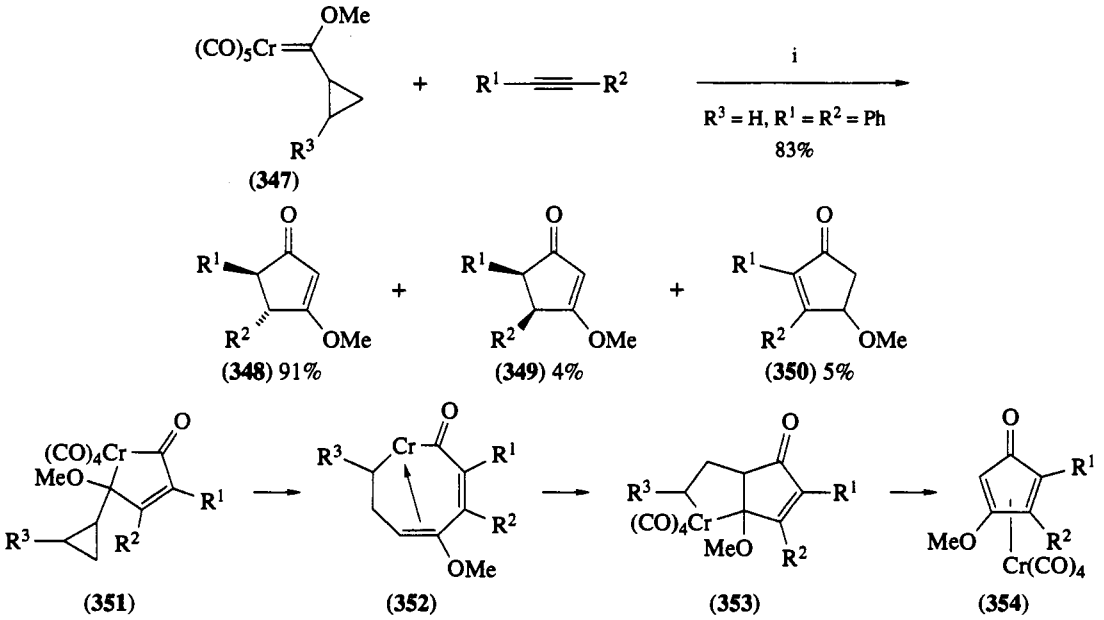
Scheme 45

Recently, two groups have reported reactions of Fischer carbene complexes with alkynes, in which intermediates have been intercepted by ring-opening reactions. The tetrahydropyridine carbene complex (**339**) was found to react with diphenylacetylene to give the two fused azabicyclics (**340**) and (**341**) in a total of 50% yield.[161,167] These products are proposed to both have a common mechanistic origin in the zwitterionic intermediate (**342**), which is a tautomeric form of the vinyl carbene complexed intermediate (**248**) in Scheme 36. Each product arises from a ring opening of the tetrahydropyridine ring at the allylic carbon–nitrogen bond of the ammonium ion in (**342**), and are differentiated by whether the chromium migrates to the α- or γ-carbon. The generality of this reaction has not been established with other alkynes; however, it has been shown to occur with diphenylacetylene with cyclic amino carbene complexes of other ring sizes (three and five). Analogous products are obtained from the reaction of a dihydropyrrole complex; however, with saturated tetrahydropyrrole complexes, ring opening cannot occur in the same manner and leads to a different ring system.[162] Ring opening also occurs with aziridine complexes, but the products isolated from these reactions differ in that they have 2 equiv. of the alkyne incorporated.[162,163]

Reaction intermediates can also be intercepted by the ring opening of carbocyclic substituents attached to the carbene carbon as illustrated by the reaction reported by Herndon involving the cyclopropyl carbene complex (**347**).[164] Depending on the nature of the alkyne, this reaction can produce varying amounts of the three isomeric cyclopentenones (**348**)–(**350**). The data given in Scheme 47 refer to the reaction with diphenylacetylene, but the reaction is general for a number of alkynes (nine examples, 0–85%). The regioselectivity was examined for terminal alkynes; it is the same as observed for the benzannulation reaction and the products from these reactions have the terminal alkynic hydrogen incorporated at R^2. The ring opening is proposed to occur at the intermediate (**351**), which is an η^2-tautomer of the vinylketene intermediate (**255**) in Scheme 36. The ultimate intermediate proposed for this reaction is the cyclopentadienone complex (**354**), which must add the elements of dihydrogen to produce the final products. This is consistent with the observation that yields are higher when the reaction is carried out in the presence of reducing agents. The reactions in Scheme 46 and 47 have opened several interesting mechanistic issues and some novel synthetic possibilities.



Scheme 46



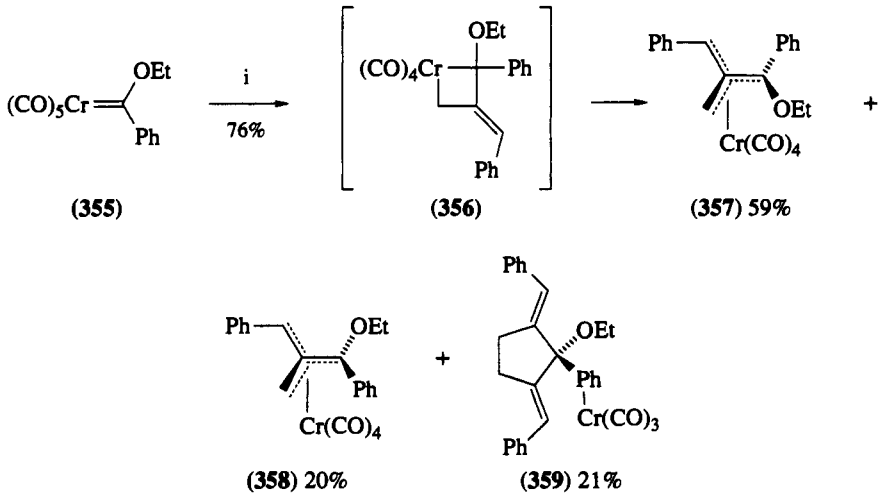
i, 1% aqueous dioxane, 101 °C, 4–6 h

Scheme 47

9.2.3.3 Coupling of the Carbene Ligand with Cumulenes and C—X π-Bonds

9.2.3.3.1 Allenes

The first reaction of a Fischer carbene complex with an allene was reported by Aumann in 1987.[165] The initial event in this reaction was presumably the formation of the methylene metallacyclobutane intermediate (**356**). This intermediate could have undergone reductive elimination to give a methylenecyclopropane, but apparently preferred to rearrange to the trimethylenemethane complexes (**357**) and (**358**). Also formed in this reaction is the bismethylenecyclopentane (**359**), which was shown either by prolonged reaction times or separate experiments to arise *via* [3 + 2] cycloaddition of a molecule of the allene with the trimethylenemethane complexes (**357**) and (**358**). Trimethylenemethane complexes of iron can be obtained in a similar manner from the reaction of iron–carbene complexes with allenes and have the advantage that they can be prepared cleanly since subsequent [3 + 2] cycloaddition of the allene with the products is not observed.[166] The [3 + 2] cycloadditions of the isolated iron trimethylenemethane complexes prepared in this manner have not yet been examined. Although this reaction has not yet been extended to other allenes or carbene complexes other than aryl, this initial observation is particularly exciting given the established synthetic utility of transition metal trimethylenemethane complexes and the uniquely functionalized trimethylene complexes that are accessible from the reaction of Fischer carbene complexes with allenes.



(**355**) (**356**) (**357**) 59%

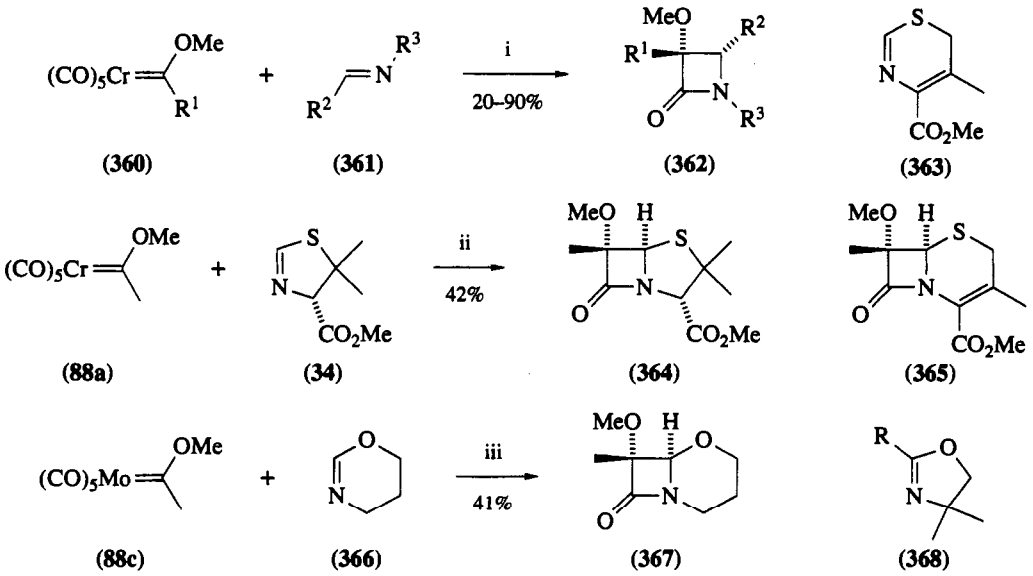
(**358**) 20% (**359**) 21%

(21)

9.2.3.3.2 Imines

The synthetic applications of photo-induced reactions of Fischer carbene complexes have been developed in the laboratories of Hegedus over several years.[167–172] The development of this chemistry as a method for cyclobutanone synthesis was discussed in Section 9.2.3.1.2. The area that has been most thoroughly developed at this time is the synthesis of β-lactams from the photo-induced reactions of carbene complexes and imines. As indicated in Scheme 48 this reaction is general for a number of substrates and gives β-lactams in fair to high yields with complete stereoselectivity.[168] This chemistry was first developed with alkoxy-substituted complexes for the complexes for the synthesis of 6- and 7-alkoxy analogs of β-lactam antibiotics.[167–169] The exposure of the complex (**88a**) to sunlight in the presence of the homochiral thiazoline ester (**34**) gave the penicillin analog (**364**) as a single diastereomer in 42% yield.[168] In a similar manner, the photolysis of (**88a**) in the presence of the thiazine (**363**) gave the cephalosporin analog (**365**) in 52% yield as a single diastereomer.[169] The preparation of oxapenam and oxacepham analogs failed with chromium carbene complexes; however, this was successful with molybdenum complexes.[169] Photolysis of the complex (**88c**) with the oxazine (**366**) gave the oxacepham analog (**367**) in 41% yield. The reaction of the complex (**88c**) with the oxazoline (**368**) gave the corresponding oxapenam analog in 14% yield.

In penicillins of the type (**370**) the position α to the carbonyl in the four-membered ring bears a hydrogen and a nitrogen substituent. This requires that unsubstituted amino carbene complexes of the type (**369**) be readily available and was the driving force for the development of the procedure for the prep-

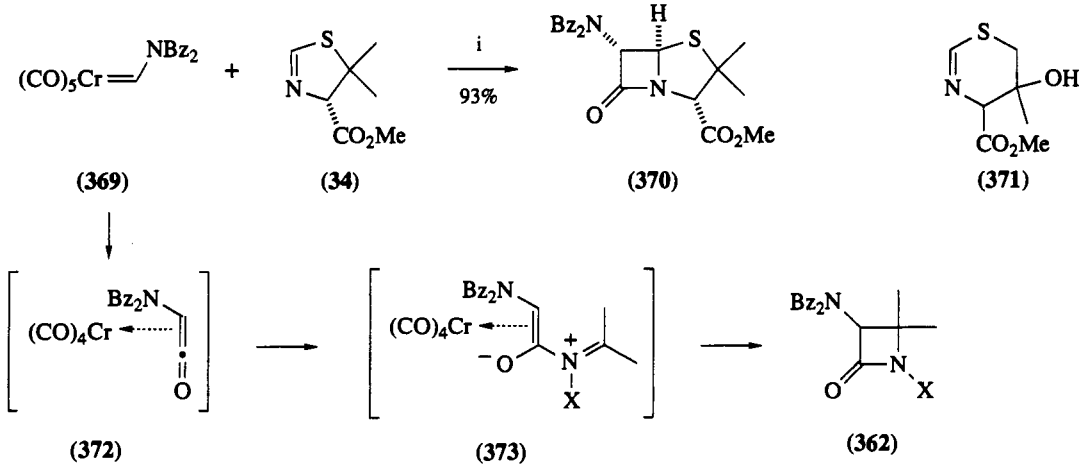


i, Et_2O, sunlight, 2–4 h, or Et_2O, vitalite fluorescent tubes, 10–20 h; ii, CH_2Cl_2, sunlight, 2 d; iii, THF, 0 °C, rayonet reactor with 3000 Å and 5000 Å lamps, 48 h

Scheme 48

aration of carbene complexes that is illustrated in Scheme 1. As it turned out, the amino complex (**369**) is more versatile in the synthesis of β-lactams than alkoxy complexes. The reaction of (**369**) with (**34**) in the presence of light allowed for the preparation of the penicillin analog (**370**) in 93% yield as a single diastereomer.[170] The reaction of (**369**) with the thiazine (**371**) proceeded in 77% yield and subsequent dehydration produced a cephalosporin analog. Unlike the alkoxy chromium complex (**88a**), the amino chromium complex (**369**) would react with oxazines and oxazolines to produce oxacephams and oxapenams.

The reactions of both alkoxy and amino complexes are highly stereoselective and give the unnatural epimer at the C-6 position in the penicillin analogs, but methods are known for inversion at this center. The mechanism of these reactions is thought to involve the intermediacy of a metal–ketene complex whose formation is photo-induced.[171,172] Early indications that this was the case came when it was found these reactions fail to give cyclic products of any kind under thermal conditions. More recently, vinylketene complexes have been trapped from these reactions.[171] With the recent realization that metal–ketene intermediates are likely to be involved in these reactions further development of the photo-induced reactions of Fischer carbene complexes can be anticipated.



i, MeCN, 0 °C, 450 W lamp, 9 h

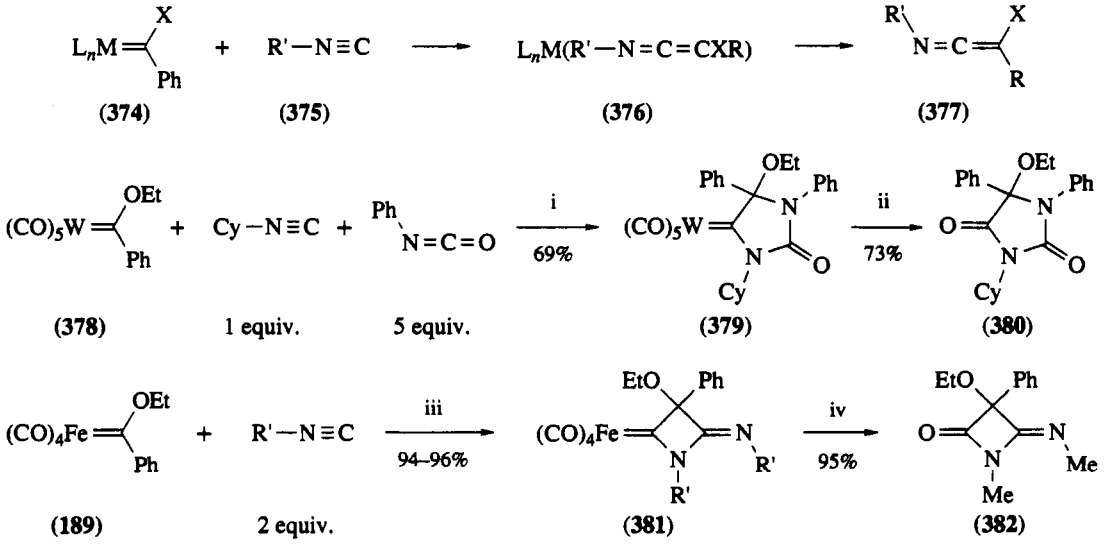
Scheme 49

9.2.3.3.3 Isonitriles

The chemistry associated with the reaction of Fischer carbene complexes with isonitriles has been investigated over the last 20 year period, mainly by Aumann. It is not possible to cover this material comprehensively in this review, however, and an excellent overview of this area has appeared in the literature.[173] All of the chemistry reported to date actually involves reactions of the ketenimine complex (**376**), which is generated by the coupling of the carbene ligand and an isonitrile. If the reaction of the carbene complex and an isonitrile is carried out in a coordinating solvent, such as acetonitrile, the free ketenimine (**377**) can be isolated. In the case of Group 6 metals, the ketenimine in complexes of the type (**376**) are bound through the nitrogen.[174] The electrophilicity of ketenimines is reversed when coordinated to a metal. Free ketenimines suffer nucleophilic attack at the central carbon, whereas the ketenimine complexes (**376**) add nucleophiles at the terminal carbon and, thereby, provide for an alternative preparation of amino carbene complexes.[175] Ketenimine complexes also will undergo head to head dimerization at the carbon–carbon bond.[176]

Ketenimine complexes can serve as three-atom components in [3 + 2] cycloadditions. The reaction of the tungsten complex (**378**) with cyclohexyl isonitrile and phenyl isocyanate produces the heterocyclic carbene complex (**379**), which is the result of the *in situ* trapping of a ketenimine complex with the isocyanate.[177] Complexes of the type (**379**) can be oxidatively cleaved to give the previously inaccessible 5-ethoxyhydantoins. [3 + 2] Cycloadditions of this type have also been carried out with aldehydes.[177]

In the presence of 2 equiv. of isonitrile, [3 + 1] cycloadditions can be effected leading to the formation of the cyclic amino carbene complex (**381**), which can be cleaved in high yield to the β-lactam (**382**). This reaction gives highest yields with iron–carbene complexes,[175] although for manganese complexes the initial ketenimine complex (**376**) reacts sluggishly with the second equivalent of isonitrile making it possible to sequentially incorporate two different isonitriles.[178]

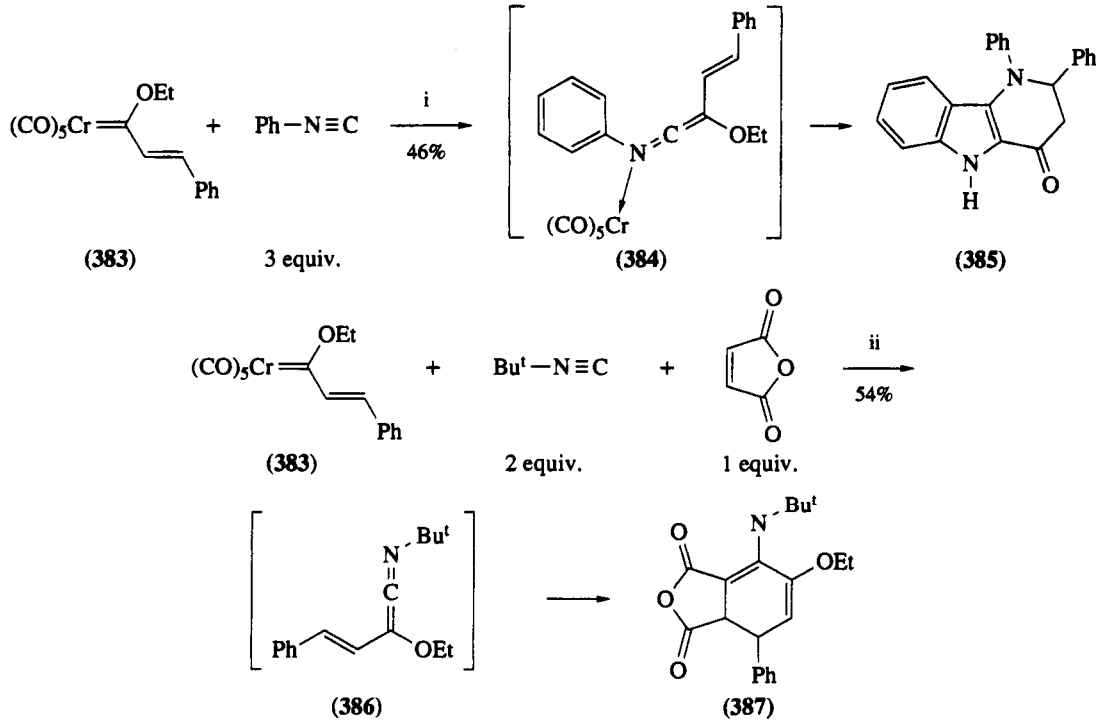


i, Et_2O, 25 °C, 24 h; ii, $KMnO_4$, $Fe(NO_3)_3$, acetone/water; iii, pentane, 20 °C, 1 h;
iv, $KMnO_4$, benzene/water, 25 °C

Scheme 50

The reactions of alkenyl carbene complexes with isonitriles can produce a variety of products whose distribution is sensitive to the nature of the isonitrile. Reacting 3 equiv. of aryl isonitrile with the alkenyl complex (**383**) produces the dihydro-γ-carbolinone (**385**).[174] The ketenimine in (**384**) is liberated with a second equivalent of the isonitrile, and the the third equivalent undergoes a formal [4 + 2] cycloaddition with the free ketenimine. With sterically encumbered isonitriles, the ketenimine is more rapidly liberated from the metal by a second isonitrile and 2 equiv. are required to drive the reaction to completion. Free ketenimines that are generated in this manner can be trapped *via* their [4 + 2] cycloadditions with maleic anhydride.[179] Primary and secondary alkyl isonitriles will react with alkenyl carbene complexes to give cycloadducts that can be converted to pyrroles[179] or products that contain five-membered ring carbocycles.[179,180]

The chemistry associated with the reactions of isonitriles and carbene complexes is extraordinarily rich and should find applications in organic synthesis.



i, pentane, 20 °C, 2 h; ii, toluene, 80 °C, 4 h

Scheme 51

9.2.4 REFERENCES

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9.3
Alkene Metathesis and Related Reactions

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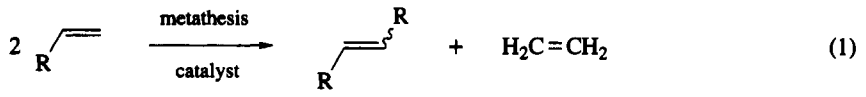
9.3.1 INTRODUCTION

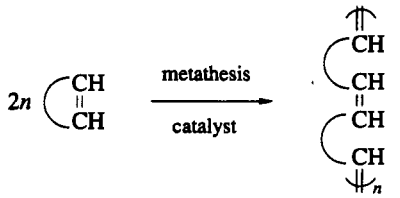
The alkene metathesis reaction between carbon–carbon double bonds is now a well-established synthetic method in industrial operations and in the laboratory.[1] Recently it has been recognized that a closely related, transition metal catalyzed reaction takes place between a carbon–carbon double bond and a carbon–oxygen double bond.[2] This latter process, which can be considered as a Wittig analog, shows promise of becoming an important tool of synthesis strategy.[3]

9.3.2 REACTIONS BETWEEN CARBON–CARBON DOUBLE BONDS

The alkene metathesis reaction represents a unique carbon skeleton rearrangement in organic chemistry. This reaction, which grew out of the studies of catalysts related to alkene polymerization, results in the cleavage of the carbon–carbon double bond of an alkene and the redistribution of the resulting alkylidene fragments (equation 1).[1] The same reaction carried out with cyclic alkenes generally results in the formation of polymers (equation 2).

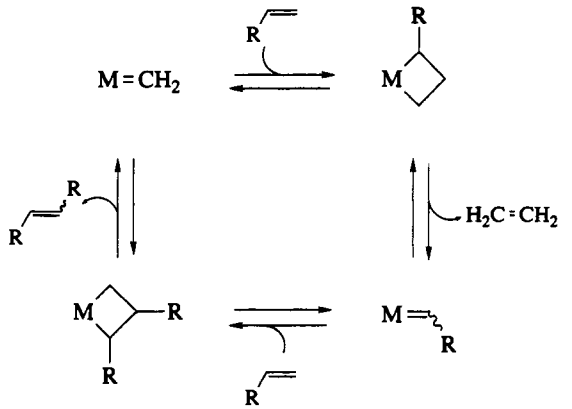


(1)



(2)

Although there was considerable controversy over the mechanism of this unique reaction, it is now generally accepted that the reaction proceeds through a series of metallacycle and carbene complexes as shown in equation (3).[4] Although the relative stabilities of the carbenes and metallacycles can change with reaction conditions, catalyst composition and alkene substitution, the fundamental mechanism appears to be the same for all catalysts.[5]



(3)

The original catalysts reported for the metathesis of acyclic alkenes were related to alkene polymerization systems. Banks and Bailey reported in 1964 that the heterogeneous cobalt molybdate complexes would promote the metathesis reaction.[6] Since that time a wide variety of catalysts that use Mo, W and Re as the active metal in combination with a variety of supports, promoters and activation conditions have been reported.[1] These heterogeneous catalysts are the systems of choice for most industrial fine chemical applications.

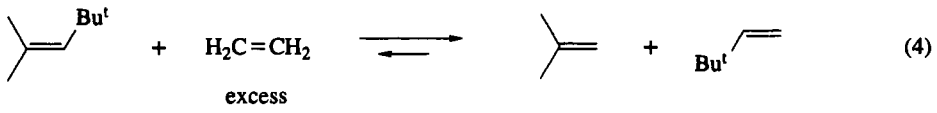
Eleuterio had described the formation of polymers by the ring opening of cyclic alkenes as early as 1957.[7] It is now well understood that the cyclic and acyclic alkene metathesis reactions, although they lead to very different type products, are the same fundamental reaction.[8] For polymerizations and other applications, a series of nonsupported catalysts have been generated. These catalysts usually result from mixing a tungsten or molybdenum halide with an alkylaluminum. Although the resulting mixture contains a low concentration of the active species, these systems can be extremely active at room temperature. For example, a room temperature catalyst mixture of WCl_6/EtOH/Et_2AlCl will convert 10^4 moles of 2-pentene per mole of tungsten in 3 min with 99.6% selectivity to 2-butene and 3-hexene. Due to the strong Lewis acidity of these systems, only a few functionalized alkenes can be successfully metathesized using these Zeigler type catalysts.[8b] In all of these systems the generation of the initial carbene complex is inefficient and appears to be the rate-limiting reaction.

Recently, highly efficient catalysts have been developed that are one component systems and contain a preformed alkylidene or metallacycle as the catalyst initiator.[2c,9–11] Some of these complexes have shown excellent utility in the synthesis of organic molecules and will be the major topic of the last part of this chapter.[2,12] These complexes will not only change many of the approaches in simple alkene metathesis but will also have a major influence on the future applications in organic and polymer synthesis.

9.3.2.1 Industrial Applications

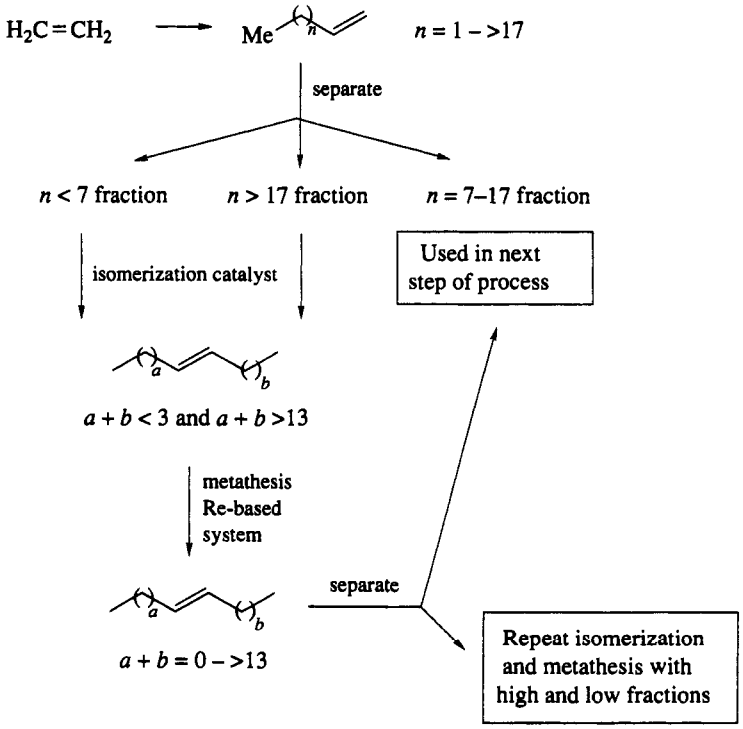
The simplest example of alkene metathesis, the disproportionation of propylene to ethylene and 2-butene, was the first commercial application of this reaction. Changes in the relative economic value of

the three alkenes resulted in the early closing of this facility.[13] The general process, called the Phillips Triolefin Process, is now used to produce neohexene from ethylene and the dimer of isobutylene (equation 4).



(4)

The largest commercial application of metathesis is as a major step in the Shell Higher Olefin Process (SHOP).[14] In this process, ethylene is oligomerized to prepare C_{10} to C_{20} alkenes to be used in the production of fatty acid alcohols. The nickel-catalyzed oligomerization process gives a broad distribution of α-alkenes. Those that are of higher and lower molecular weight than desired are separated and isomerized to internal alkenes. This mix of high and low molecular weight internal alkenes is metathesized to a new broad distribution of alkenes. The desired molecular weight materials are removed and the remainder is again recycled. By this process most of the ethylene can be redistributed to the desired molecular weight range (equation 5).



(5)

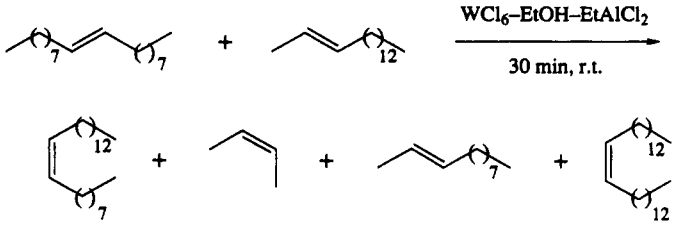
Cross metathesis of ethylene with internal alkenes provides a facile route to terminal alkenes. A number of processes have been described that use this transformation; however, the only products, besides neohexene,[13] that appear to be important are the α,ω-dienes that result from metathesis of cyclic alkenes with an excess of ethylene.[15] This family of compounds should find a wide variety of applications.

9.3.2.2 Fine Chemical Synthesis

Applications of metathesis to the synthesis of more complex organic molecules has been limited by the lack of tolerance of the catalyst systems for functional groups. Many of the new catalyst systems that are being developed appear to be less sensitive to basic functional groups.[11,16] It is anticipated that there will be numerous advances in this area over the next few years as better and more easily synthesized catalysts become available.

9.3.2.3 Pheromone Synthesis

Since a number of insect pheromones are nonfunctionalized alkenes, they are potential target molecules for synthesis from petrochemicals by the metathesis reaction. Cross metathesis between unsymmetrical internal alkenes can lead to a complex mixture of products; however, in some cases, this reaction provides the easiest method for production of such alkenes. For example, the pheromone for *Musca domestica*, tricosene, has been prepared from 2-hexadecene and 9-octadecene (equation 6).[17] Both of these alkenes are readily available.

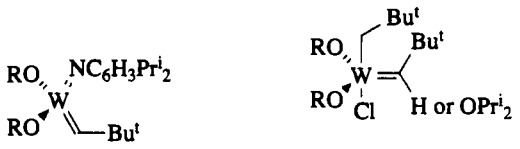


9-Tricosene, 9% isolated

other cross products

(6)

A few of the heterogeneous catalysts will catalyze a number of turnovers of nonconjugated unsaturated esters.[8b] The catalysts (**1** and **2**) appear to be of too low efficiency to be used commercially.



(1) (2)

As will be seen later in this chapter, many early transition metal alkylidenes and metallacycles of the type required for metathesis (examples containing Ti, Ta, W and Mo as transition element) will undergo reactions with many organic functional groups. Although it was believed that this reactivity would limit the application of metathesis to nonfunctionalized alkenes, recent advances in the synthesis of one component catalysts of tungsten and molybdenum and the development of catalysts based on the later transition metals Re and Ru, suggest that catalysts can be prepared that are much less sensitive to basic functionalities. The key to functional group tolerance is to develop complexes that will react with alkenes in competition with heteroatom functionality. The tungsten catalysts prepared by the group of Schrock[11] and of Basset[9] will catalyze the metathesis of methyl oleate to the corresponding diester (equation 7).

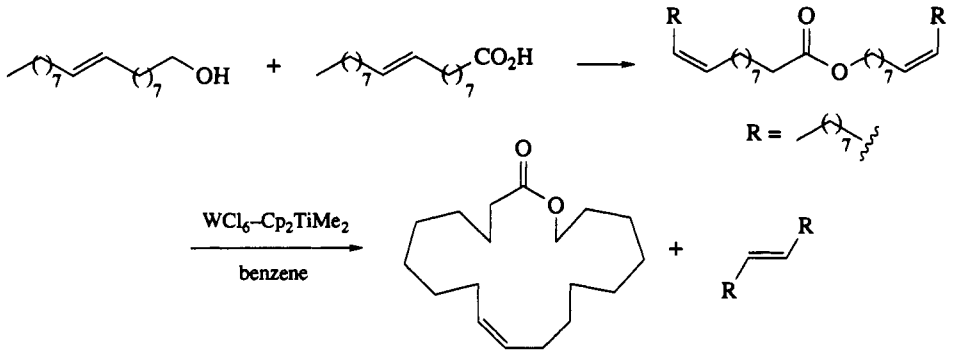
(7)

Related molybdenum catalysts appear to show even more functional group tolerance. To date, the major test of functional group compatibility has been in the synthesis of polymers; however, it is anticipated that this activity will persist into acyclic metathesis. Later transition metals are active in the metathesis polymerization of highly functionalized cyclic alkenes. These catalyst systems, which appear to tolerate almost all functional groups, show very low activity for acyclic alkene metathesis.[18] If these systems can be activated, the problems associated with the use of alkene metathesis in the synthesis of multifunctional organics will be solved.

9.3.2.4 Synthesis of Macrocycles

Two approaches to the formation of large rings by metathesis have been attempted. The first approach is demonstrated by the synthesis of 9-octadecen-18-olide by Tsuji[19] by the closure of an α,ω-diene

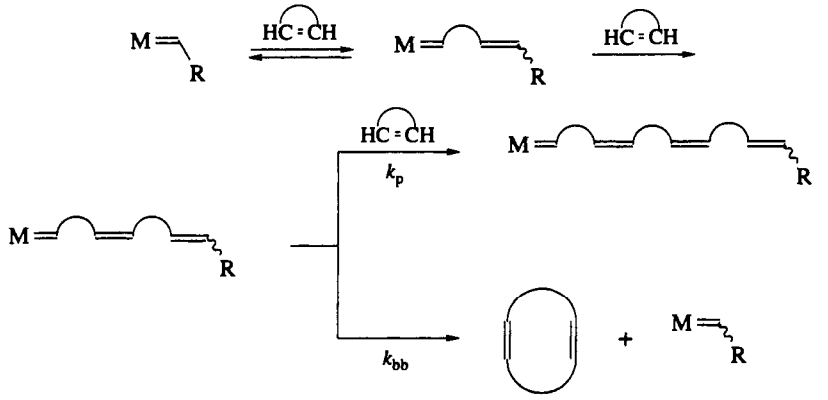
(equation 8). Although the yield in this reaction is low (18%), the result demonstrates the potential of this approach, especially in view of the functional group tolerant catalysts that are now available.



(8)

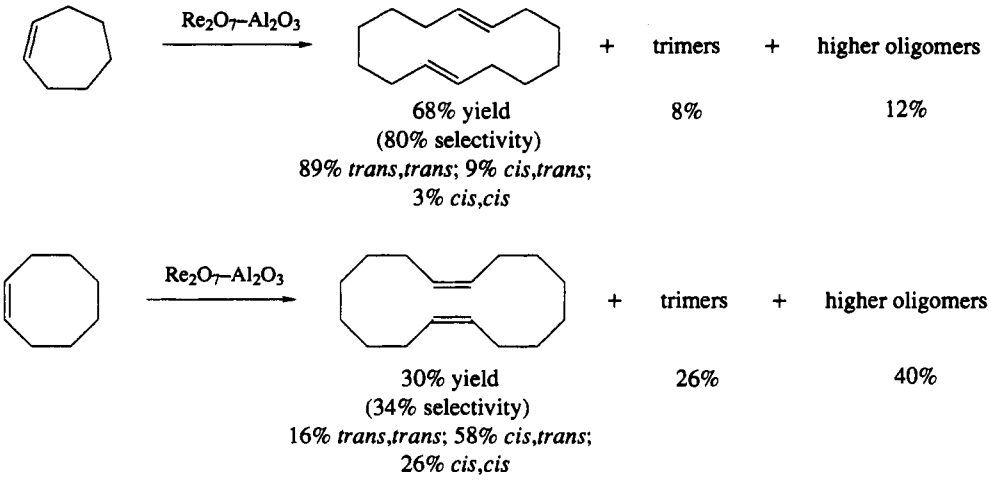
18% yield
9-Octadecen-18-olide

The second approach, which involves the dimerization of cyclic alkenes to larger cyclic dienes, appears to be successful for certain ring sizes. For example, cyclooctene can be dimerized to 1,9-cyclohexadecadiene in 34% yield and cycloheptene is dimerized in an 80% yield to 1,8-cyclotetradecadiene.[20] A careful consideration of the mechanism of this transformation is important in understanding the experimental conditions required to obtain dimers instead of the thermodynamically favored ring-opened polymer. Each step in the reaction is reversible and the rate of chain growth is related to the rate of the forward bimolecular reaction between the growing polymer chain and more monomer, k_p, and the unimolecular back-biting reaction with a double bond in the tail of the polymer, k_{bb}. If reaction takes place with the last double bond formed, starting material is produced. However, if a double bond further down the chain reacts, a larger cycle is formed (equation 9).



(9)

Consequently, in order to optimize the yield of the dimer resulting from a unimolecular reaction, the concentration of the starting material in contact with the catalyst must remain low. Also, since the product dimer can also react with the catalyst to produce larger rings, it must be removed from the reaction as it is formed. Both of these requirements are accomplished by using a soxhlet extractor as the reactor. A heterogeneous catalyst is used to facilitate the separation of the products from the catalyst. The catalyst (Re_2O_7/Al_2O_3) is maintained in the cup of the apparatus and the reactant is circulated over the catalyst by heating the reactant in a lower boiling solvent such as pentane or hexane. In this way only a low concentration of the reactant is in contact with the catalyst at any time, and the products are rapidly removed from the catalyst. Since the products are much higher boiling than the reactants, only small amounts of the products are recycled (equation 10). In both cases, the thermodynamic mixture of stereoisomers is formed. The high yield of the dimer from cycloheptene is attributed to the exceptional conformational stability of the *trans,trans*-1,8-cyclotetradecadiene.



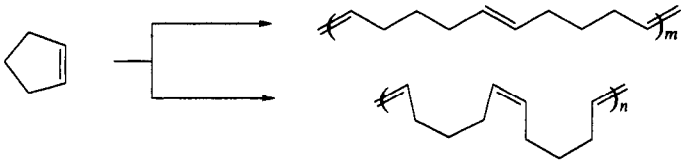
(10)

9.3.2.5 Polymer Applications

The developments of the metathesis reaction for polymer synthesis have paralleled the opportunities in acyclic chemistry. Acyclic and cyclic metathesis were discovered independently and only later were recognized as the same reaction. Most of the work in the area of ring-opening metathesis polymerization (ROMP) is outside the scope of this article, and only those areas where the results suggest possibilities in organic synthesis will be discussed in detail.

As discussed above in the mechanism of the alkene dimerization reaction, the polymerization of simple alkenes proceeds by the basic metathesis mechanism. Since polymers that are prepared from complex monomers require homogeneous catalysts, much of the early 'organometallic' catalyst development has had polymer synthesis as the driving force. Recently, developments in the synthesis of organometallic complexes that serve as well-defined catalysts for metathesis have opened many opportunities in the area of polymer synthesis.[21]

The speed and efficiency of chain growth relative to termination of the metathesis catalysts provides high molecular weight polymers. Different catalyst mixtures produce different double bond geometries and tacticities.[22] These factors have been studied in detail since one of the first promising polymers produced by ROMP was polypentenamer. The all-*trans* isomer is an elastomer and was studied as an excellent material for tire manufacture, while the *cis* isomer is a nonelastomeric solid (equation 11).[23]



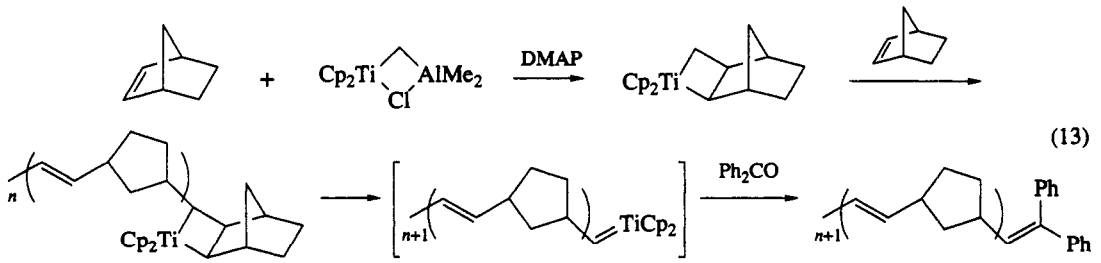
(11)

To date, low volumes of materials have been produced commercially from norbornene and cyclooctene.[24] Numerous products are expected to result from the material produced by the ROMP of dicyclopentadiene in a RIM (reaction injection molding) process. In a RIM process, two streams of a monomer are mixed in the mold where it is polymerized to the final part.[25] In this case, one of the monomer streams contains a tungsten complex while the second contains an alkyl aluminum activator. When the two streams of dicyclopentadiene are mixed, the metathesis catalyst is formed and the monomer is ROMP polymerized (equation 12).

(12)

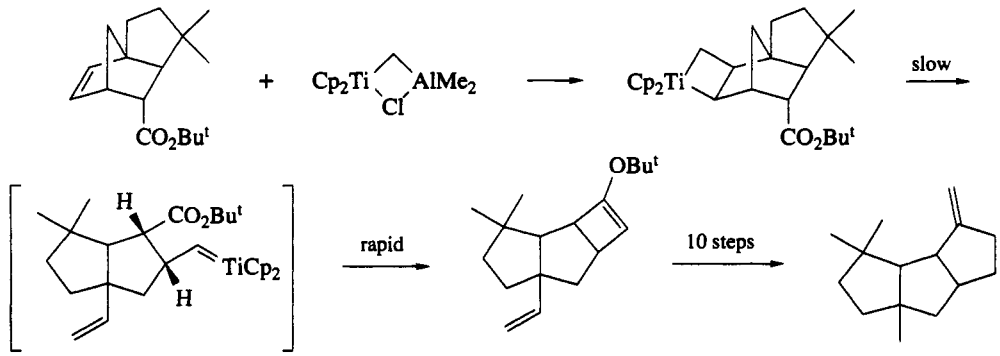
Recent advances in ROMP chemistry have resulted from the finding that the isolated organometallic carbene and metallacycle complexes give living polymers. These systems continue to add monomers to

the end of the growing chain without chain transfer or termination. From a polymer synthesis viewpoint, this result opens the way for the synthesis of monodispersed polymers, block copolymers and a variety of materials with tailored properties. For example, the metallacycle formed from norbornene and the Tebbe reagent[2c] can be isolated and characterized. When this metallacycle is heated with more norbornene, polynorbornene is produced.[26] If the reaction is cooled to room temperature, the reaction stops and a polymer can be isolated that contains a metallacycle at the end. When this metallacycle is heated with a carbonyl compound, the intermediate alkylidene undergoes a Wittig type reaction, of the type that will be discussed later, to give a high yield of an end-capped polymer (equation 13).[27]



(13)

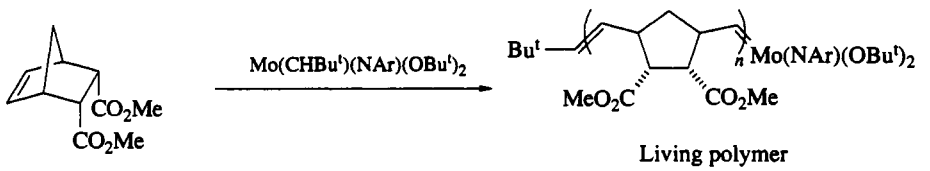
If this reaction is carried out as an intramolecular reaction, interesting ring systems are produced. This reaction was used to produce a precursor to capnellene[28] and involves all the same reactions as used in the polymer synthesis (equation 14).



(14)

$\Delta^{9,12}$-Capnellene

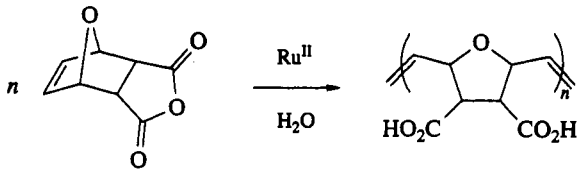
With the availability of the newer catalysts discussed above that are more tolerant of functionality, it is anticipated that a wide variety of synthetically useful carbon skeleton rearrangements can be carried out. For example, the molybdenum catalyst shown in equation (15) gives a high molecular weight, living polymer with *endo,endo*-5,6-dicarbomethoxynorbornene. This result demonstrates that the rate of reaction of the growing alkylidene with the alkene double bond is much faster than the competing 'Wittig' reaction of the alkylidene with the carbonyl functionality.[16]



(15)

Living polymer

Another area of ROMP in the early stages of development is the polymerization of highly functionalized monomers in protic and aqueous solutions. These catalysts appear to tolerate most organic functional groups and will polymerize highly functionalized monomers (equation 16).[18] The development of the organometallic chemistry of these catalysts will open a variety of new applications of metathesis in organic synthesis.



(16)

9.3.3 REACTIONS BETWEEN CARBON–CARBON AND CARBON–OXYGEN DOUBLE BONDS

Alkene metathesis catalysis involves intermediates in which a transition metal is multiply bonded to carbon. These species are often referred to as nucleophilic carbenes when the carbon atom is negatively polarized. A more functional description is to name these compounds as alkylidene complexes, since they react to transfer an alkylidene moiety from a transition metal to a substrate carbon atom.[2d] Previous sections of this chapter have focused on a common example of this chemistry; the process of metathesis that involves transition metal mediated interaction of carbon–carbon multiple bonds.

In this section we will consider the interactions between transition metal complexes and carbon–oxygen double bonds, *i.e.* carbonyl groups. The transition metal functions as a reagent to deliver an alkylidene fragment and replace the oxygen atom. The process is analogous to a Wittig reaction (equation 17).[29]

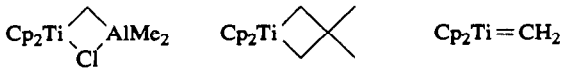
(17)

M = metal

Compounds of the early transition metals have been found to function in this way. Titanium, zirconium, tantalum and tungsten are among the most prominent metals in these complexes. The complexes of titanium form the basis for most of the reagents currently reported in synthesis applications.

9.3.3.1 Titanium Based Reagents

The titanium–aluminum methylidene (**3**), commonly known as the Tebbe reagent,[2c] was the first well-characterized compound in this series. The Tebbe reagent (**3**) and related metallacycles (**4**) have been used principally as methylidene sources toward carbonyl groups. Both are believed to provide the titanium methylidene (**5**).[2c,3]



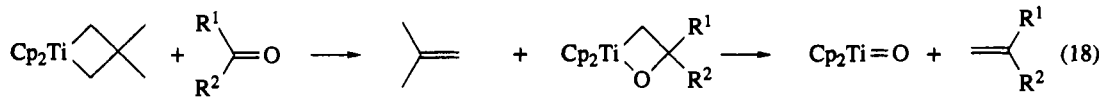
(**3**) (**4**) (**5**)

In the case of the Tebbe reagent, the titanium methylidene is presumably released by some Lewis base. That base is often the heteroatom of the substrate. A Lewis base such as tetrahydrofuran or pyridine may be added to the reaction and usually enhances reactivity relative to reaction with the substrate alone.[2a,b]

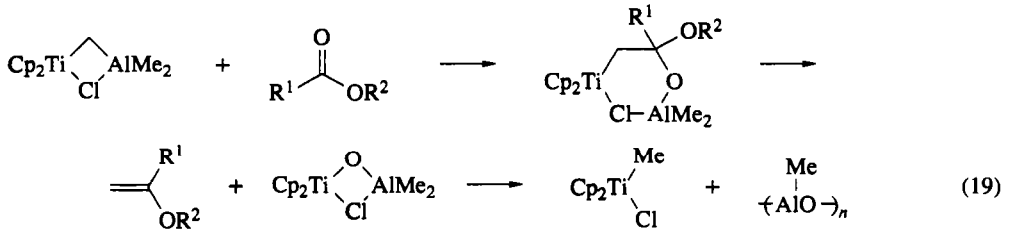
The metallacycles (**4**) generate the requisite titanium methylidene thermally. Consistent with this is the observation that reaction with a carbonyl compound is first order in the metallacycle and zero order in the carbonyl compound.[30] Metallacycle stability depends on the alkene moiety that has replaced the aluminum–chlorine portion of (**3**) and thus could provide a series of reagents whose reactivity is temperature dependent.[31]

The titanium methylidene interacts with the carbonyl carbon–oxygen double bond in a sequence that is believed to resemble the metathesis process. With the metallacycle (**4**), a titanium oxametallacycle is believed to be formed, which then decomposes to generate the new carbon–carbon double bond and a titanium–oxygen product.[3] The driving force for the reaction has been attributed to the oxophilicity of titanium (equation 18).[32]

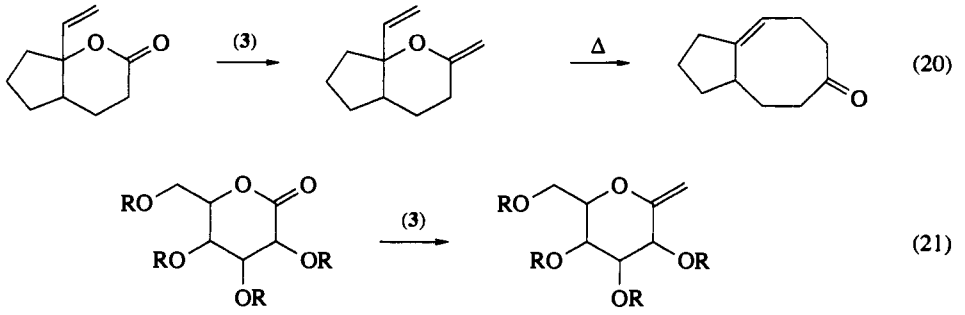
Reaction of the titanium–aluminum reagent (**3**) is more complex. If no additional Lewis base is employed, the carbonyl compound takes that function. Interaction with the aluminum atom is required to



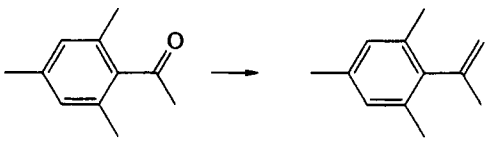
'release' the methylidene. Kinetic studies of the reaction with esters indicate a second-order process, first-order in the reagent and first-order in the ester.[33] The large negative entropy for this process suggests that an intermediate forms, possibly a six-membered ring metallacycle, which then leads to the observed product. In contrast to the related reaction with the metallacycle, the major titanium-containing product is Cp2TiClMe while the oxygen of the original carbonyl group is found in a methylaluminoxy polymer (equation 19).



The Tebbe reagent and its metallacycle analogs have proven particularly valuable for the formation of enol ethers from esters.[2a,b,3,34] This methylenation of an ester carbonyl is not normally accomplished using the classical Wittig phosphoranes.[29,35] The same methylenation process takes place with lactones.[2a,b,3,36] In fact, the sequence has been used to methylenate a lactone, and the methylidene product then allowed to undergo an electrocyclic reaction (equation 20).[37] Similarly, the carbonyl group of sugar lactones reacts with the reagent (equation 21).[38]



The Tebbe and metallacycle reagents are also effective at ketone and aldehyde methylenation.[2b,c,39] In this reaction, they are similar to the Wittig reagent, methylenetriphenylphosphorane. A comparison of the effectiveness of the Tebbe reagent and the Wittig reagent indicates that the Tebbe reagent is comparable to or better than the Wittig reagent for the methylenation of ketones. The value of the Tebbe re-

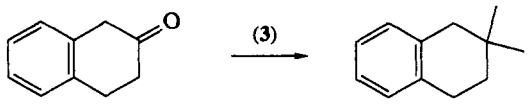


Tebbe reagent, 77%; Wittig reagent, 4%

agent for methylenation is particularly obvious when the carbonyl substrate is hindered (equation 22).[40]

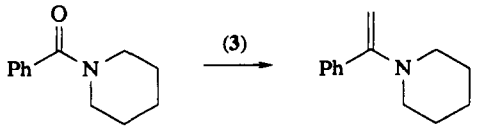
Stereochemistry is retained in substrates containing carbon–carbon double bonds.[2a] Furthermore, the absence of a basic medium provides a process in which epimerization of a chiral center is not a problem.[3,41] The method also accomplishes methylenation of enolizable ketones,[42] a process not very successful with the Wittig reagent.

In some cases, there appears to be competition between reaction of (3) with the carbonyl and with the terminal alkene product. In the latter case a metallacycle is believed to be formed, which, on protonolysis, leads to the product of *gem*-dimethylation of the original carbonyl.[2b,3] This transformation has only been observed with unhindered aldehydes and ketones, but does, in itself, provide a rather useful synthetic sequence (equation 23).

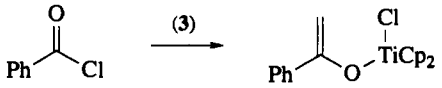


(23)

Amides are converted to enamines by reaction with the Tebbe reagent (equation 24),[2b] whereas acyl halides lead to enolates (equation 25).[43] Anhydrides lead to a combination of enolate formation, methylenation and enolization.[44]



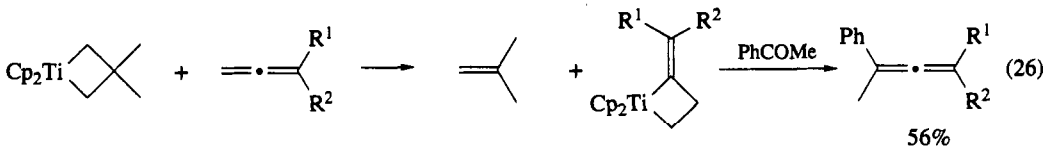
(24)



(25)

The Tebbe reagent is a methylidene transfer reagent. Attempts to prepare the homologous titanium–aluminum reagents, *i.e.* ethylidene, *etc.*, have failed, presumably because β-hydride abstraction destroys the complex.[45] However, some success at homologous alkylidene transfer has been attained through hydroalumination of an alkenyltitanium complex. A spectroscopically identified intermediate is formed which then alkylidenates a ketone carbonyl.[46] This, along with other titanium–aluminum reagent mixtures, suggests the possibility of alkenylation,[47] though none of these potential methods have been used in synthesis.

A rather novel approach makes use of the reaction between the titanium metallacycle (4) and one double bond of an allene to produce a new metallacycle. That new metallacycle then transfers the allene to a carbonyl compound (equation 26).[48]

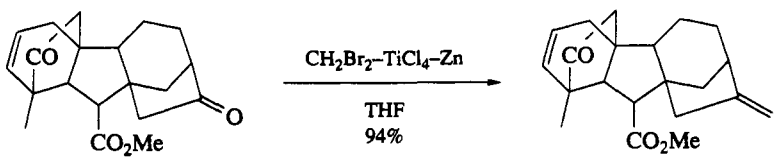


(26)

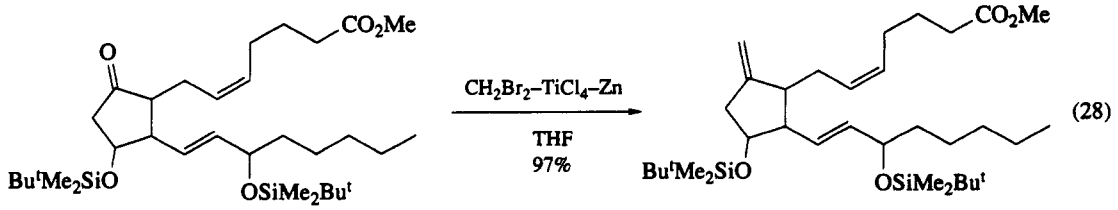
56%

The synthesis of capnellene discussed earlier is an interesting example in which (3) was used to generate a new titanium alkylidene which then underwent an intramolecular reaction with an ester carbonyl. The process effectively involved carbonyl alkylidenation by a substituted titanium alkylidene (equation 14). In this case steric factors apparently account for the desired reaction selectivity.[28]

The Tebbe reagent can be isolated before use or prepared as an *in situ* mixture.[49] Other *in situ* reaction mixtures which mimic many of the synthetic results of the Tebbe reagent have been introduced. For example, a mixture of $TiCl_4$, Zn and CH_2Br_2 provides a reagent that methylenates ketones,[50] including those that are commonly enolized under the conditions of the Wittig reaction.[51] The procedure was used for the methylenation of gibberellins and their analogs (equation 27)[52] and has also been used with other natural products (equation 28).[53]



(27)



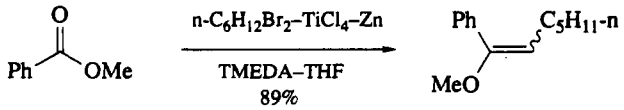
(28)

Dideuteriomethylenation has been accomplished by utilizing CD_2Br_2,[52,54] and ^{13}C has been introduced using $^{13}CH_2Br_2$.[55] The method has been developed as an organic synthesis procedure[50a] and is currently the most widely used of the titanium based methylenating reagents.

The compositions of these types of reagents are not yet understood, though it has been suggested that the active agent may be a *gem*-dimetallic methylene reagent rather than a carbenoid. For example, the reaction of $CH_2(ZnI)_2$ with Cp_2TiCl_2 in THF gives a reagent which methylenates ketones and whose NMR spectral data suggest $Cp_2TiCH_2{\cdot}ZnX_2{\cdot}(THF)$.[56] A reagent containing titanium and magnesium has also been reported to methylenate ketones.[57]

The reagent formed with $TiCl_4$ is reported to give good yields with ketones, though pinacol-type products often result when the carbonyl compound is an aldehyde. However, the use of $Ti(OPr^i)_4$ is reported to be selective for methylenation of aldehydes.[58]

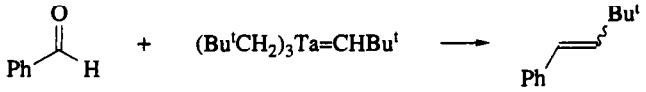
All of the dihaloalkane-based reagent mixtures discussed above have only been reported to be effective for alkylidenation of ketones and in some cases aldehydes. Modification of the $TiCl_4$/Zn dibromoalkane reagent by adding *N,N,N'N'*-tetramethylethylenediamine (TMEDA) is reported to alkylidenate esters,[59] a reaction similar to that of the Tebbe reagent and its metallacycle analogs. The reagent mixtures derived from $TiCl_4$ and Zn have recently been reported to accomplish C_2 and higher alkylidenation by using dihaloalkanes (equation 29).[60]



(29)

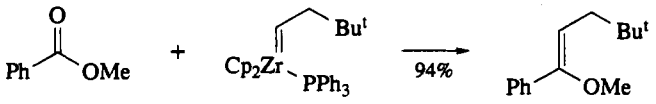
9.3.3.2 Other Transition Metal Based Reagents

Compounds of tantalum and niobium were among the earliest reagents investigated for alkylidene transfer to carbonyl.[2d,61] Ketones, aldehydes, esters and amides were found to react with a neopentylidene reagent. Note that there are no β-hydrogen atoms in this reagent, so that the instability associated with most nonmethylene examples is not present (equation 30). Interestingly, the tantalum analog of the Tebbe reagent ($Cp_2Ta{=}CH_2$) is not an effective methylenation reagent for ketones.[61]



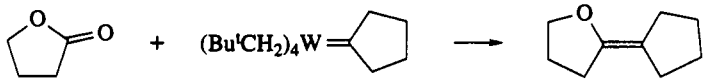
(30)

Zirconium–aluminum analogs of the Tebbe reagent have been reported to react with carbonyl compounds slowly, in low yield[62] or not at all.[63] However, zirconium alkylidenes which are stabilized by a phosphorus rather than an aluminum ligand do transfer their alkylidene moiety to carbonyl.[64] These results provide some of the few examples of long chain alkylidene transfer to carbonyl from an organometallic reagent (equation 31).



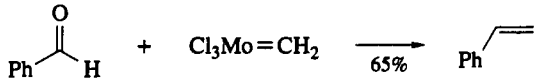
(31)

Tungsten alkylidenes have also been shown to accomplish carbonyl alkylidenation.[65] Aldehydes, ketones, esters and amides have been used as the carbonyl moiety. These reactions involve metallacycle intermediates and appear to parallel much of the metathesis chemistry (equation 32).



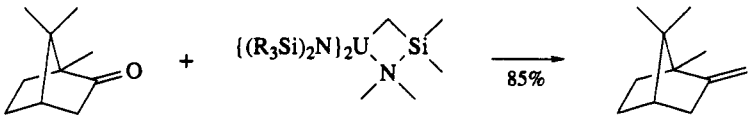
(32)

A series of molybdenum alkylidene complexes react with aldehydes, and in some cases ketones, to give the product of methylenation (equation 33).[66] Some of the examples appear to involve an alkylidene, while others may follow an addition–elimination route typical of the Peterson alkenations.[67] Probably the most interesting aspect of this work is the observation that some of the methylenation reactions can be carried out in aqueous or ethanolic media (equation 33).[66]



(33)

A metallacycle in which uranium, silicon and nitrogen atoms connect to the methylene group has been shown to methylenate a variety of aldehydes and ketones, including some carbonyl compounds which do not react well in the Wittig process (equation 34).[68] This material exemplifies the complexity and sophistication that is being used to develop reagent and catalyst systems.



(34)

9.3.4 CONCLUSIONS

The metathesis reaction between carbon–carbon double bonds (alkene metathesis) is well established in commercial scale synthesis. It is a key component of some polymerization processes and is the route to nonfunctionalized alkenes which find applications in fine chemical synthesis. The development of well-defined, functional group tolerant catalysts will lead to a much greater role for alkene metathesis in synthesis.

The related reaction between carbon–carbon and carbon–oxygen double bonds is just beginning to be developed. This Wittig analog provides new routes for carbonyl alkylidenation of aldehydes, ketones and members of the carboxylic acid family.

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9.4
[2 + 2 + 2] Cycloadditions

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9.4.1 INTRODUCTION

This section will address transition metal mediated cycloaddition processes that fall into the [2 + 2 + 2] category: reactions involving three components, each of which formally contributes two electrons towards the final product of cycloaddition. Since the designation (in square brackets) refers to the electrons and not the atoms contributed by each cycloaddition component, reactions involving cycloaddition participants such as CO, isonitriles and heteroatoms are included. Products formed will include four-membered rings from 2 + 1 + 1 cycloaddition (atom, not electron designation), five-membered rings from 2 + 2 + 1 cycloaddition, and, of course, six-membered rings from 2 + 2 + 2 processes. Several reactions which fall into the formal [2 + 2 + 2] category are covered elsewhere: the Pauson–Khand (2 + 2 + 1) reaction (Volume 5, Chapter 9.1), 2 + 1 + 1 and 2 + 2 + 1 cycloadditions of metal carbenes (Volume 5, Chapter 9.2), and zirconium-promoted 2 + 2 + 1 bicyclization of enynes (Volume 5, Chapter 9.5).

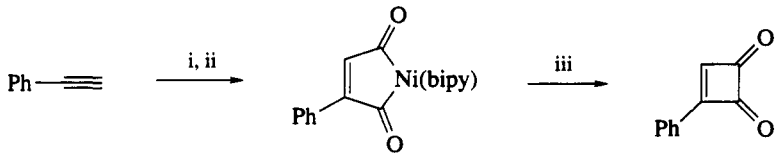
Mechanistically, the term cycloaddition applies in only a formal sense to most of the reactions in the section; virtually none of these reactions involves true single-step cycloaddition of all three components that appear in the final product. More typically, cycloaddition involving a transition metal fragment and one or two other components leads to a metallacyclic intermediate whose reaction with the remaining

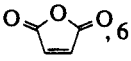
component(s) ultimately gives rise to the final organic ring system.[1] As organic synthesis is the focus of these volumes, this section will not cover cycloaddition reactions that give rise to metal-containing species from which the metal-free organic product cannot readily be liberated.

9.4.2 SYNTHESIS OF FOUR- AND FIVE-MEMBERED CARBOCYCLIC RINGS

9.4.2.1 Cyclobutenediones and Related Compounds

A number of Ni^0 complexes with donor ligands react with unsaturated substrates to give five-membered ring nickelacycles. Upon reaction of either phenyl- or diphenyl-acetylene with (bipy)$Ni(CO)_2$ (bipy = 2,2′-bipyridyl) under carbon monoxide a nickelacyclopentenedione complex forms in high yield. Further reaction with either higher pressures of CO or with maleic anhydride induces reductive elimination, liberating a cyclobutenedione, formally the product of a six-electron 2 + 1 + 1 cycloaddition (Scheme 1). Complex formation also occurs from alkylacetylenes, but subsequent reductive elimination does not, restricting the utility of this chemistry.[2] Similar chemistry had earlier been found in the reactions of $Ni(CNAr)_4$ with diarylalkynes, from which varying yields of diiminocyclobutenes could be isolated.[3]



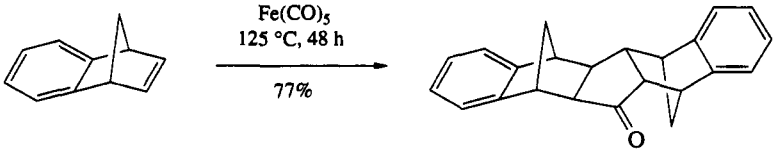
i, (bipy)$Ni(CO)_2$, THF, 24 h; ii, CO, 80 °C, 64% overall; iii,  , 6 h, 80%

Scheme 1

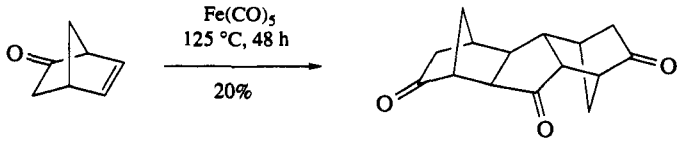
9.4.2.2 Cyclopentanones: Regio- and Diastereo-selectivity

A number of cycloaddition reactions of alkenes with transition metals are known to produce metallacyclopentanes, which in turn may yield cyclopentanones upon treatment with carbon monoxide, the net result being that of a formal 2 + 2 + 1 cycloaddition process. The most general involves the use of any of the iron carbonyls to generate polycyclic ketones directly from strained alkenes, generally compounds related to norbornadiene.[4,5] The reaction may be carried out thermally or photochemically, usually with less than a full equivalent of iron carbonyl. The metallacyclic intermediate is not observed, but proceeds directly to product. Yields are lower with most norbornene derivatives. The reaction is normally completely diastereoselective, generating *exo,trans,exo*-fused cyclopentanone rings, and it proceeds with complete regioselectivity from homoconjugated substrates (equations 1 and 2).[6] The stereochemical course of the reaction may be altered dramatically by remote groups capable of metal coordination (equation 3).[7] A few mixed cycloadditions are known.[8]

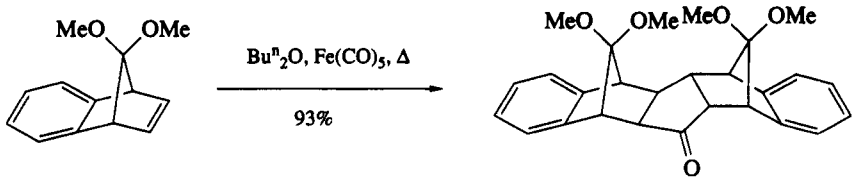
Among simpler cyclic alkenes, cyclobutenes are reported to undergo similar transformations.[9] Cyclopentenes and cyclohexenes react only under extreme conditions, giving very low yields.[10]



(1)

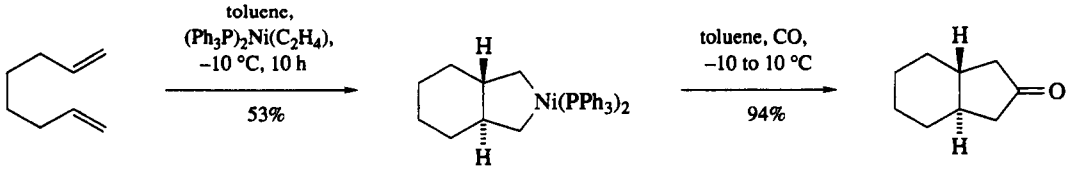


(2)



(3)

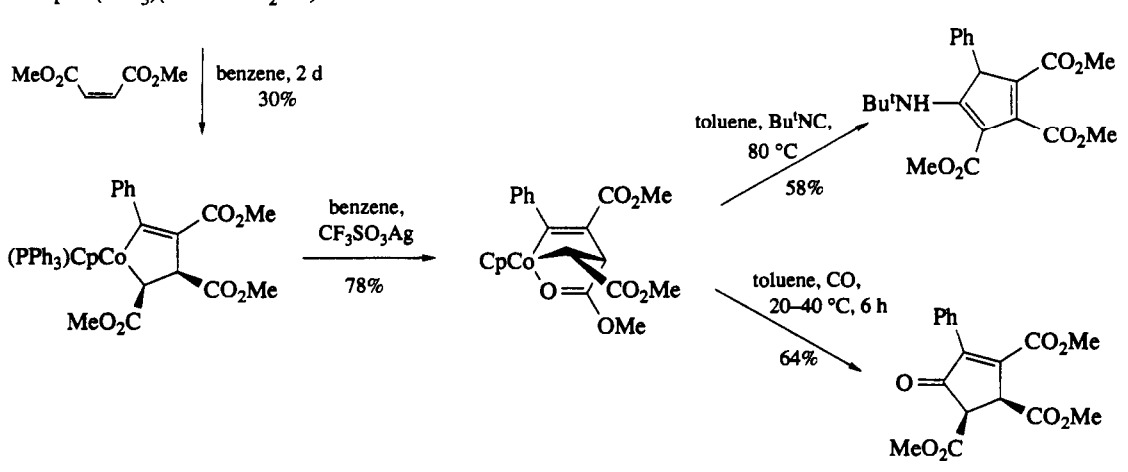
In general, acyclic alkenes do not give cyclopentanones upon reaction with low-valent metals and CO. Although a large number of metallacyclopentanes are known, many of which give cyclopentanones upon carbonylation, most are not readily formed from the corresponding alkenes and must be prepared in other ways.[11–14] Noteworthy exceptions include the completely regioselective reaction of methyl acrylate with iron carbonyl[15] and an intramolecular variant using α,ω-dienes with Ni^0 (Scheme 2). The latter reaction is completely diastereoselective to give the *trans*-fused bicyclic from the 1,7-diene; reaction of 1,6-heptadiene to give bicyclo[3.3.0]octan-3-one is however a much lower yield process (25%) exhibiting only 3:1 *trans/cis* diastereoselectivity.[16]



Scheme 2

9.4.2.3 Cyclopentenones and Related Compounds: Chemo-, Regio- and Diastereo-selectivity

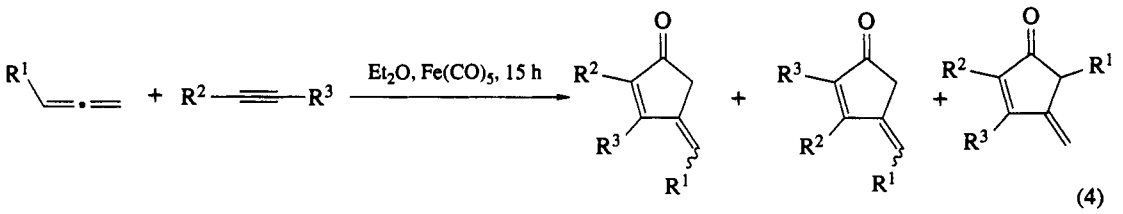
Although the Pauson–Khand reaction (Volume 5, Chapter 9.1) and the Negishi bicyclization (Volume 5, Chapter 9.5) are the two most thoroughly studied cyclopentenone syntheses using transition metals, several additional methods exist. Metallacycles derived regioselectively from alkynes, alkenes containing ester groups, and the CpCo fragment (Cp = η^5-C_5H_5) react with carbon monoxide to give cyclopentenones, and with isonitriles to give the corresponding enamines (*i.e.* 1-amino-1,3-cyclopentadienes) (Scheme 3).[17] As the Pauson–Khand reaction is ill-suited for substrates bearing electron-withdrawing groups, this method is complementary in scope.



Scheme 3

A cycloaddition of alkynes, *allenes* and CO under conditions that generate the $Fe(CO)_4$ fragment gives rise completely regioselectively to 4-methylenecyclopentenones (equation 4). Terminal alkynes are incorporated with the substituent largely or totally in the 2-position of the product, and the substituent in unsymmetrical allenes ends up preferentially on the exocyclic carbon rather than at position 5. Although

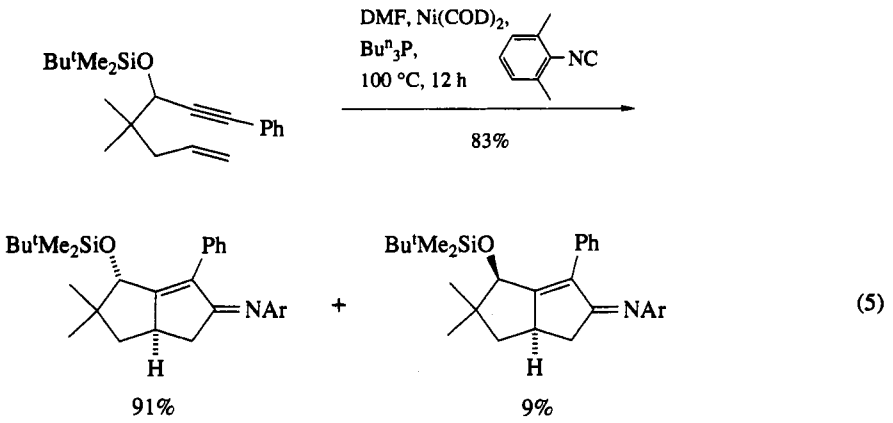
the (*Z*) diastereoisomer of the exocyclic double bond appears to be the kinetic product, isomerism readily occurs thermally in the presence of the metal carbonyl.[18]



(4)

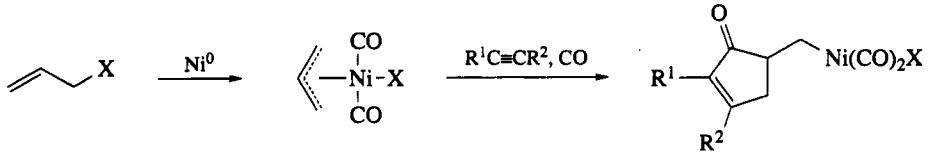
R^1	R^2	R^3					
H	Ph	H	15%	75%		25%	–
Ph	H	H	48%		100%		0%
Ph	Ph	H	18%	100%		0%	0%
$PhCH_2$	Ph	Ph	25%		80%		20%

An intramolecular reaction of 1,5- and 1,6-enynes with isonitriles takes place in the presence of $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) and phosphines, giving bicyclic cyclopentenone imines (equation 5).[19] Stereochemical characteristics in substituted systems appear to parallel those in the intramolecular Pauson–Khand: enynes with substituents in propargylic positions cyclize preferentially to products in which those substituents occupy *exo* positions relative to the newly created ring fusion. It is likely that these reactions proceed *via* similar mechanisms involving insertion into bonds of metallacycles, although the order of incorporation of the three two-electron systems into the precursor to the final product is open to question in the nickel system.



(5)

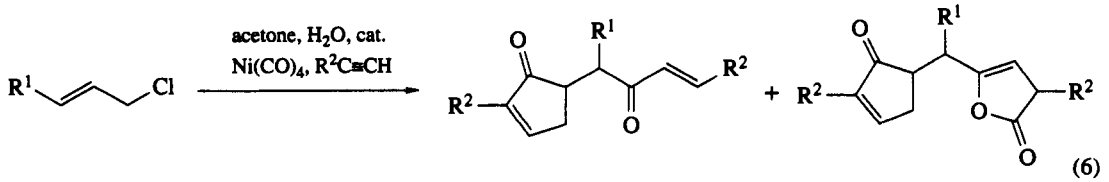
In a mechanistically quite different process $Ni(CO)_4$ is the catalyst precursor and the double bond of an allylic halide serves as the alkene component in another cyclopentenone synthesis. Sequential insertion of the alkyne and CO into an initially formed allyl–Ni complex leads to the primary cyclization product, a (2-oxo-3-cyclopenten-1-yl)methylnickel complex (Scheme 4). The final product of the sequence depends on which of several possible reactions of the latter take place. Important features of this reaction have been described in several reviews.[20–22]



Scheme 4

A variety of alkynes follow this reaction sequence in reactions with allyl and crotyl chlorides, as well as with methyl 4-bromocrotonate. All examples proceed with total regioselectivity with respect to carb-

on–carbon bond formation between unsubstituted carbon atoms of unsymmetrical alkynes and allyl derivatives. The final products are derived from further insertions of CO and alkyne, followed either by protonolysis to give an enone side chain, or another CO insertion and cyclization to a lactone (equation 6).[23] Chemoselectivity is to some extent possible by control of reaction conditions. Methallyl halides are anomalous in giving rise to six- instead of five-membered ring products.[24]

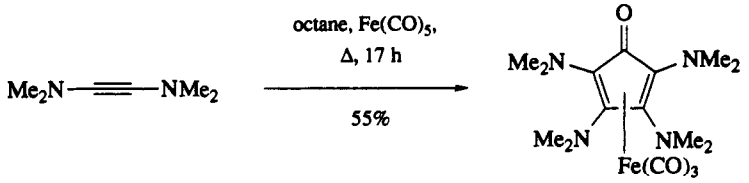


(6)

R^1	R^2			
H or Me	H		0%	major product
H	Me	84%	33%	67%
H or Me	Ph	68–71%	94–100%	0–6%

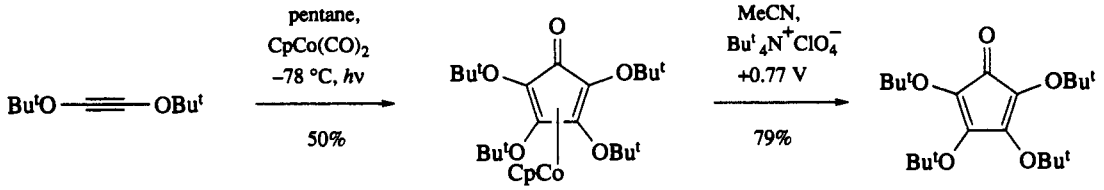
9.4.2.4 Cyclopentadienones and Related Compounds: Chemo- and Regio-selectivity

In 1953 Reppe reported the isolation of 1-indanone, the product of decarbonylation of the Diels–Alder dimer of cyclopentadienone, from the reaction of acetylene with $Ni(CO)_4$.[25] A wide variety of metal-based systems have been found to be capable of such chemistry, and both indanone and cyclopentadienone dimer are occasionally encountered as byproducts of reactions involving acetylene and metal carbonyl systems.[26] The interaction of a variety of transition metal fragments with alkynes has also long been known to give rise to cyclopentadienones in the form of metal-bound complexes.[27] Reactions of the iron carbonyls with alkynes are typical, producing varying yields of cyclopentadienone–$Fe(CO)_3$ complexes under thermal conditions. Examples include $Fe(CO)_3$-complexed tetrakis(dimethylamino)cyclopentadienone, which is obtained in moderate yields from $Fe(CO)_5$ in refluxing octane,[28] and the tetracyclopropyl[29] and tetraisopropyl[30] analogs, which are accessible in somewhat lower yields, from $Fe_3(CO)_{12}$ at 175–180 °C (equation 7). Treatment of the latter two complexes with trimethylamine oxide enables isolation of the metal-free dienones and is the most reliable general method for liberation of stable cyclopentadienones from complexation with metal carbonyl fragments.



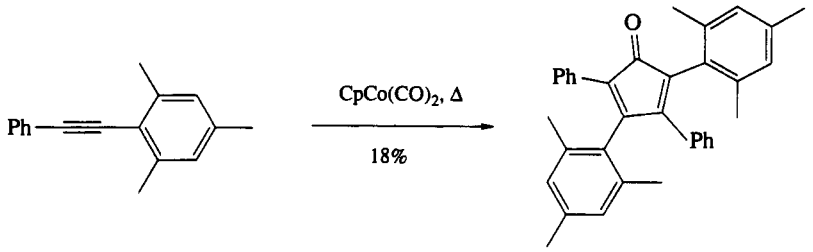
(7)

Stable, isolable metallacycles are also obtained from reaction of complexes that serve as sources of the CpCo fragment (*e.g.* $CpCo(PPh_3)_2$) and alkynes. Upon carbonylation these typically give high yields of cobalt-complexed cyclopentadienones.[31,32] Direct reaction of $CpCo(CO)_2$ with alkynes is similarly useful. The cycloaddition of di(*t*-butoxy)acetylene upon photolysis with $CpCo(CO)_2$ is an example (Scheme 5). In all these systems the final complexes lack coordinated CO, and therefore amine oxides are not suitable reagents for liberating the stable cyclopentadienones. Tetra(*t*-butoxy)cyclopentadienone is accessible on a preparative scale *via* controlled electrochemical oxidation.[33] Other oxidants such as Cr^{VI} have been used as well in other systems.



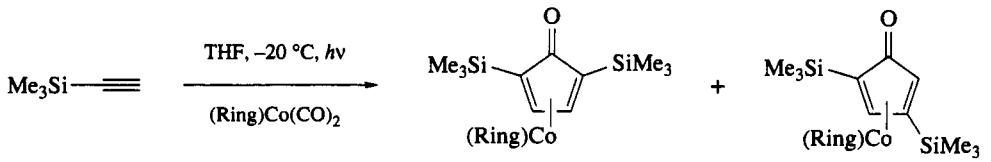
Scheme 5

Unsymmetrically substituted alkynes display a significant degree of regioselectivity in these reactions, usually in favor of products with the larger substituents in positions 2 and 5, with lesser amounts of 2,4-disubstituted products.[34] Isolated examples are known where the latter, unsymmetrical products predominate, usually as a result of extreme steric interactions that would be generated around the metal upon coupling the less-hindered ends of the two alkynes (equation 8).[35,36]



(8)

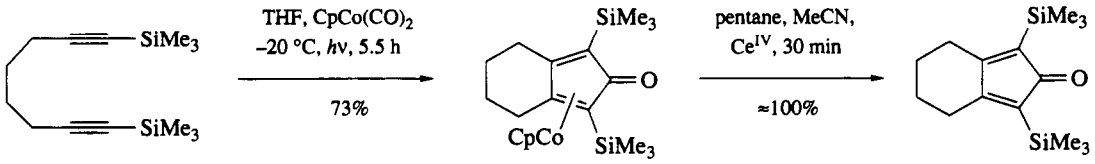
A number of examples exist involving reactions of $CpCo(CO)_2$ and silylated alkynes. Cycloaddition of $Me_3SiC{\equiv}CH$ gives a 3:1 mixture of 2,5- and 2,4-bis(trimethylsilyl)cyclopentadienone complexes. The use instead of $[C_5Me_5]Co(CO)_2$ reverses the regioselectivity to 1:3.7, presumably due to the increased steric crowding about cobalt (equation 9).[37] This effect has yet to be exploited in synthesis.



(9)

Ring		
Cp	75%	25%
C_5Me_5	21%	79%

In this general area quite efficient intramolecular examples have been described as well (Scheme 6). A thorough examination of the intermediates and likely mechanisms associated with this system has been published.[38] In particular, it has been found that the type of metallacycle formed depends on the length of the chain separating the two alkyne units in the diyne. Efficient intramolecular cycloaddition to a bicyclic metallacycle occurs only from 1,6- and 1,7-diynes. The poor results on attempted cyclization of 1,5-diynes to give highly strained bicyclo[3.2.0]hepta-1,4-dien-3-ones result from resistance towards closure of the strained four-membered ring upon metallacycle formation.[39]

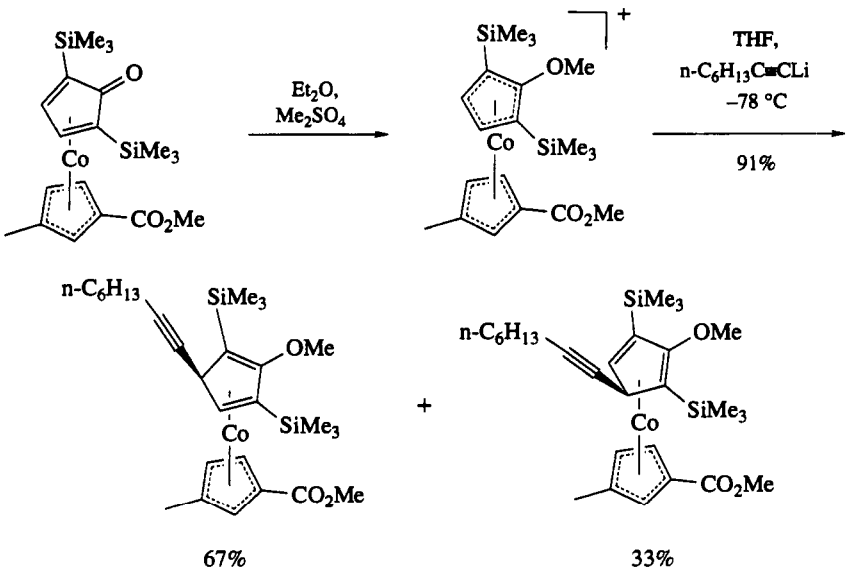


Scheme 6

The use of complexes in which unsymmetrical disubstitution is present on the Cp ring leads to diastereoselection in the cycloaddition process, leading to chiral cyclopentadienone complexes.[40] In the course of subsequent transformations stereochemical information has been shown to be transferable to the complexed cyclopentadienone ring (Scheme 7).[41]

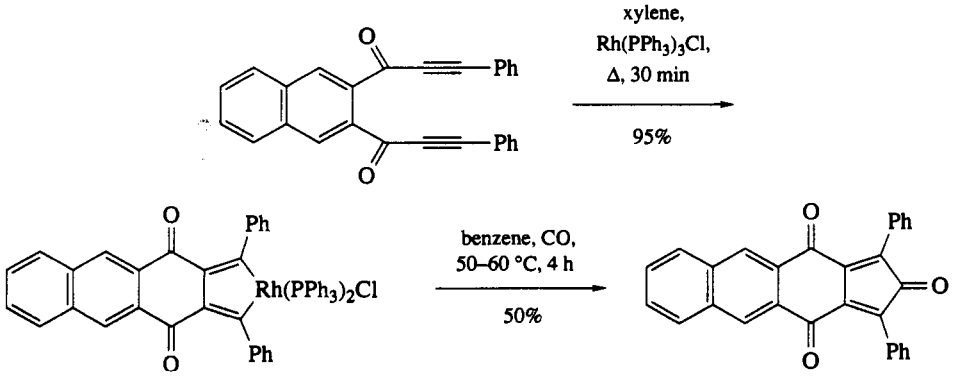
Although catalytic preparations of cyclopentadienones with other metal systems are known, chemoselectivity is often a problem. For example, the reactions of 2-butyne, 3-hexyne and diphenylacetylene with $[(CO)_2RhCl]_2$ at 80 °C give mixtures of hexasubstituted benzenes, metal-complexed, tetrasubstituted cyclopentadienones and quinones.[42] An exception is the preparation of the stable tetrakis(trifluoromethyl)cyclopentadienone from the alkyne;[43] the unusual electronic properties of the product make this result lack generality.

Also lacking generality due to chemoselectivity problems are attempts at achieving intramolecular cycloadditions from α,ω-diynes in the presence of iron carbonyls.[44,45] An efficient two-stage intramolecu-



Scheme 7

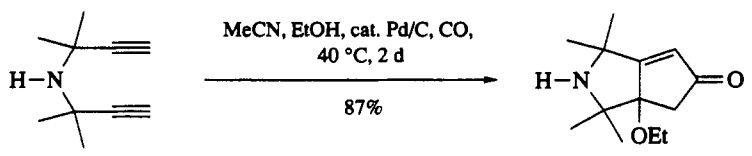
lar process starting with a variety of α,ω-diphenyldiynes and a rhodium-based reagent is known, however. Reaction with tris(triphenylphosphine)rhodium(I) chloride gives excellent yields of the corresponding rhodacyclopentadienes, which give the dienones upon carbonylation (Scheme 8). In addition, the corresponding imines are formed upon reaction with isonitriles.[46]



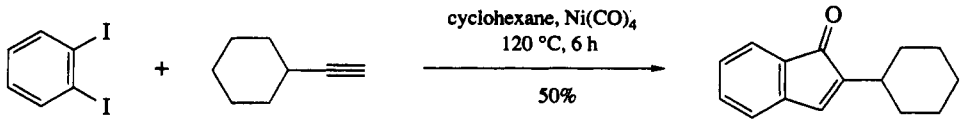
Scheme 8

A catalytic, completely regioselective conversion of 4,4-dimethyl-2-pentyne (methyl-*t*-butylacetylene) to 2,5-di(*t*-butyl)-3,4-dimethylcyclopentadienone is mediated by $(PhCN)_2PdCl_2$.[47] Other examples exist for early[48] as well as late transition metals, and an isonitrile has been used as a CO equivalent in one Ni^0-based system as well.[49] Finally, a heterogeneous catalytic intramolecular cycloaddition of diynes has been developed, leading to cyclopentadienones which either dimerize (Diels–Alder) or in certain cases may be trapped by nucleophiles (equation 10).[50]

Using $Ni(CO)_4$ as both reducing agent and cycloaddition mediator, *o*-diiodobenzene may be induced to serve as a benzyne equivalent in a cycloaddition with alkynes leading to indenones. Yields are consistently good and regioselectivity with terminal alkynes for the 2-substituted product excellent (equation 11).[51,52]



(10)

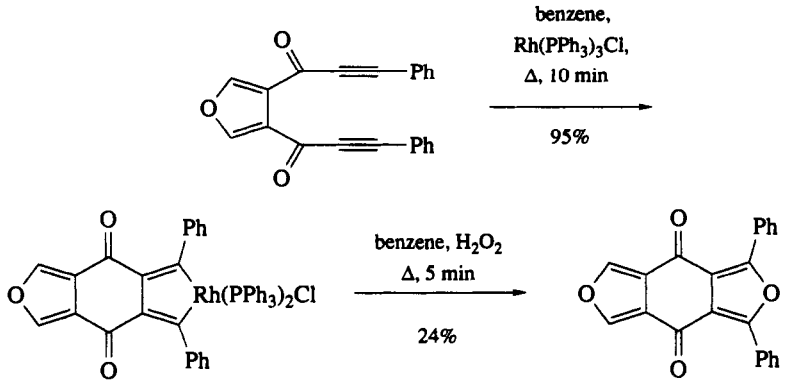


(11)

9.4.3 SYNTHESIS OF FIVE-MEMBERED HETEROCYCLIC RINGS

9.4.3.1 Furans

Oxidation of rhodacyclopentadienes, prepared from diynes as shown in Scheme 8, with either atmospheric oxygen or with peroxides gives furans in modest yields (Scheme 9).[46]



Scheme 9

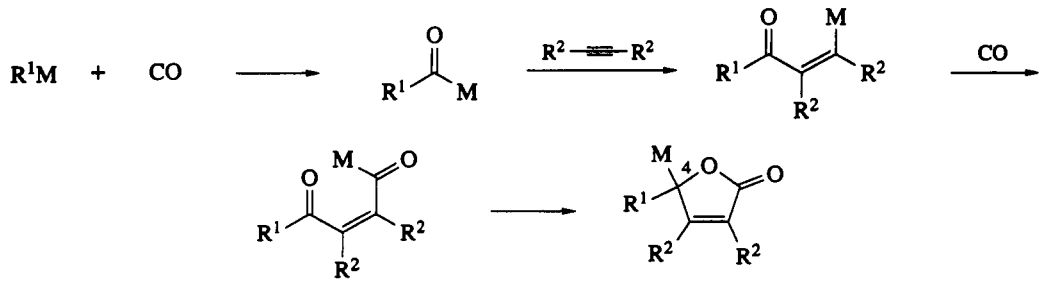
In an isolated intermolecular example air oxidation of the polymeric metallacycle derived from dimethyl acetylenedicarboxylate and a source of Pd^0 gives a 45% yield of the corresponding furan tetraester.[53]

9.4.3.2 Furanones: Regioselectivity

The synthesis of furanones (γ-lactones) from alkynes and carbon monoxide consititutes a unique variation of the [2 + 2 + 2] pattern. The ring incorporates both carbons from the C≡C, the carbon from one CO, and both carbon and oxygen from the other CO. The process is therefore a 2 + 2 + 1 cycloaddition of the form $[2\pi_{C\equiv C} + 2\pi_{C=O} + 2n_{CO}]$. The formal result of such a cycloaddition is a carbene at position 4, the carbon atom of the π_{CO} participant (equation 12).

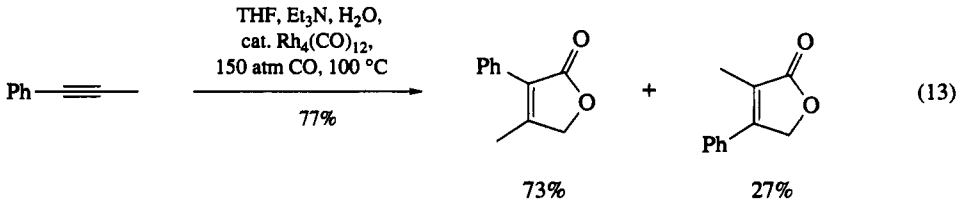
(12)

In one common mechanistic version of the reaction one of the molecules of CO is incorporated as a metal acyl. Insertions of alkyne and CO lead to a 4-keto-2-alkenoyl metal derivative. Cyclization *via* insertion of the 4-keto group into the acyl–metal bond generates a 4-metallalactone complex containing both the metal and the R group originally present in the starting acyl RCOM attached to C-4 of the new ring (the 'carbenoid' carbon mentioned above) (Scheme 10). Regioselectivity with regard to alkyne insertion is normally controlled sterically, with the first new carbon–carbon bond forming between the acyl carbonyl and the less sterically hindered alkyne carbon. This places the larger alkyne substituent closer to the lactone carbonyl group. Model studies have confirmed the feasibility of mechanistic variations such as η^3 (allyl) complexation to the metal.[54]



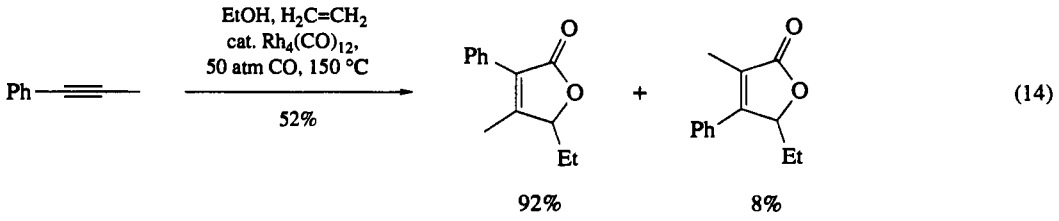
Scheme 10

Unsaturated lactones lacking substitution at C-4 are the simplest ones available *via* this general type of cycloaddition. Several syntheses of these lactones are of practical value, including two Pd-based methods.[55] However, the considerable utility of metal carbonyl anions in lactone synthesis is illustrated by a rhodium carbonyl anion catalyst system which gives very high yields upon reaction with a variety of internal alkynes under weakly basic aqueous conditions, essentially water–gas shift conditions. These conditions were established to maximize chemoselectivity with respect to other possible alkyne carbonylation products. Regioselectivity is modest in this process, but was not examined systematically (equation 13).[56]



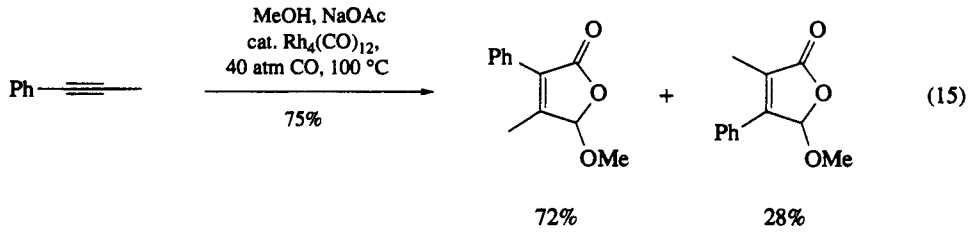
(13)

Addition of an alkene insertion step to the sequence above prior to reductive elimination of the final product gives an alkene-derived R group. Although for reliable results the reaction is restricted to ethylene, giving an ethyl substituent at C-4, yields and alkyne regioselectivity are reasonable (equation 14).[57]



(14)

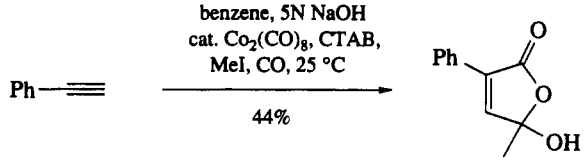
In still another variation on the above Rh-catalyzed system, lactones with 4-alkoxy substitution are obtained from internal alkynes by omitting the alkene and introducing one of several oxygen bases (equation 15).[58] As before the reaction is characterized by good yields and modest regioselectivity. The mechanism involved here is not well understood.



(15)

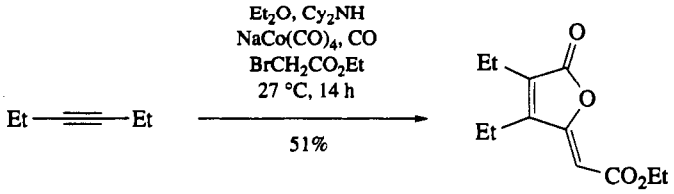
Several first-row metals display varying utility in stoichiometric lactone syntheses. The general mechanism described above is followed in a reaction sequence that begins with acyl complexes derived from reaction of $^{-}Co(CO)_4$ with MeI and CO. Under phase transfer conditions these react with alkynes to give

4-keto-2-alkenoylcobalt intermediates. These in turn react with hydroxide to give an unsaturated keto acid, which cyclizes spontaneously to a γ-hydroxylactone (equation 16).[59] The reaction is general for terminal alkynes and displays total regioselectivity. Saturated 2,4-disubstituted-γ-butyrolactones are formed in a similar process that uses manganese carbonyl anions instead of cobalt.[60]



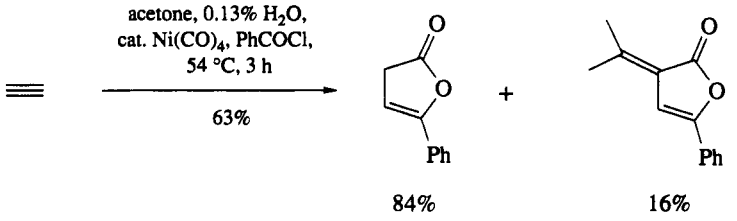
(16)

When the acylcobalt species is derived from a compound containing halogen on an activated carbon (*e.g.* an α-halo ester or nitrile) an elimination may occur to introduce an exocyclic double bond in the final product. This sequence, leading to lactones of pentadienoic acids, is general for both terminal and internal alkynes in the presence of amine bases (equation 17).[61]



(17)

Acyl halides and alkynes also give lactones upon reaction with $Ni(CO)_4$ in an aqueous acetone medium. The result in this system is typically a β,γ-unsaturated lactone, formed together with some product derived from condensation with molecules of solvent (equation 18).[62] Lactones are also formed in low yield as byproducts from the reactions of acylnickel carbonyl anions (derived from addition of RLi to $Ni(CO)_4$) with terminal alkynes at –30 °C.[63] A single example of γ-aminolactone formation is reported from 2-butyne, CO and diethylamine, catalyzed by $(Et_2NH)_2NiBr_2$.[64]

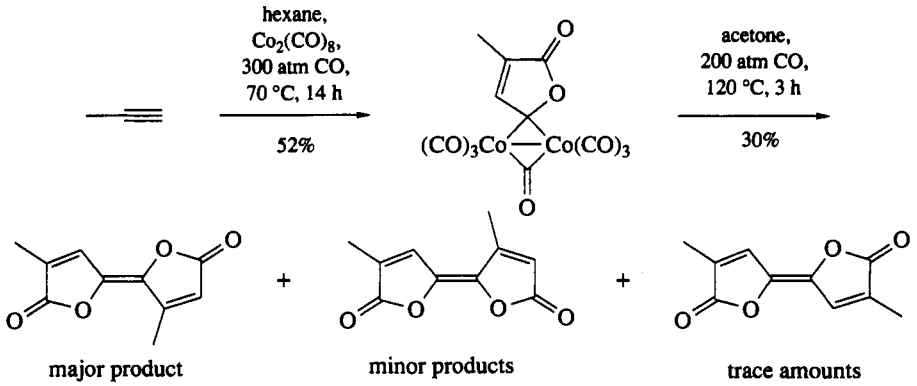


(18)

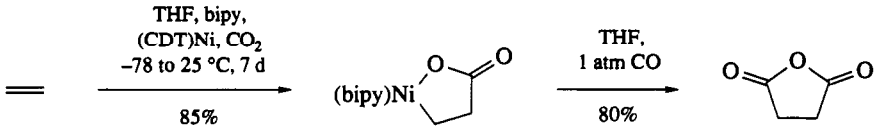
Of more specialized interest is the reaction of alkynes with $Co_2(CO)_8$ in polar solvents under conditions of elevated temperature and CO pressure. The major products are the (*E*) and (*Z*) isomers of so-called bifurandiones, the products of formal (but not actual) carbene dimerization.[65] An intermediate, a complex of this lactone-derived carbene bridging a $Co_2(CO)_7$ moiety, may be isolated from reactions of alkyl-, aryl- or dialkyl-acetylenes with $Co_2(CO)_8$. Its formation is completely regioselective even for ethyl *vs.* methyl, placing the larger group α to the lactone carbonyl.[66,67] In the subsequent formation of the bifurandione itself regioselectivity in alkyne incorporation into the second ring is incomplete and in the *opposite direction*, an observation which remains unexplained (Scheme 11).[68–70]

9.4.3.3 Furandiones

Formal $[2\pi_{C=C} + 2\pi_{CO_2} + 2n_{CO}]$ and $[2\pi_{C\equiv C} + 2\pi_{CO_2} + 2n_{CO}]$ cycloadditions give rise to 2,5-furandiones (succinic and maleic anhydrides). Thus the complex (CDT)Ni^0 (CDT = 1,5,9-cyclododecatriene) reacts with either alkenes or alkynes and CO_2 in the presence of diamines or diphosphines to give 5-nickelafuranones. Upon exposure to CO these give the corresponding anhydrides (Scheme 12).[71] Ethylene, acetylene and 2-butyne have been carried through this sequence.



Scheme 11



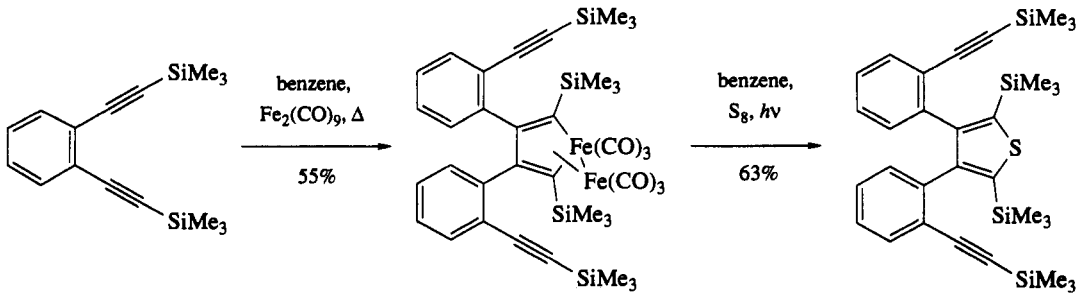
Scheme 12

9.4.3.4 Thiophenes, Selenophenes and Similar Heterocycles: Regioselectivity

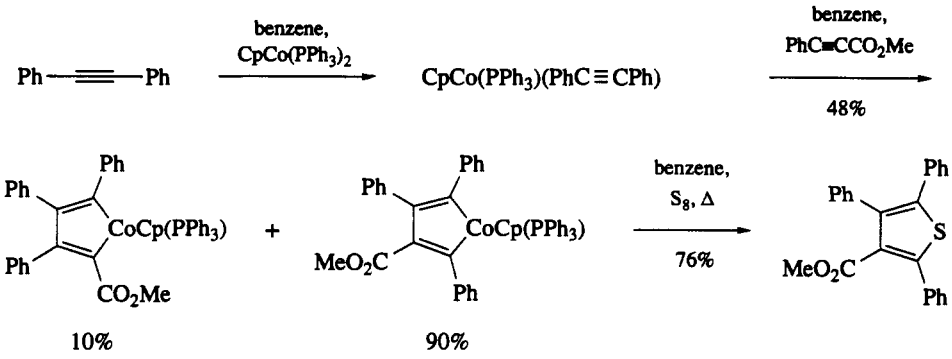
In contrast to the limited number of approaches to furans, several metallacyclopentadienes derived from reactions of alkynes with appropriate metal complexes may be used as precursors to other five-membered ring heteroaromatics. As was the case with furans, rhodacyclopentadienes are usable for conversion to thiophenes and selenophenes, although yields are typically low.[46,72] Iron-containing metallacycles may also be employed as precursors to thiophenes, however, and some of the yields obtained in reactions with S_8 are quite good (Scheme 13).[73] Greater flexibility is obtained using a cobalt-based process which allows the sequential incorporation of two different alkynes, followed by a heteroatom, into a heterocyclic product.[74] Typically reaction of $CpCo(PPh_3)_2$ at room temperature with first one and then a second alkyne proceeds in good yield to the cobaltacycle with good to excellent regioselectivity in most cases, forming the new carbon–carbon bond between the least sterically hindered alkyne carbons. Reaction with elemental sulfur or selenium gives rise to the final heterocycle (Scheme 14).

In one case, formation of the thiophene from sulfur and dimethyl acetylenedicarboxylate, a viable catalytic procedure was optimized (75% yield) by using CpCo(COD) and elemental selenium, which promotes thiophene formation in refluxing toluene. The role of the Se is not known, and the implications of these results have not been explored.[75]

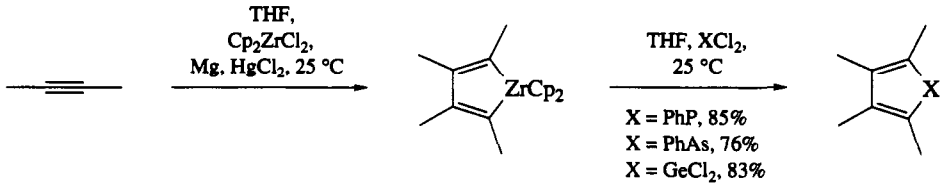
A wide variety of main group heteroatom-containing ring systems are formed by the reaction of appropriate reagents with metallacycles derived from cycloaddition of 'Cp_2Zr^{II}' with alkynes, diynes, dienes, enynes or alkynenitriles. This is an exceptionally general process of considerable potential, especially for the synthesis of less-common types of heterocycles (Schemes 15 and 16).[76]



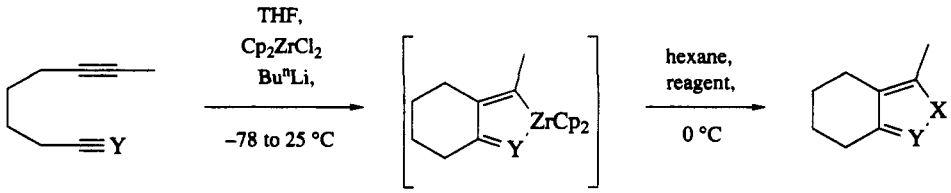
Scheme 13



Scheme 14



Scheme 15

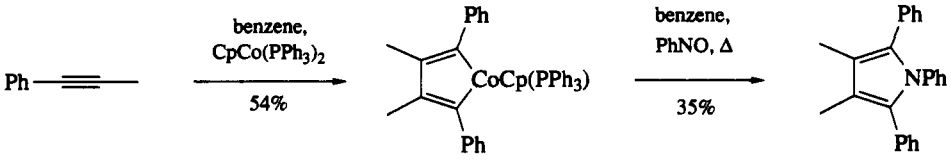


Y	*Reagent*	*Yield (%)*	*X*
CH	S_2Cl_2	55	S
CH	Se_2Cl_2	53	Se
CH	Me_2SnBr_2	82	$SnMe_2$
N	S_2Cl_2	65	S

Scheme 16

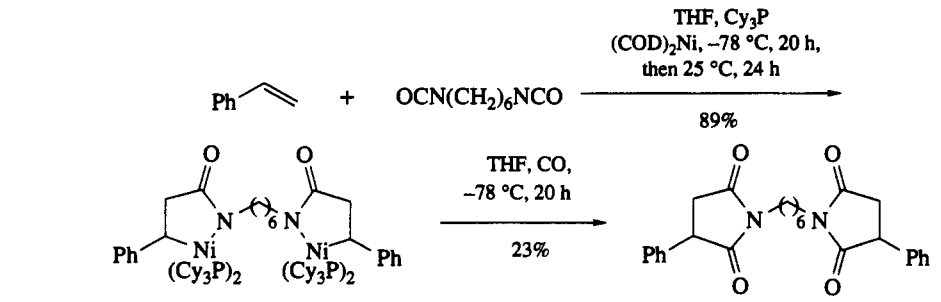
9.4.3.5 Pyrroles and Related Compounds

Both the rhodium- and cobalt-containing metallacycles described in the previous section react with nitrosobenzene to give low yields of *N*-phenylpyrroles (Scheme 17).[46,72,74]

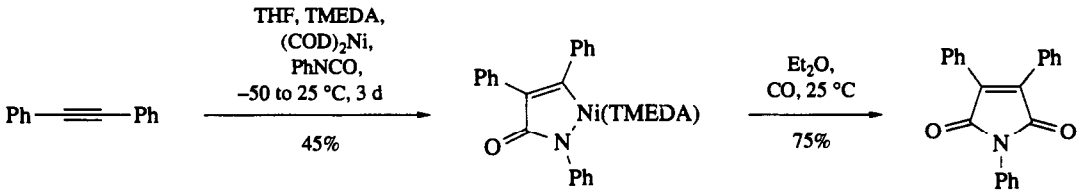


Scheme 17

Succinimides and maleimides are accessible *via* processes analogous to those described for the corresponding anhydrides (see Section 9.4.3.3). Reactions of $(COD)_2Ni^0$ with either alkenes or alkynes and isocyanates (*i.e.* heterocumulene analogs of CO_2) give azametallacycles that upon carbonylation yield cyclic imides. With alkenes high yields of metallacycles are formed from both simple isocyanates as well as α,ω-diisocyanates. Carbonylation yields are variable, however (Scheme 18). Alkynes give lower metallacycle yields but high yields of the final imide (Scheme 19).[77]

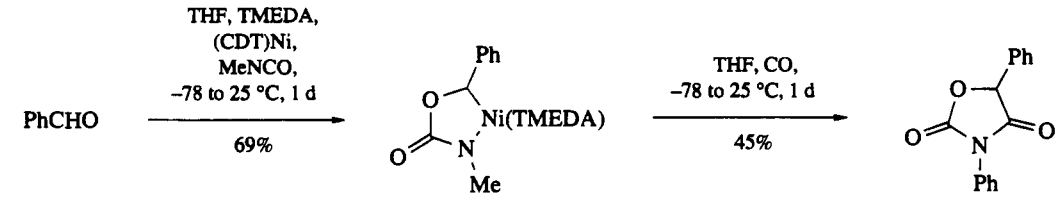


Scheme 18



Scheme 19

Allenes may take the place of alkenes in this process, leading to *exo*-methylenesuccinimides as products. With unsymmetrically substituted allenes, the less-substituted double bond is chemoselectively incorporated into the heterocyclic ring.[78] The alkene may also be replaced by an aldehyde in this cycloaddition, leading to 1,3-oxazole-2,4-diones (Scheme 20).[79]



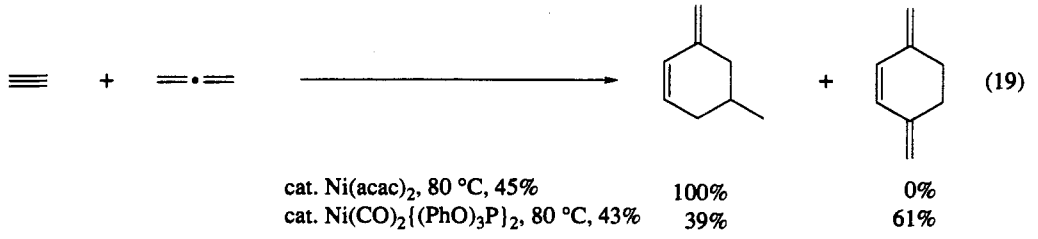
Scheme 20

9.4.4 SYNTHESIS OF SIX-MEMBERED CARBOCYCLIC RINGS

9.4.4.1 Cyclohexanes and Cyclohexenes: Regioselectivity

There are few cycloadditions involving either three alkenes, to produce cyclohexanes, or two alkenes and an alkyne, to produce cyclohexenes.[80] The appropriate metallacyclic precursors containing the CpCo fragment have in fact been prepared and examined for reactivity. Both cobaltacycloheptanes and cobaltacycloheptenes undergo β-hydride elimination, producing 1-heptenes and 1,6-heptadienes respectively, in preference to reductive elimination of the metal and coupling to produce cyclic products.[81]

Nonetheless, there are a small number of systems that do mediate such [2 + 2 + 2] cycloadditions. With allenes as the 'alkene', cycloaddition with both acetylene and terminal alkynes proceeds regioselectively to give 3,5-dimethylenecyclohexenes using Ni^{II} catalysts, and mostly 3,6-dimethylenecyclohexenes using Ni^0 catalyst precursors (equation 19).[82] Norbornadiene undergoes so-called 'homo-Diels–Alder' cycloaddition with both alkenes and alkynes in the presence of nickel catalysts.[83] Further elaboration of this chemistry with alkynes but not alkenes has been described using a Co/Al catalyst system (equation 20).[84] Attempts to produce cyclohexenes *via* all-intramolecular [2 + 2 + 2] cycloaddition of 1,13-dien-7-ynes or 1,11-dien-6-ynes have been unsuccessful.[85]



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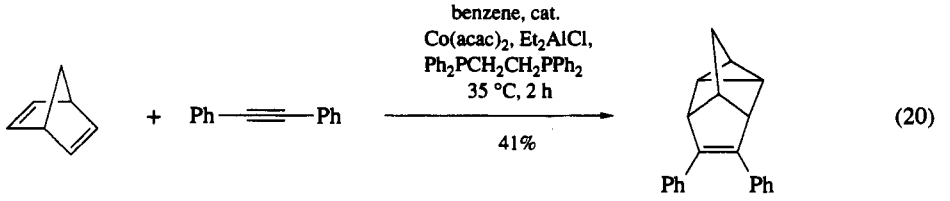


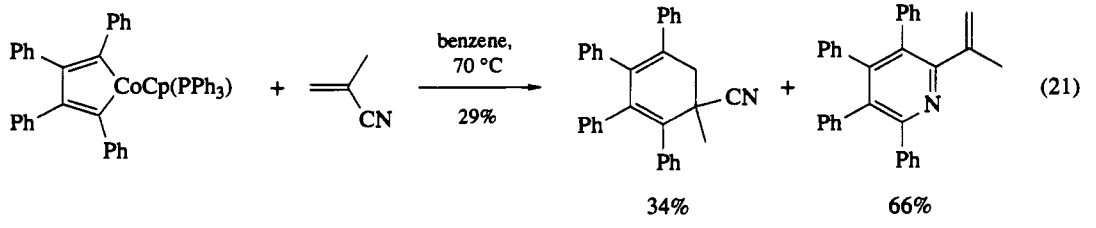
(20)

9.4.4.2 Cyclohexadienes: Regio- and Diastereo-selectivity

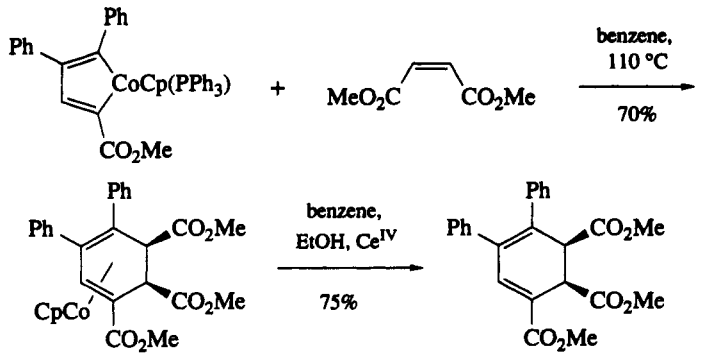
The synthesis of the 1,3-cyclohexadiene system using transition metals has generally involved reaction of the intermediate metallacyclopentadiene derived from two alkynes and a metal fragment with an alkene. Many systems have been developed for this process, although sensitivity of the product diene towards aromatization or other subsequent reactions is an occasional problem.[86] The alternative insertion sequence, involving a metallacyclopentene derived from one alkyne and one alkene, is generally unsuitable as reactions of such species with alkynes usually give linear products. Thus the cobaltacyclopentadiene derived from diphenylacetylene reacts *stoichiometrically* with methacrylonitrile to give both cyclohexadiene and pyridine products (equation 21) (see Section 9.4.5.1). However, reaction of diphenylacetylene with methacrylonitrile in the presence of catalytic amounts of the monoalkyne complex $CpCo(PPh_3)(PhC{\equiv}CPh)$ leads only to acyclic products. Thus the alkene and not the alkyne preferentially complexes to the metal, and the cobaltacyclopentene, once formed, reacts with additional alkene to form linear products instead of undergoing cycloaddition with the alkyne.[87] Only occasionally does the alkyne compete sufficiently well for complexation to the metal to prevent metallacyclopentene formation, in which case catalytic cycloaddition is possible.[74] Thus under most circumstances cyclohexadiene formation requires that the metallacyclopentadiene be preformed, and then reacted stoichiometrically with alkene. Incorporation of the alkene is highly diastereoselective with retention of stereochemistry. Typically the product is isolated as a diene–metal complex from which the metal is removed by oxidation (Scheme 21).[88]

Although cobaltacyclopentene complexes react preferentially with alkenes, they can be preformed and reacted with alkynes, providing an alternative stoichiometric permutation for 1,3-cyclohexadiene synthesis (Scheme 22).[89]

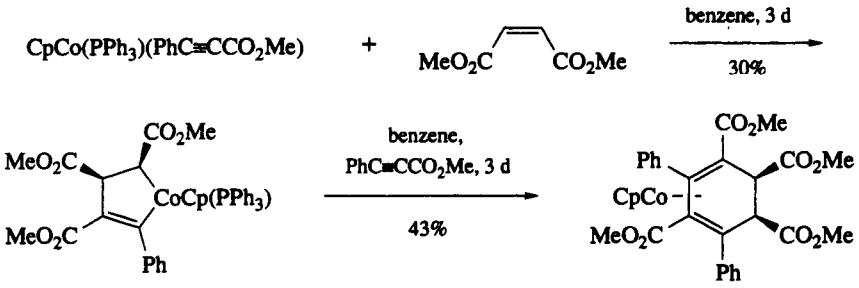
Regioselectivity in metallacyclopentadiene formation has been considered in earlier sections (Sections 9.4.2.4 and 9.4.3). As the examples show, mixtures are typically formed containing isomers in which the larger alkyne substituents are either in positions 2 and 4 or positions 2 and 5, resulting in cyclohexadienes with the large groups in either a 1,3- or a 1,4-disposition. Total regioselectivity (larger group at C-2 or C-5 in the metallacycle) may be achieved with alkynes containing attached groups sufficiently different in size, *e.g.* Ph or CO_2Me *vs.* Me, or anything *vs.* H. Systematic examination of alkene regioselectivity has not been done. Exceptional 1,3-selectivity is found in the Ni^0-catalyzed cocycloaddition of phenylacetylene with *N*-methylmaleimide (equation 22).[90]



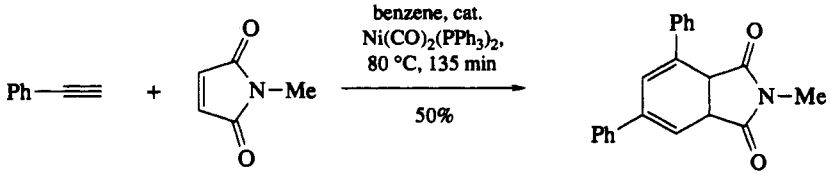
(21)



Scheme 21

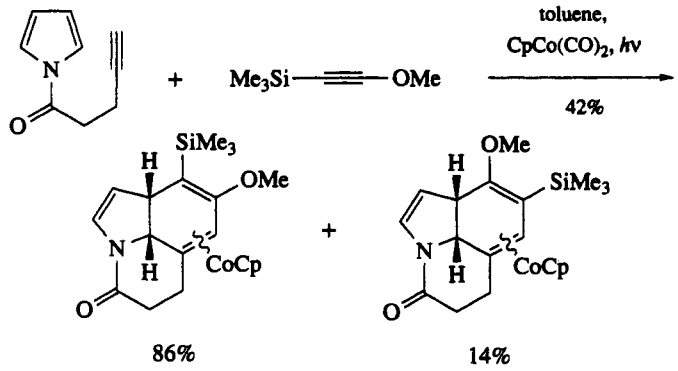


Scheme 22



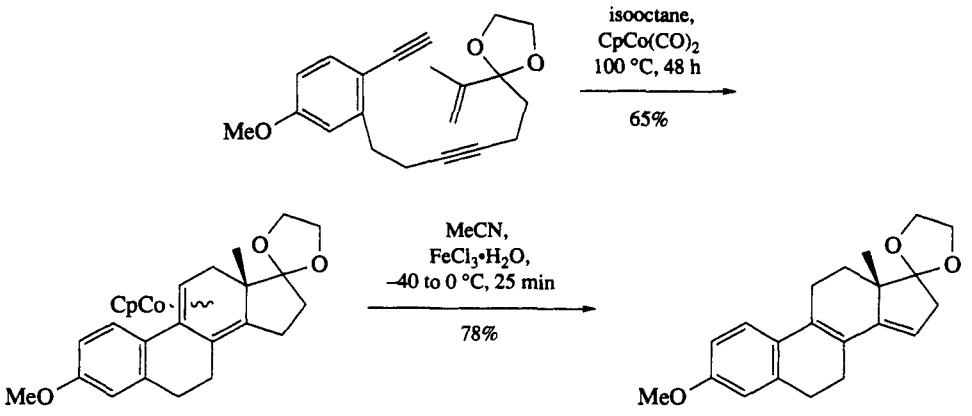
(22)

Partially intramolecular versions of this process, *e.g.* cycloadditions of α,ω-enynes with alkynes, give only low yields of ring-fused 1,3-cyclohexadienes, even when hindered alkynes incapable of cyclotrimerization side reactions (*e.g.* $Me_3SiC{\equiv}CSiMe_3$) are used (see Section 9.4.4.3).[91] However, when the alkene portion of the enyne is part of a heteroaromatic ring such as a pyrrole, an indole or an imidazole, cycloaddition has been found to proceed smoothly, allowing access to remarkably complex heteropolycyclic products.[92–94] Regioselectivity with regard to incorporation of the alkyne is variable, but tends to favor large alkyne substituents at C-1 of the cyclohexadiene ring (equation 23). Although either $CpCo(CO)_2$ or $CpCo(CH_2{=}CH_2)_2$ may be used as the CpCo source in these reactions, the latter gives rise to higher regioselectivities with unsymmetrical alkynes.



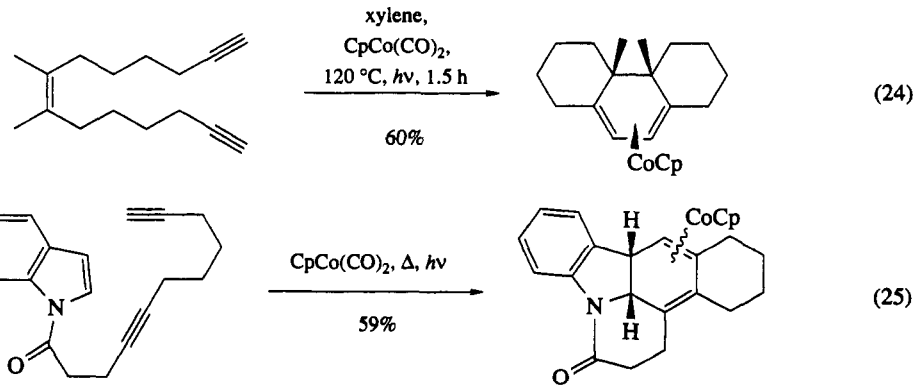
(23)

Upon extended heating with stoichiometric $CpCo(CO)_2$ all-intramolecular cycloadditions of 1-ene-6,12-diynes to form cobalt-complexed cyclohexadienes take place in good yields (Scheme 23).[95,96] High diastereoselectivity in the formation of the complex is sometimes observed in these processes, as is considerable tolerance for steric hindrance.[97,98]



Scheme 23

Complementary cycloadditions of 7-ene-1,13-diynes proceed with similar success, and are noteworthy in their ability to incorporate tetrasubstituted alkenes with total diastereoselectivity (equation 24).[99,100] Incorporation of the alkene into a heteroaromatic ring is compatible with all-intramolecular cycloadditions of this type as well (equation 25).[93]

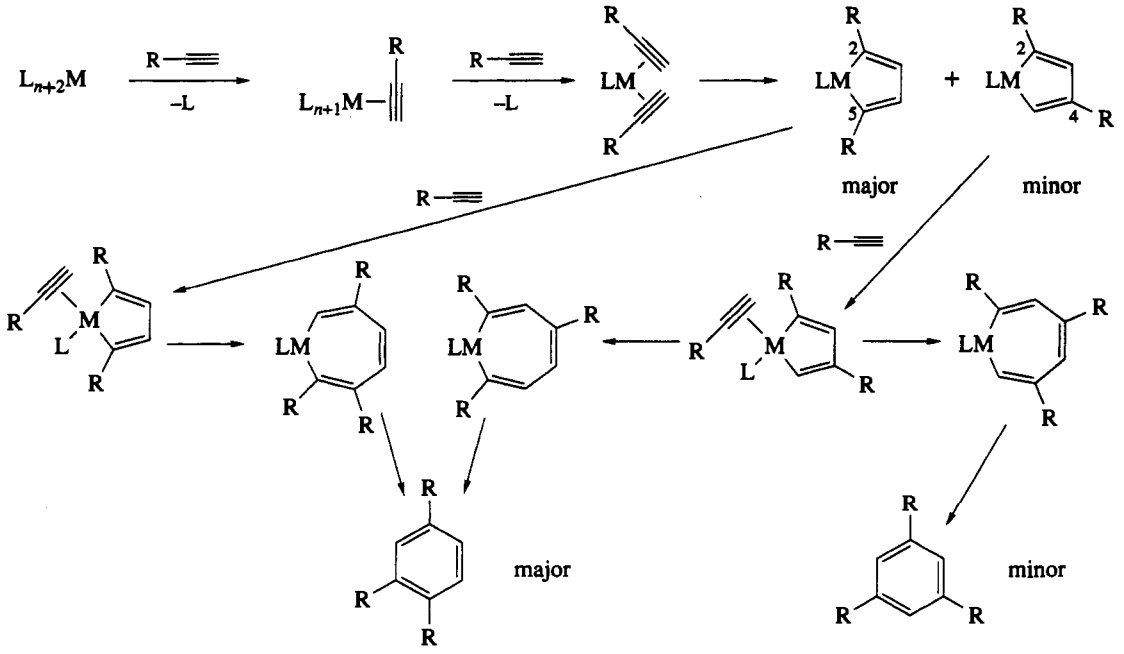


9.4.4.3 Benzenes: Chemo- and Regio-selectivity

The cyclotrimerization of alkynes to give benzene derivatives is perhaps the most general reaction of these compounds in the presence of transition metal complexes. Practically any mono- or di-substituted alkyne, in addition to acetylene itself, may be cyclotrimerized. In addition, cocycloadditions involving more than one different alkyne are possible with some degree of selectivity, and intramolecular versions of the reaction have seen sophisticated development.

A wide variety of homogeneous and heterogeneous catalysts are available for alkyne cyclotrimerization. As a result, numerous mechanistic pathways have been established for the different versions of this process, each characteristic of the metals involved in the system.[101] The most common involves the intermediacy of metallacyclopentadienes, derived as already shown from any number of metal fragments and two alkynes. Upon opening a vacant coordination site, these systems may readily complex a third alkyne, which may insert to give a transient metallacycloheptatriene from which the benzene product is ultimately released *via* reductive elimination of the metal (Scheme 24).[102]

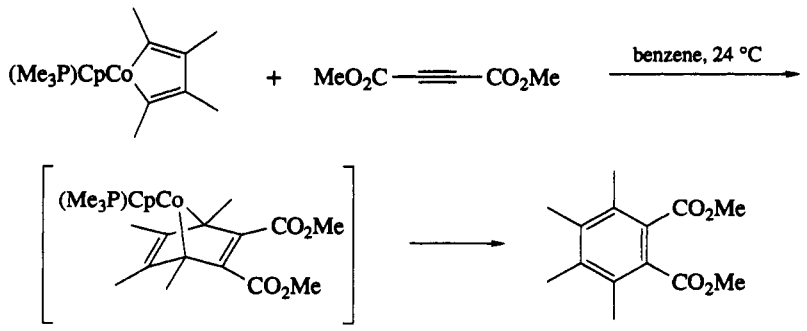
The major regiochemical consequence of this mechanism is that trimerization of unsymmetrically substituted alkynes gives rise mostly to benzenes in which the most sterically demanding substituents occupy positions 1, 2 and 4 around the ring. To a lesser extent products with the 1,3,5-substitution pattern



Scheme 24

are also obtained. In the sequence regioselection can be seen to occur at two stages: in the formation of the metallacyclopentadiene, and in the subsequent insertion of the third alkyne. The preference for formation of the metallacyclopentadiene with the larger substituents at positions 2 and 5 has been noted, and must lead exclusively to the 1,2,4-substitution pattern, irrespective of the sense of the final insertion.[103] The formation of products with a 1,3,5-pattern requires the intermediacy of a metallacycle with a 2,4-disubstitution pattern. Even so, the latter can still give rise to 1,2,4-products as well (illustrated for terminal alkynes in Scheme 24). Although examples of reactions showing quite high levels of regioselectivity towards either 1,2,4- or 1,3,5-trisubstituted benzenes are well-known, few of these systems have been studied to the extent that rational control of regioselectivity is possible.

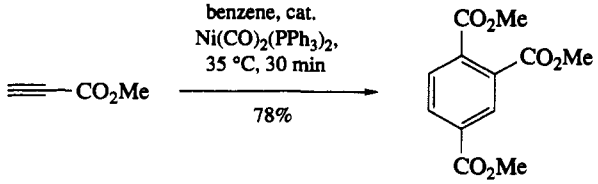
Supporting evidence for the above mechanistic patterns in the majority of metal systems was first established in elegant isotopic labeling studies, which showed clearly that no intermediate with the symmetry of a cyclobutadiene was involved.[104] In one system, the reaction of a cobaltacyclopentadiene with $MeO_2CC{\equiv}CCO_2Me$, benzene formation does not involve direct complexation of the third alkyne to the metal. It has therefore been suggested that the conventional insertion process has been here replaced by a direct Diels–Alder reaction with the metallacycle, perhaps as a result of electronic factors (Scheme 25).[105]



Scheme 25

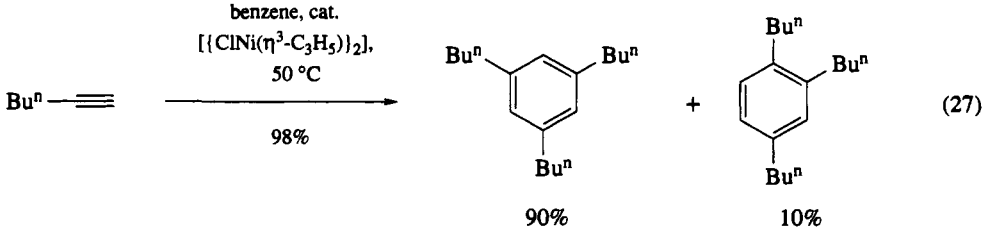
The general mechanistic picture presented above applies to a number of synthetically useful systems including the first to be discovered, in which trimerization of acetylene to benzene, and propargyl alcohol to a 1:1 mixture of 1,2,4- and 1,3,5-trisubstituted benzene derivatives was catalyzed by $(Ph_3P)_2Ni(CO)_2$.[80] Phosphine nickel carbonyls are usually much more highly regioselective for 1,2,4-

products, although their reactivity in simple trimerizations is mostly limited to terminal alkynes, preferably with carbonyl substitutents (equation 26).[106]



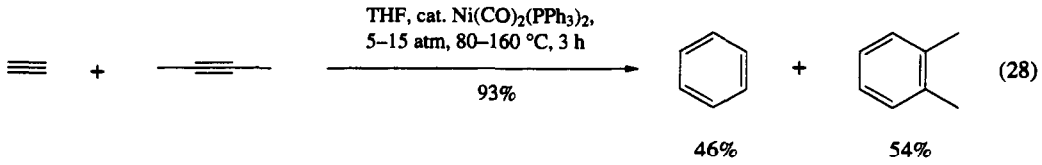
(26)

Another system that appears to follow the same pattern utilizes (η^5-indenyl)Rh(C_2H_4)$_2$, which is remarkably effective for the regioselective trimerization of 3,3-dimethyl-1-butyne (*t*-butylacetylene), giving rise to 1,2,4-tri(*t*-butyl)benzene in 76% yield, and only 8% of the 1,3,5-isomer.[107] On the other hand, unusually high 1,3,5-regioselectivity has been observed from certain Ni^{II}-based catalysts: (Bu_3P)$NiBr_2$, which converts (*S*)-3-methyl-1-butyn-3-ol exclusively into the corresponding 1,3,5-trisubstituted benzene derivative in moderate yield,[108] and [(η^3-allyl)NiCl]$_2$, which gives 1,3,5-trisubstituted benzenes from terminal alkynes in excellent yields with very good selectivity (equation 27).[109]



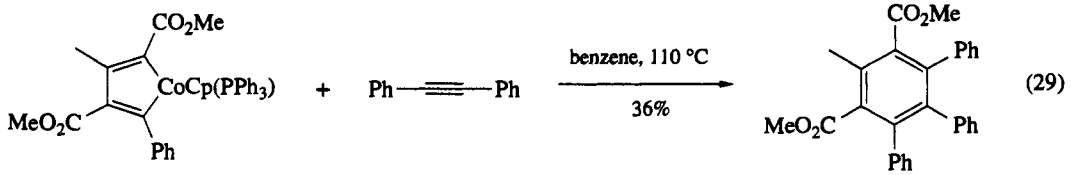
(27)

Chemoselective cocycloaddition of two molecules of a terminal alkyne together with one molecule of an internal alkyne into a benzene product is possible due to the relative unreactivity of phosphine nickel carbonyls towards simple trimerization of the internal alkyne itself (equation 28).[106,110] Careful control of reaction conditions has also permitted selective intermolecular cocycloaddition in the presence of cobalt catalysts as well; for example, diphenylacetylene and 3-hexyne give rise to a 57% yield of 1,2,3,4-tetraphenyl-5,6-diethylbenzene.[111]



(28)

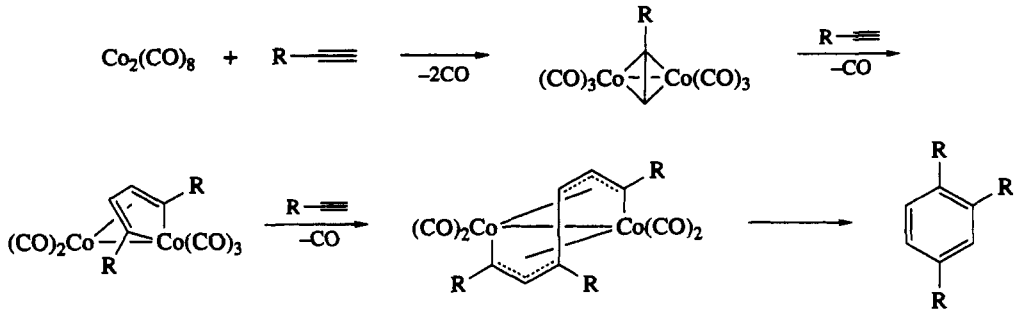
The feasibility of carrying out chemoselective cocycloadditions by reacting a preformed metallacyclopentadiene and an alkyne has been explored. Despite some success in the area (*e.g.* equation 29),[53,74] chemoselectivity is generally compromized by the fact that the metal fragments liberated after one cocycloaddition cycle are catalytically active in promoting simple cyclotrimerization of the added alkyne.[102]



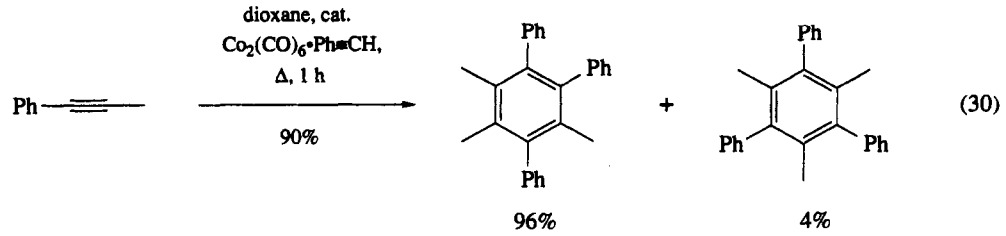
(29)

A number of other mechanistic sequences are thought to occur in alkyne trimerizations mediated by other metal systems. Catalysts derived from $Co_2(CO)_8$ follow a characteristic sequence of steps that involves exclusively dinuclear complexes (Scheme 26). The nature of the final '(alkyne)$_3Co_2(CO)_4$' intermediate, a so-called 'flyover' complex, is supported by both X-ray crystal structure data as well as its involvement in forming other products besides benzenes.[26,32] These dinuclear cobalt systems are note-

worthy due to their wide scope of reactivity as well as their ability to trimerize alkynes in high yield with high 1,2,4-selectivity (equation 30).[111]

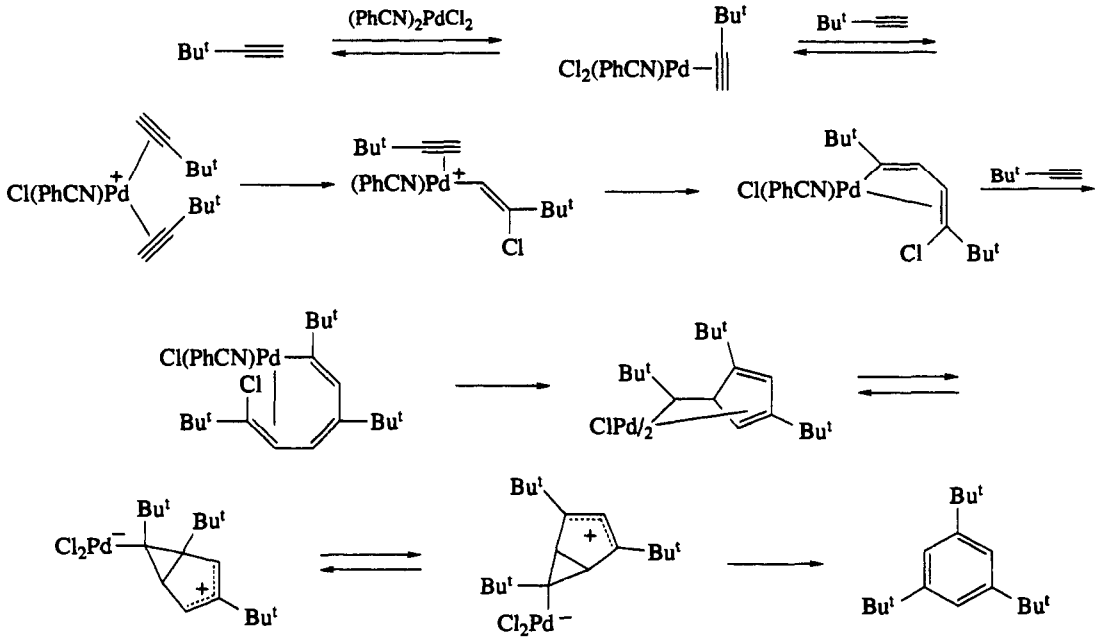


Scheme 26



(30)

A characteristically different mechanism appears to operate in alkyne trimerization systems based on $PdCl_2$.[112] Cationic metal complexes are involved in which initial halide transfer to an alkyne carbon is followed by sequential linear insertion of two more alkyne moieties. Metallacyclopentadiene intermediates are not involved in this sequence. Unique to this mechanism is the subsequent ring-closure to a *cyclopentadienylmethyl* metal derivative, which, *via* halide transfer back to the metal, eventually leads to benzene *via* a bicyclo[3.1.0] system (Scheme 27). Support for this mechanism comes in part from the isolation of methylcyclopentadienyl-derived structures in several cases, including pentalene derivatives from further alkyne insertion followed by a second ring-closure.[113]

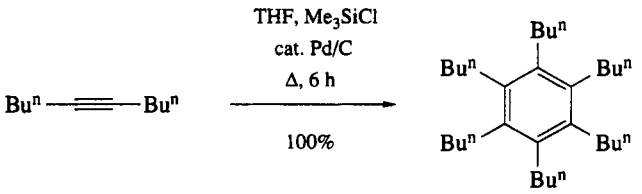


Scheme 27

Regiocontrol in the insertion sequence appears to be steric in origin, with large groups directed away from the bulky metal. A tail-to-tail linkage sequence followed by rearrangement leads to 1,3,5-tris(*t*-butyl)benzene as the sole benzenoid product from trimerization of *t*-butylacetylene in the presence of $PdCl_2$.

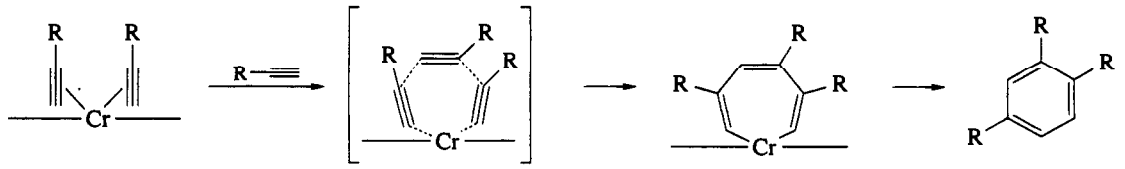
The dual characteristics of sequential insertion and lack of metallacyclopentadiene formation appear to apply to other high-valent metal halide catalysts as well, *e.g.* $NbCl_5$. Regioselectivity varies from one system to the next, however. The related Ziegler-type catalysts typically give 1,3,5-systems in comparable or greater amounts relative to their 1,2,4-isomers.[114] For example, $TiCl_4/AlEt_2Cl$ converts phenylacetylene in high yield into a mixture of 1,3,5- and 1,2,4-triphenylbenzenes, with 80:20 regioselectivity.[115] These systems display extraordinary reactivity; for example, the trimerization of ω-chloro-1-alkynes is complete in 5 min at 0 °C in the presence of $TiCl_4/AlBu^i_3$.[116] A mechanistic study dealing with Ziegler-type catalysts confirmed the lack of involvement of metallacyclopentadienes and concluded that benzene formation involved a template-type concerted cycloaddition, although the sequential insertion mechanism outlined above appears equally consistent with the results.[117] Catalysis of alkyne trimerization by $AlCl_3$ is a mechanistically distinct process which does involve a complexed cyclobutadiene.

High yields of benzenes are formed from internal alkynes (and a few select terminal alkynes) upon heating in the presence of a soluble catalyst generated by combining Me_3SiCl and Pd/C. Although neither the mechanism nor the structure of any active intermediate is known, the procedure is so simple operationally as to be the method of choice for symmetrical systems (equation 31).[118] Regioselectivity is mixed in the few instances reported; it is impossible at this time to draw conclusions as to possible similarities with $PdCl_2$ systems.



(31)

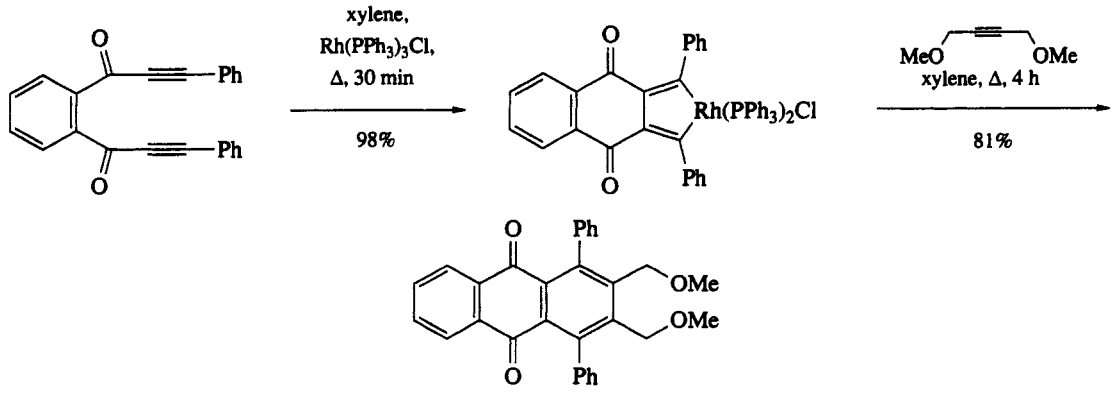
A commercially available heterogeneous catalyst derived from coating K_2CrO_4 on a silica/alumina support is capable of trimerizing alkynes in good yields under very mild conditions.[119] This system has been found to be quite useful in the syntheses of ^{11}C-radiolabeled benzenes from the corresponding alkynes. Regioselectivity with unsymmetrical alkynes is moderate and favors 1,2,4-isomers. For example, propyne is trimerized to give a 4:1 ratio of 1,2,4- and 1,3,5-trimethylbenzenes.[120] The mechanism proposed invokes a unique concerted cycloaddition route to a surface-bound metallacycloheptatriene (Scheme 28). Chemoselective cotrimerizations have also been demonstrated with this catalyst.



Scheme 28

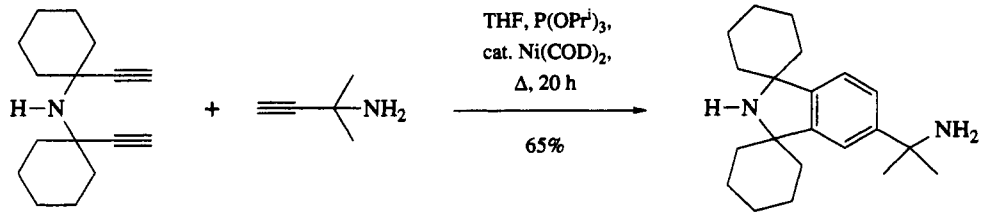
Without question, the metal-promoted cycloaddition of three alkynes to produce benzenes is the most extensively studied organometallic cycloaddition in intramolecular versions. Early work indicated the utility of Ni^0 systems (*e.g.* $Ni(CO)_2(PPh_3)_2$), Ziegler catalysts and rhodacyclopentadienes in the partially intramolecular cocycloaddition of α,ω-diynes with additional alkynes.[46,121–123] Ziegler catalysts were noteworthy in giving rise to products containing the benzocyclobutene moiety from reactions of 1,5-hexadiyne, while the Rh systems showed considerable utility in the preparation of anthraquinone derivatives from appropriate diyne precursors (Scheme 29).

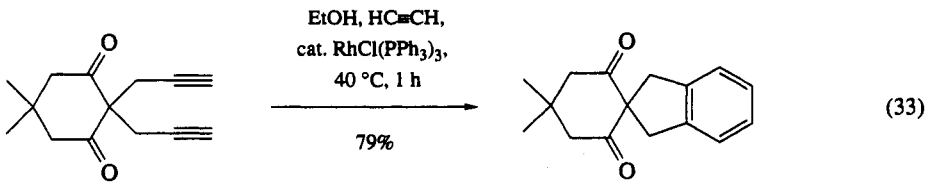
As is the case with totally intermolecular cocycloadditions, chemoselectivity is a potential problem in partially intramolecular systems where the desired process, combination of a diyne with a monoyne, may face competition from cycloadditions involving either exclusively the diyne or exclusively the monoyne. In practice chemoselectivity is readily achieved. Phosphite complexes of Ni^0 chemoselectively catalyze rapid and efficient cycloaddition of alkynes to heteroatom-containing diynes in good yields (equation



Scheme 29

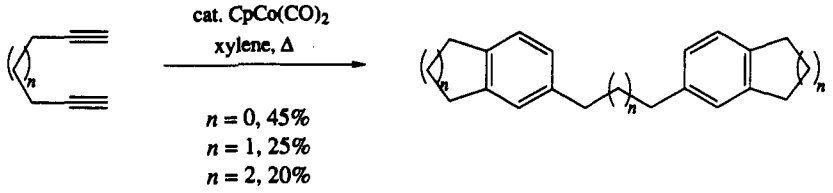
32).[124] Wilkinson's catalyst ($RhCl(PPh_3)_3$) is similarly effective, and both systems show considerable functional group tolerance (equation 33).[125]





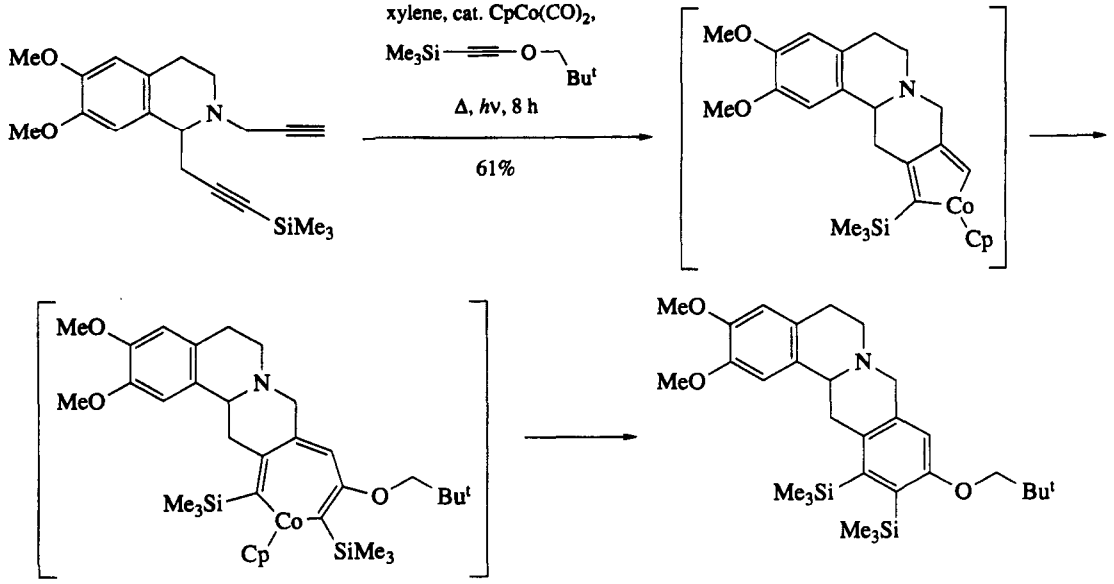
The most extensively studied system for partially intramolecular cycloadditions is also the one with the widest demonstrated scope, a system in which any one of several $CpCoL_2$ species acts as a catalyst precursor.[126] The CpCoL fragments actually involved in catalysis are extremely reactive, being relatively unhindered sterically. The principal factor determining the conditions necessary for cycloaddition to occur is the ease of inducing the $CpCoL_2 \rightarrow$ CpCoL transformation to take place. Although the earliest work, in which L = CO, required temperatures approaching 200 °C, these methods have been superseded by either combined thermal/photochemical conditions for dissociation of CO from $CpCo(CO)_2$, or the use of more labile precursors, in which L = PPh_3 or $CH_2{=}CH_2$. Instances in which catalytic activity is exhibited at −78 °C are known for the latter system. Careful selection of substrate characteristics is necessary for control of chemoselectivity in such highly reactive systems. Reactivity towards simple α,ω-diynes is very similar to that found from Ziegler systems: trimerization to give alkanes α,ω-substituted with annulated benzenes occurs and, again, benzocyclobutene derivatives are accessible (equation 34; n = 0). Benzocyclobutene formation follows a slightly different mechanistic pathway than formation of benzocyclopentenes and benzocyclohexenes. In the latter two cases an intramolecular first step forms a bicyclic metallacycle, which goes on to react with the additional alkyne. This pathway is unavailable for 1,5-hexadiynes due to strain in closing the metallabicyclo[3.2.0]heptadiene. Instead, the first step is *intermolecular*, combining one end of the diyne with the additional alkyne. Only then does reaction at the free end of the diyne occur. As a result, four-membered ring formation is delayed to a later stage in the sequence, where it is fused to a larger ring.[38]

Chemoselectivity in cocycloadditions is typically poor unless the additional alkyne is resistant to simple cyclotrimerization. Examples of alkynes which satisfactorily fulfill this requirement include $Me_3SiC{\equiv}CSiMe_3$, $Me_3SiC{\equiv}COMe$ and $Me_3SnC{\equiv}CSnMe_3$. In the case of the unsymmetrical alkyne,



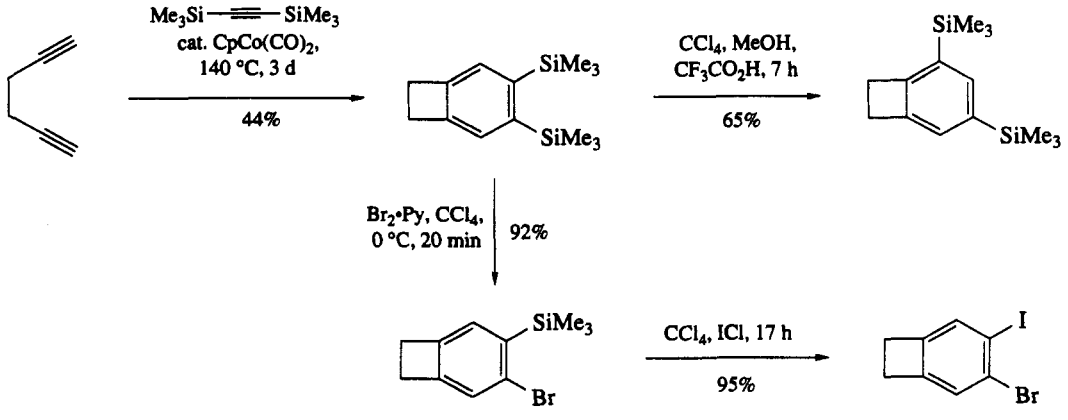
(34)

cycloaddition typically proceeds with total or near-total regioselectivity, as is illustrated in syntheses of tetracyclic isoquinolinoid alkaloids in the protoberberine series. Regiocontrol arises from the steric preference for forming bonds between the least sterically hindered carbons, with the relatively unhindered metal atom becoming linked to the more hindered end of the inserting alkyne (Scheme 30).[127]



Scheme 30

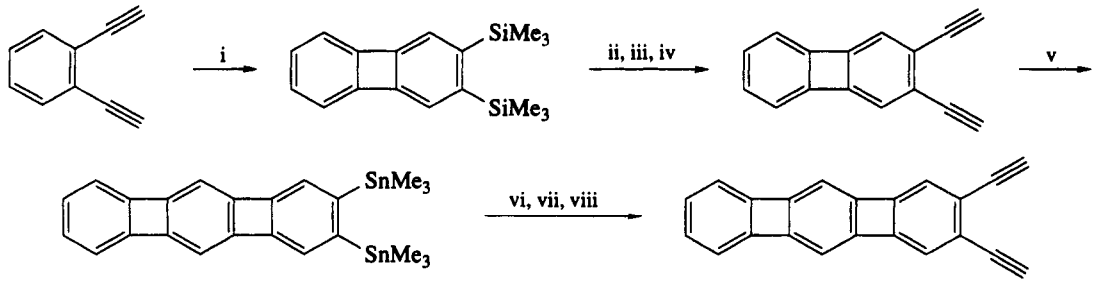
The utility of this chemistry in synthesis is considerably enhanced by the versatility of the arylsilane and stannane functionalities in further transformations such as electrophilic substitution and migration reactions (Scheme 31).



Scheme 31

The availability of benzocyclobutenes from cocycloadditions of 1,5-hexadiynes and hindered alkynes has been elaborated into an iterative synthesis of a variety of novel polycyclic biphenylene derivatives.

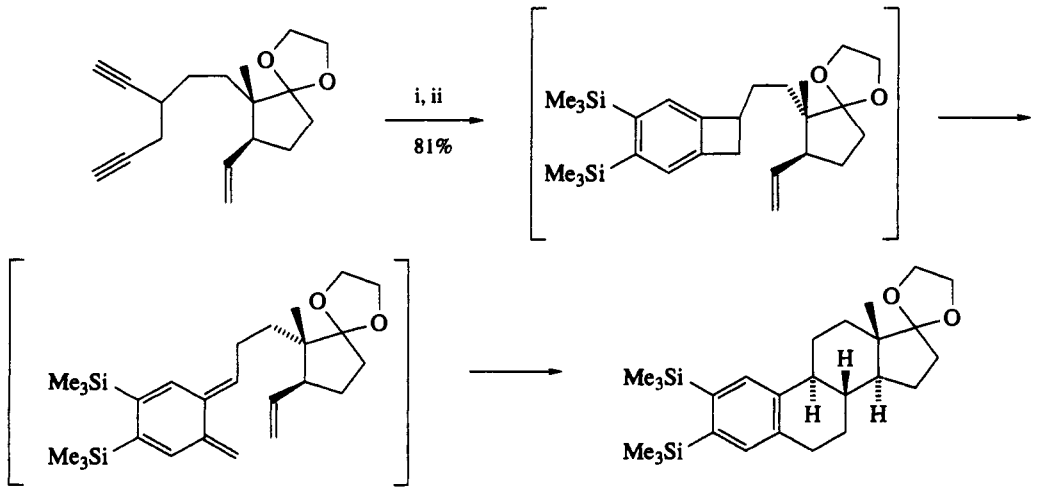
Repetitive annulations have been achieved by a cycloaddition/refunctionalization/coupling sequence: cycloaddition of an *o*-di(ethynyl)arene to $Me_3SiC{\equiv}CSiMe_3$ gives an *o*-bis(trimethylsilyl)arene, which represents the product of formal 'cyclobutabenzannulation' on the original arene. Electrophilic iodination of the silyl groups generates a new *o*-diiodoarene, suitable for another cycle. As the polycyclic becomes more extended, the sensitivity of the system to electrophilic conditions increases. To compensate, $Me_3SnC{\equiv}CSnMe_3$ is used in later cycles in order to exploit the higher reactivity of arylstannanes towards electrophilic substitution under mild conditions (Scheme 32).[128] Similar methodology has provided routes to both linear and nonlinear polycyclics and heterocyclics of theoretical and synthetic interest.[129–131]



i, $Me_3SiC{\equiv}CSiMe_3$, cat. $CpCo(CO)_2$, Δ, *hν*, 10 h, 96%; ii, ICl, CCl_4, 0–20 °C, 1 h, 63%; iii, $Me_3SiC{\equiv}CH$, piperidine, cat. $PdCl_2(PhCN)_2$, CuI, 20–85 °C, 2 h, 75%; iv, KOH, MeOH, Et_2O, 10 min, 100%; v, $Me_3SnC{\equiv}CSnMe_3$, xylenes, cat. $CpCo(CO)_2$, Δ, *hν*, 3.5 h, 20%; vi, I_2, $CHCl_3$, 1 h, 80%; vii, $Me_3SiC{\equiv}CH$, Et_3N, cat. $PdCl_2(PhCN)_2$, 23 °C, 20 h, 75%; viii, KOH, MeOH, 1 h, 95%

Scheme 32

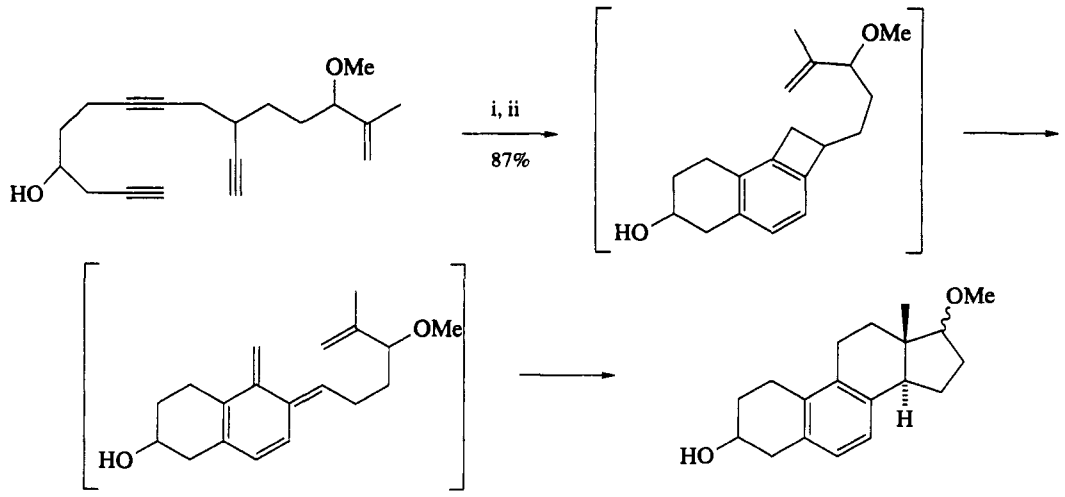
Further synthetic utility is derived from the reactivity of benzocyclobutenes towards thermal electrocyclic ring opening, producing highly reactive *o*-quinodimethanes (*o*-xylylenes). In suitably designed systems, efficient intramolecular Diels–Alder cycloaddition can follow ring-opening, leading to products of substantial complexity in a single experimental operation.[132,133] The landmark synthesis of A-ring aromatic steroids in general and estrone in particular by Vollhardt represents the epitome of development of the general sequence, which has also made accessible several other types of polycyclics and heteropolycyclics (Scheme 33).[134,135]



i, $Me_3SiC{\equiv}CSiMe_3$, cat. $CpCo(CO)_2$, Δ, 41 h; ii, decane, 180 °C, 20 h

Scheme 33

Finally, a spectacular example involving the totally intramolecular cyclization of an enetriyne has been demonstrated in an approach to a novel B-ring aromatic steriod (Scheme 34).[136]



i, xylene, cat. $CpCo(CO)_2$, Δ, *hv*, 1 h; ii, decane, Δ, 20 h

Scheme 34

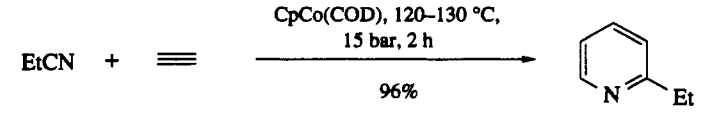
9.4.5 SYNTHESIS OF SIX-MEMBERED HETEROCYCLIC RINGS

9.4.5.1 Pyridines: Chemo- and Regio-selectivity

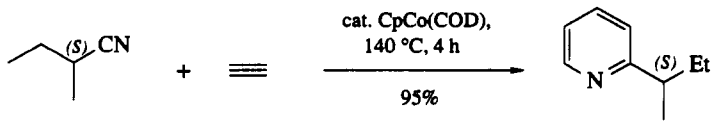
The synthesis of the pyridine ring system by incorporation of a nitrile in a cocycloaddition reaction with two alkynes is closely related to the synthesis of benzenes. The same catalysts are generally active in both processes. Questions concerning chemoselectivity and regioselectivity considered in the section on benzenes apply here as well, but in the case of pyridine synthesis the critical chemoselection is the competition between pyridine formation and benzene formation: *i.e.* the ability of the nitrile to successfully compete for incorporation into a cycloaddition process. As virtually all the early examples of this process involved cobalt-based systems, much of the mechanistic work developed in connection with alkyne trimerization can be applied to pyridine synthesis. It is generally accepted that the same metallacyclopentadiene intermediates involved in alkyne trimerizations form on the pathway to pyridines as well. This is supported by kinetic data that indicate that rates of pyridine formation are independent of nitrile concentration. As cobalt in the CpCo fragment is initially in the +1 oxidation state, the preference for π-complexation to moderately π-acidic alkynes in preference to σ-donor nitriles is reasonable. Once ring-formation to the cobaltacyclopentadiene has taken place, however, complexation preferences at the now oxidized (+3) metal center are reversed. There should be a natural chemoselectivity preference for nitrile complexation, and, consequently, pyridine formation, and this expectation is generally realized. The sense of insertion of the nitrile is such that the nitrogen remains bound to the metal, and a new carbon–carbon bond is formed (see equation 39, below).

Early attempts at direct reaction of nitriles with cobaltacyclopentadiene complexes gave modest yields of pyridines, but, more importantly, demonstrated that the reaction was catalytic. With $CpCo(PPh_3)$(alkyne) as catalyst precursor, reaction occurs even at room temperature with a variety of nitriles.[137,138] Through a painstaking series of studies Bönnemann demonstrated practical improvements in convenience and overall yield through the use of more labile CpCoL sources, while maximizing chemoselectivity by maintaining an excess of nitrile and adding the alkyne in portions. In this way excellent yields of 2-alkyl- and 2-aryl-pyridines are synthesized from acetylene and nitriles, using either CpCo(COD) as catalyst, or any of a variety of soluble Co^I species capable of generating catalytic fragments *in situ*.[139,140] Pyridine itself is also accessible from acetylene and hydrogen cyanide.[141] Yields of pyridines equal to or greater than 90% are commonplace using this methodology, the reaction requiring only 2–3 h at 120–130 °C, and exhibiting catalytic turnover numbers of several hundred (equation 35).[142] Applications of this methodology in the preparation of pyridines containing chiral substituents at C-2 exist (equation 36).[143,144] A significant extension of this reaction makes use of the fact that arylnitriles, and pyridylnitriles in general, may be employed in further cycloaddition processes. Thus conversion of the product of equation (36) into a new 2-cyanopyridine allows access *via* a second cycloaddition with acetylene to a

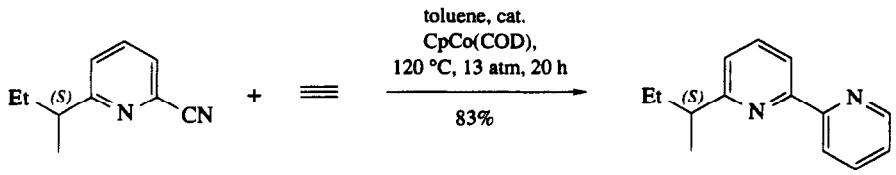
new optically active *bi*pyridine, of potential value as a ligand for transition metal systems involved in asymmetric synthesis (equation 37).[145,146]



(35)

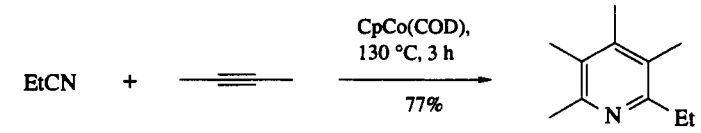


(36)

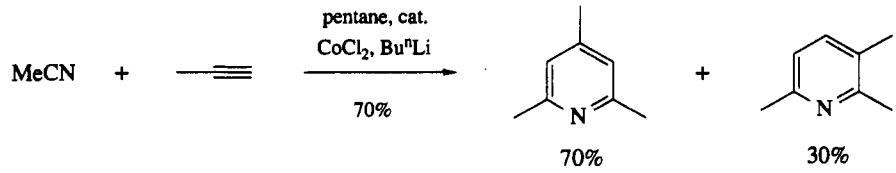


(37)

Substituted alkynes react readily with nitriles in the presence of these catalysts to generate substituted pyridines. Symmetrically disubstituted internal alkynes give rise to excellent yields of pentasubstituted pyridines (equation 38). In the case of monosubstituted and unsymmetrically disubstituted alkynes regioselectivity becomes an important issue, and one which is not generally amenable to good control from a synthetic point of view. Although pyridines are formed in good (*ca.* 65%) yields from nitriles and monoalkyl- or aryl-alkynes, regioselectivity is only modest in most cases: both 2,4,6- and 2,3,6-trisubstituted pyridines form in substantial amounts.[103] Ratios of *ca.* 2:1 in favor of the 2,4,6-trisubstituted pyridine are typical (equation 39).[147] The 2,4- and 2,5-disubstituted cobaltacyclopentadiene intermediates must therefore both participate in these processes, with the *former* being the predominant reactive species, in contrast to the situation encountered in the trimerization of alkynes. Insertion of the nitrile is regioselective for bond formation with the less sterically hindered carbon attached to the metal.[148] Not surprisingly, the lack of overall regiocontrol renders attempts at cocycloaddition using a nitrile and two different alkynes essentially worthless as a synthetic technique.[139]



(38)



(39)

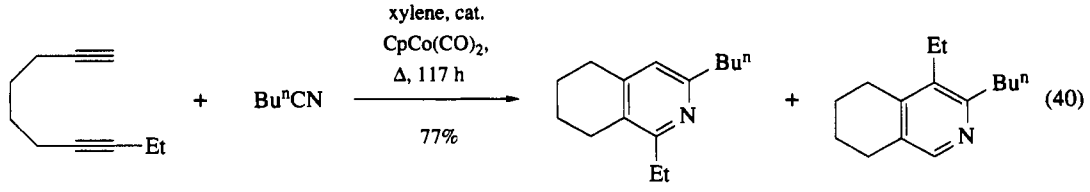
The properties of the Co^{I}-based catalysts are a sensitive function of ligand structure. Both reactivity and regioselectivity have been studied in an extensive series of systems containing a variety of substituted cyclopentadienyl and other related ligands. The ease of dissociation of the two-electron ligands determines the ease with which the active 16-electron catalytic species may be generated. Thus $CpCo(CH_2{=}CH_2)_2$ is capable of initiating cycloaddition at room temperature, while CpCo(COD) is inactive below *ca.* 125 °C. Since reasonable turnover rates still require elevated temperatures, this distinction is not a particularly important one in practice.

For a series of complexes containing the same dissociating ligand(s), the electron density at the metal is the most important remaining factor, and is of considerable practical importance. Electron-poor metal centers such as that in $(C_5H_4COMe)Co(COD)$ exhibit the highest reactivity but the lowest regioselectivity (*ca.* 1.5:1). In contrast, the electron-rich metal in $(C_5Me_5)Co(COD)$ is much more selective, giving better than a 3.5:1 ratio of 2,4,6- to 2,3,6-trisubstituted products, but exhibits greatly reduced

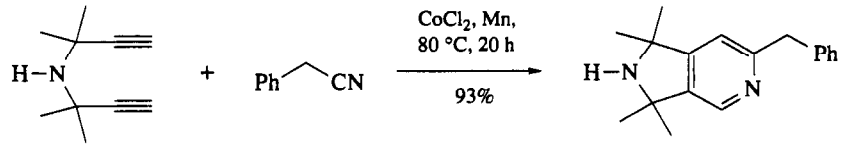
reactivity and gives chemical yields that are too low to be preparatively useful. It is reasonable to assume that complexation of the nitrile to the intermediate metallacycle is facilitated by electron deficiency at the metal center, while regioselectivity in favor of the 2,4-disubstituted metallacycle benefits most from extreme steric crowding. A reasonable compromise is found in the 1,2-bis(trimethylsilyl)cyclopentadienylcobalt system, which gives regioselectivity approaching that in the C_5Me_5 system, but preserves both reactivity and excellent pyridine *vs.* benzene chemoselectivity.[149,150] Vapor-deposited Co atoms are also effective catalysts for pyridine formation, like $CpCo(CH_2{=}CH_2)_2$ showing activity even at room temperature, but giving optimal results at 120 °C: 80% yields, 7:1 chemoselectivity and *ca.* 2:1 2,4,6-regioselectivity.[151] Similar results are obtained with both soluble and polymer-bound Rh^I-based catalyst systems. With these regioselectivity in reactions of nitriles with terminal alkynes varies over a wider range than is found with Co; the $(C_5Me_5)Rh$ system in particular gives better than a 4:1 preference for 2,4,6-trisubstituted products, and exhibits higher reactivity than its Co counterpart. However, yields and chemoselectivities are generally lower than with Co-based catalysts, especially in the more regioselective systems.[152]

Although extensive work with heteroatom-containing nitrile analogs has not been done, successful cycloadditions along these lines include the synthesis of 2-aminopyridine from cyanamide,[140] and syntheses of 2-alkylthiopyridines from alkyl thiocyanates.[153] However, nitriles containing strongly electron-withdrawing substituents are poor substrates.[140]

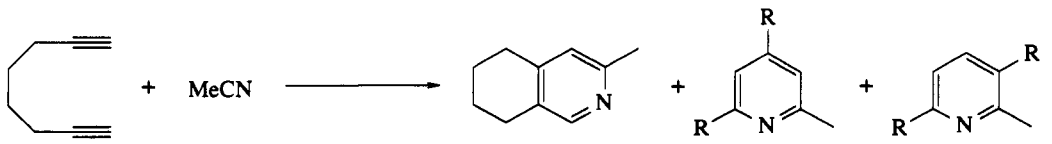
Partially intramolecular cycloadditions of nitriles with α,ω-diynes have proven to be excellent means by which di- and poly-cyclic pyridine derivatives may be prepared. Nitrile insertion is highly regioselective, as expected from the results of intermolecular analogs (equation 40).[154] Heteroatom-bridged diynes have been used equally successfully: dipropargyl ethers, in synthetic approaches to pyridoxine, and dipropargylamines, in chemoselectivity studies where Co^I-based catalysts were found to be most pyridine-selective, although a $CoCl_2$/Mn-derived catalyst is also useful in certain cases (equation 41).[155–157] A novel form of intra- *vs.* inter-molecular chemoselectivity has been uncovered in cycloadditions of α,ω-diynes catalyzed by Co atoms from vapor deposition: deposition in toluene gives predominantly the expected partially intramolecular cycloaddition of 1,7-octadiyne to the corresponding bicyclic pyridine. In contrast, deposition in mesitylene gives largely *inter*molecular cycloaddition involving only one triple bond from each diyne, forming mostly di(5-hexynyl)methylpyridines as products (equation 42).[158]



(40)



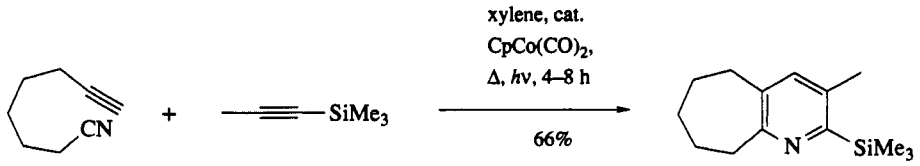
(41)



(42)

Co, toluene, 25 °C, 73%	86%	12%	2%
Co, mesitylene, 25 °C, 66%	45%	44%	11%

The cocycloaddition of α,ω-cyanoalkynes with alkynes is another efficient entry to bicyclic pyridines. In this process an intermediate metallacyclopentadiene is formed intermolecularly from the cyanoalkyne and the alkyne. The larger alkyne substitutent ends up nearer the metal with very high regioselectivity except in the case of 2-hexyne, where selectivity is reduced to about 3:2 (equation 43).[159]



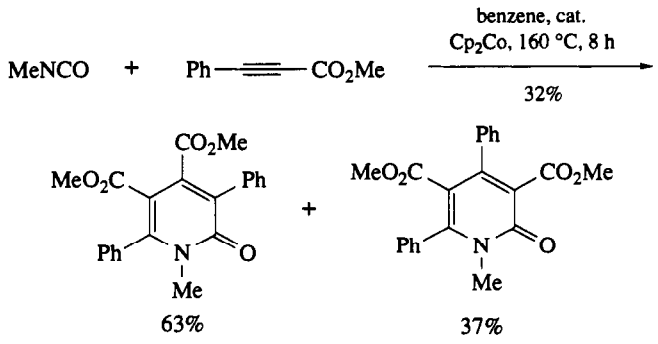
(43)

Intramolecular cycloaddition does not occur with α,ω-dinitriles; each cyano group instead undergoes independent cocycloaddition with two molecules of alkyne to afford high yields of di(2-pyridyl)alkanes. The reaction may also be controlled to give high yields of 2-(ω-cyanoalkyl)pyridines.[151]

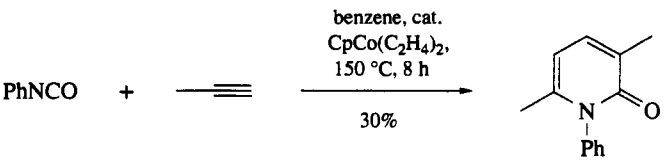
9.4.5.2 Pyridones and Related Compounds: Chemo- and Regio-selectivity

Pyridones are accessible from formal [2 + 2 + 2] cycloaddition of two alkynes and an organic isocyanate. Two quite distinct catalyst systems have been developed for this reaction, with significant differences between them in mechanism and mechanistic implications on selectivity.

The first system to be developed utilizes CpCoL fragments in a catalytic cycle that proceeds through the usual cobaltacyclopentadiene intermediate. Indeed, preformed cobaltacyclopentadienes are effective catalyst precursors for this reaction; cobaltocene has also been used. As was the case in trimerization reactions of unsymmetrical alkynes, a preference is found for product formation through the metallacycle with larger groups at positions 2 and 5. When the metallacycle is unsymmetrical, total regioselectivity is observed in the subsequent insertion of the isocyanate, with the carbon of the latter bonding exclusively to the less-hindered end of the cobaltacyclopentadiene system. The result is primarily the formation of the pyridone ring system with the larger alkyne substituents at positions 3 and 6, from the 2,5-metallacycle, with lesser amounts of the isomer with large groups at positions 4 and 6, from the 2,4-metallacycle (equation 44).[160] Stoichiometric reactions between preformed cobaltacyclopentadienes and isocyanates are high yield, completely regioselective processes, consistent with this mechanism.[161] Another catalyst precursor, $CpCo(C_2H_4)_2$, is useful for terminal alkynes, and is especially regioselective for 3,6-disubstituted pyridones when an aryl substituent is present in either substrate, although chemoselectivity relative to benzene formation is not so good (equation 45).[162]



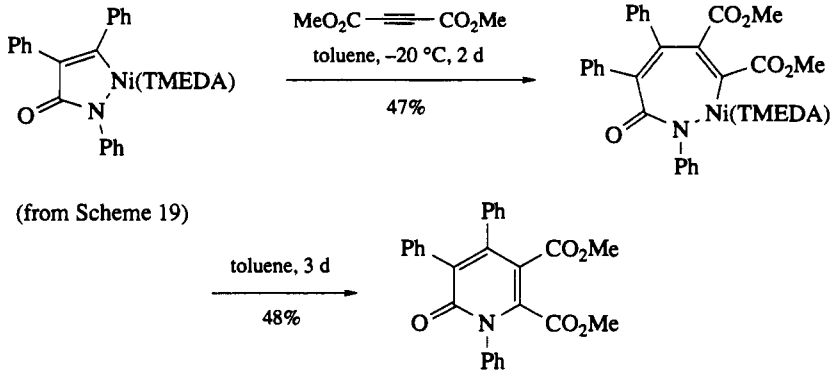
(44)



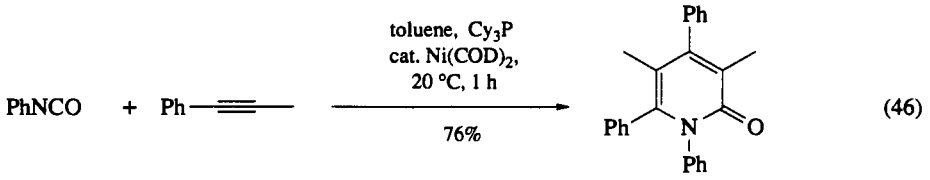
(45)

A Ni^0-based system related to those already described in connection with syntheses of both cyclobutenediones and several five-membered heterocycles (Sections 9.4.2.1, 9.4.3.3 and 9.4.3.5) is also capable of catalyzing pyridone synthesis from isocyanates and alkynes. However, the structures found for the isolable metallacyclic intermediates in this system imply a completely different insertion sequence: isocyanate first, followed by the two alkynes (Scheme 35). As a consequence, the regiochemistry found in the products of reaction of unsymmetrical alkynes is the reverse of that typical of Co^I: larger substituents end up at positions 4 and 6. Thus, starting with the carbonyl carbon of the isocyanate, each carbon–carbon bond forming event is strongly regioselective for the less-hindered alkyne carbon (equation 46). The

yield shown is typical for reactions with internal alkynes; terminal alkynes give much poorer results.[163] An Rh-based system is also regioselective for the same substitution pattern, but chemoselectivity with regard to competing alkyne trimerization is poor.[164]

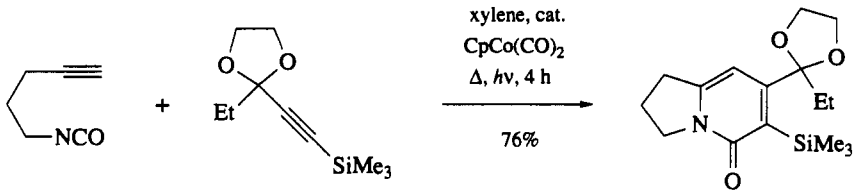


Scheme 35



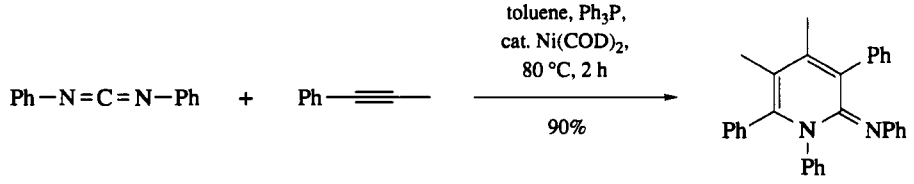
(46)

Among partially intramolecular versions of this cocycloaddition, α,ω-diynes have been found to cycloadd only with low efficiency to isocyanates in the presence of CpCo precursors. In contrast, ω-isocyanatoalkynes react smoothly with silylated alkynes in the presence of $CpCo(CO)_2$, giving high yields of products formed with excellent chemoselectivity and modest to excellent regioselectivity (equation 47). The regioselectivity is most likely controlled in a manner similar to that in equation (43).[165]



(47)

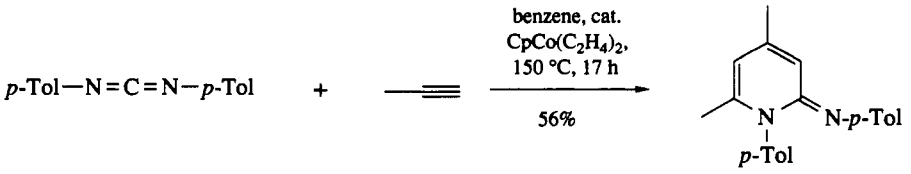
Replacement of organic isocyanates by carbodiimides in cycloadditions with alkynes results in a synthetic entry into the closely related 2-iminopyridine series of heterocycles. Both Co^I and Ni^0 catalysts have been used for such cycloadditions. Remarkably, however, in each catalyst system the regioselectivity is reversed as compared with the otherwise analogous isocyanate cycloaddition. Either catalytic Ni^0 or a preformed Ni^0 complex of the carbodiimide reacts to produce excellent yields of cocycloaddition products from internal alkynes, with larger substituent groups ending up at positions 3 and 6 (equation 48, *cf.* equation 46).[166]



(48)

Similarly, although the yields are lower, the Co^I catalysts also show generally reversed regioselectivity in reactions with carbodiimides as compared with isocyanates.[160,162] In fact, the 4,6-disubstituted product is formed with complete regioselectivity in reactions of di(*p*-tolyl)carbodiimide with terminal alkynes,

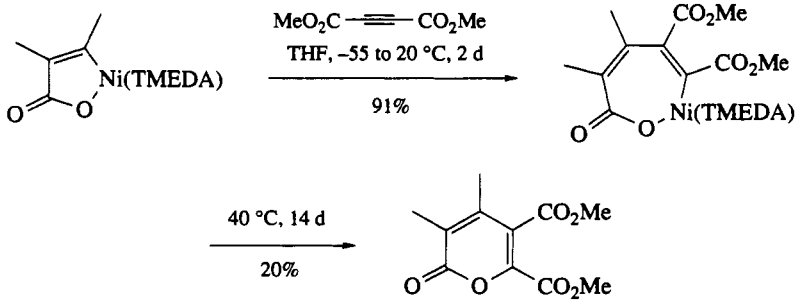
although dialkylcarbodiimides are rather unselective; internal alkynes give mixtures as well (equation 49). Chemoselectivity with respect to benzene formation is moderate in these systems.



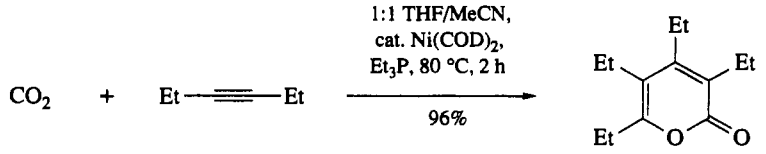
(49)

9.4.5.3 Pyrones and Similar Heterocycles: Chemo- and Regio-selectivity

In a reaction completely analogous to the pyridone synthesis in Scheme 35, 5-nickelafuranones formed from Ni^0, an alkyne and carbon dioxide (see Section 9.4.3.3) react with additional alkyne to give 2-pyrones (Scheme 36).[71,167] Under catalytic conditions this becomes a viable synthesis of the heterocycle beginning with internal alkynes, especially when the solvent system and ligand environment of the metal are properly optimized (equation 50).[168] Regioselectivity with unsymmetrical systems is similar to that shown in equation (46): large groups at positions 4 and 6, as a result of carbon–carbon bond forming steps that involve the less-hindered carbon of each inserting alkyne. Unfortunately neither terminal alkynes nor alkynes with aryl substituents are useful substrates.[169]

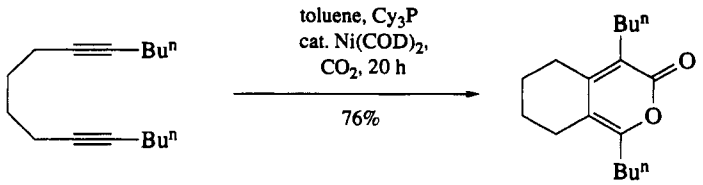


Scheme 36



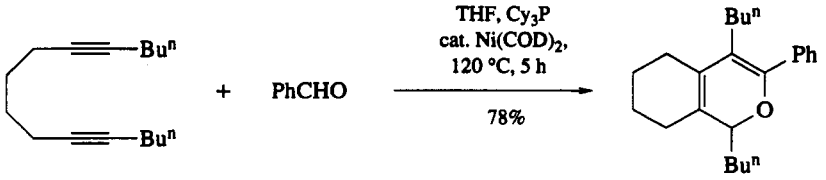
(50)

An intramolecular version of this process has been described, leading to bicyclic 2-pyrones. Diynes in which both alkyne functions are internal and are linked by three-, four- or five-atom chains cycloadd to carbon dioxide in the presence of catalytic Ni^0 and various trialkylphosphines (equation 51). Terminal diynes require stoichiometric metal and give lower yields, however. Extensive studies of ligand effects on yield and chemoselectivity have established a broad scope for the process and pointed out important practical differences between it and the intermolecular reactions described above.[170]



(51)

A novel cycloaddition of diynes with aldehydes is catalyzed by the same metal system, giving rise to bicyclic α-pyrans after 1,5-hydrogen shifts. Yields of these sensitive compounds are remarkably high (equation 52).[171]



(52)

9.4.5.4 Other Heterocycles

Cobaltacyclopentadienes react with CS_2 to form thiopyran-2-thiones, and with methyl isothiocyanate to form pyridine-2-thiones, respectively, in two little-explored analogs of the processes described above.[137,172]

Multiple insertion reactions of isocyanates have been observed in the presence of Ni^0 catalysts. Pyrimidinediones are obtained in low yield from reaction of diphenylacetylene with excess alkyl isocyanates in the presence of Ni(COD).[163a] Similarly, alkyl and aryl isocyanates undergo simple cyclotrimerization to form symmetrical triazinetriones in the presence of both low-valent Ni and Ti catalysts.[173]

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9.5
Zirconium-promoted Bicyclization of Enynes

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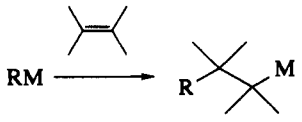
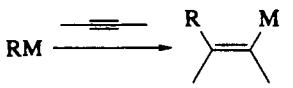
9.5.1 INTRODUCTION

Carbometallation,[1,2] as represented by equations (1a) and (1b), is one of only several fundamentally different types of transformations permitting carbon–carbon bond formation that organotransition metals undergo.[3] It is, in fact, a ubiquitous process observable with a wide variety of organotransition metals, one of the most representative examples being the Ziegler–Natta polymerization.[4]



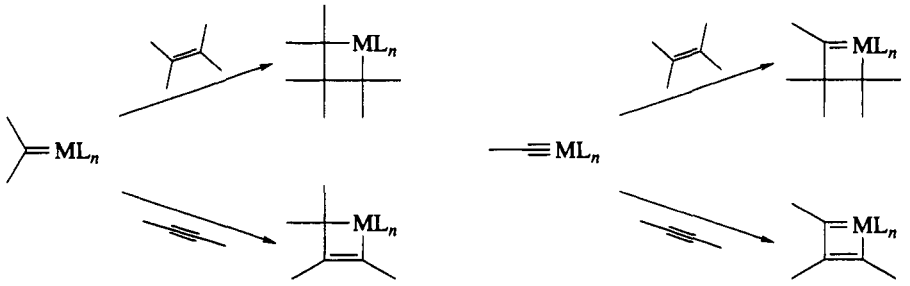
(1a)



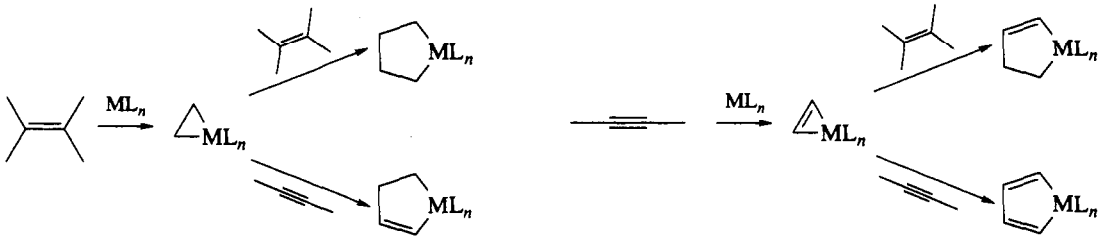
(1b)

Until recently, most of the organic compounds prepared *via* carbometallation had been relatively simple and highly symmetrical cyclic or polymeric compounds.[5] More recently, however, intensive efforts have been made to utilize carbometallation reactions in the synthesis of complex molecules. In particular, the fact that two new bonds, *i.e.* one carbon–carbon and one carbon–metal, are formed in carbometallation has led to the development of a number of cyclization methodologies.[6] Furthermore,

carbometallation can, in principle, be observed with metal–carbene and metal–carbyne complexes as well as with metallacyclopropanes and metallacyclopropenes (Schemes 1 and 2).

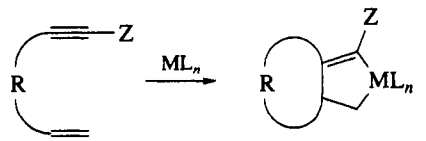


Scheme 1

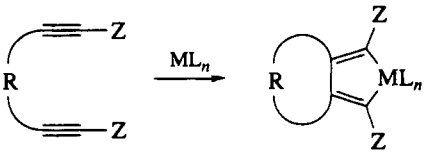


Scheme 2

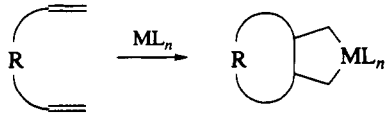
This chapter summarizes cyclization reactions of alkynes and alkenes promoted by Zr and other Group IV metals that are thought to proceed *via* transformations shown in Scheme 2. It is clear from Scheme 2 that the formation of five-membered metallacycles can be complicated by at least two potential problems, one dealing with pairing alkynes and alkenes, pair selectivity hereafter, and the other dealing with the regiochemistry of alkynes and alkenes. These difficulties can be substantially alleviated by linking the two unsaturated units. Of particular interest is the bicyclization reaction of enynes (equation 2), since the desired products, *i.e.* metallacyclopentene derivatives, would readily allow further regioselective transformations. Also attractive are the related reactions of diynes that can give exocyclic conjugated dienes of defined stereochemistry suitable for use in the Diels–Alder reaction (equation 3) and those of dienes (equation 4).



(2)



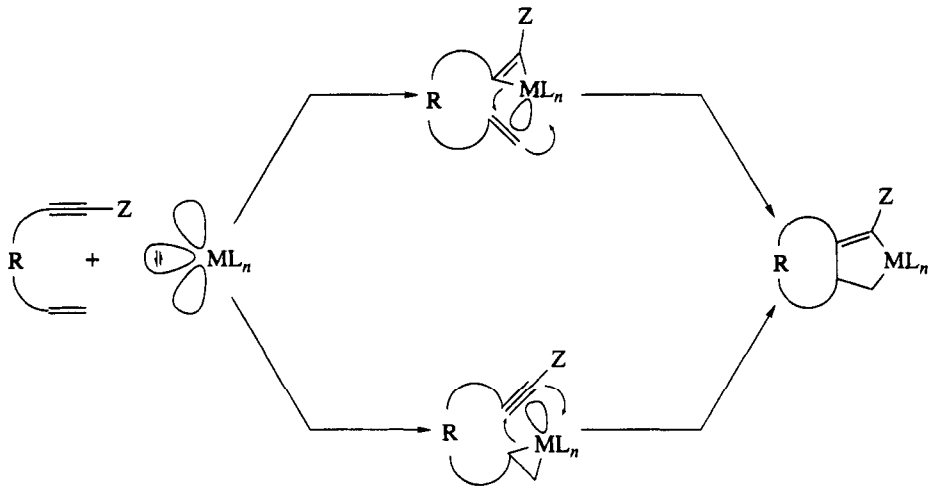
(3)



(4)

Consideration of molecular orbital interactions suggests that it would be ideal to use a transition metal complex having at least two empty and one filled nonbonding metal valence shell orbital, *i.e.* a ≤14-electron species, for observing facile bicyclization reactions shown in equations (2)–(4). This is based on assumptions that effective π-complexation of an alkyne or an alkene with a metal complex requires the

simultaneous availability of one empty and one filled nonbonding metal orbital[7] and that carbometallation is greatly facilitated by the availability of an empty orbital.[1] These points are illustrated for the case of enyne bicyclization in equation (5).



(5)

9.5.2 ENYNE BICYCLIZATION

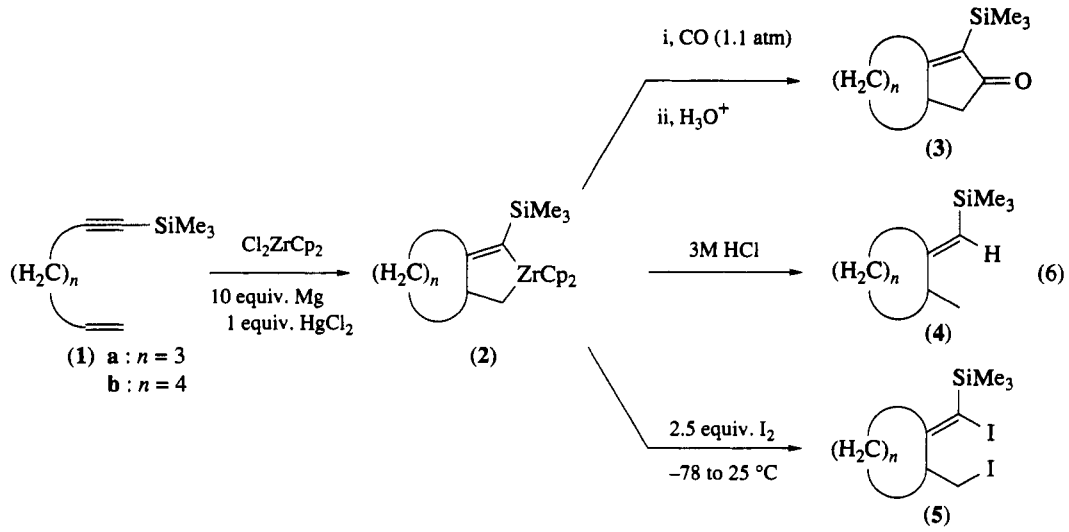
Prior to the development of enyne bicyclization reactions promoted by Zr and other Group IV metals, the Co-catalyzed enyne bicyclization–carbonylation reaction (the Pauson–Khand reaction[8]) was known. This reaction is discussed in Volume 5, Chapter 9.1. In the Pauson–Khand reaction, the overall transformation is the conversion of enynes into bicyclic enones, and the organometallic bicyclic intermediates are usually neither readily available nor isolated. The use of $Co_2(CO)_8$, an 18-electron species, necessitates relatively high reaction temperatures. These and other limitations suggested the desirability of developing alternative enyne bicyclization reactions.

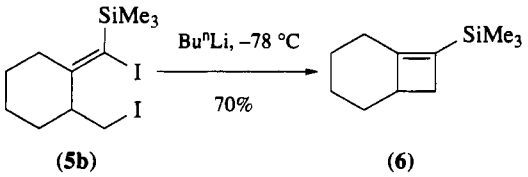
9.5.2.1 Zirconium-promoted Bicyclization and Reactions of Zirconabicycles

It was reported earlier that treatment of 2 equiv. of an alkyne with '$ZrCp_2$', generated by reduction of Cl_2ZrCp_2 by various methods, produced the corresponding zirconacyclopentadienes.[9,10] Using Farona's procedure,[10] consisting of treatment of Cl_2ZrCp_2 with Mg (10 equiv.) and $HgCl_2$ (1 equiv.), 7-(trimethylsilyl)-1-hepten-6-yne (**1a**) can be converted into (**2a**) in 90% yield (equation 6).[11] The product shows two distinct singlets for the two Cp protons at δ 5.78 and 5.82 p.p.m. in toluene-d_8. Carbonylation of (**2a**) with 1.1 atm of CO at 0 °C for 2 h gives the corresponding bicyclic enone (**3a**) in 55–75% isolated yield based on (**1a**). Protonolysis of (**2a**) with 3 M HCl provides (**4a**) in 90% yield, while its iodinolysis affords (**5a**) in 75% yield. The stereochemistry of (**4a**) has been clearly established by comparing its spectral data with those of an authentic sample prepared by an independent method.[12] Similarly, 8-(trimethylsilyl)-1-octen-7-yne (**1b**) can be converted into (**2b**), (**3b**), (**4b**) and (**5b**) in 90, 60, 87 and 76% yields, respectively. Treatment of (**5b**) with 1 equiv. of Bu^{n}Li in ether at –78 °C[13] cleanly gives (**6**) in 70% yield (equation 7).

Although Farona's procedure is satisfactory in the cases shown above, the use of a large excess of Mg and $HgCl_2$ is not synthetically attractive. In the search for an alternative procedure for generating '$ZrCp_2$', treatment of Cl_2ZrCp_2 with 2 equiv. of an alkyllithium, especially Bu^{n}Li, or an alkylmagnesium halide has been shown to serve as a more convenient and satisfactory procedure.[14] The bicyclization–carbonylation of (**1a**) run in THF, ether, benzene, toluene and hexane gives (**3a**) in 73, 62, 77, 74 and 66% yields by GLC, respectively.[15] Thus, the yields are quite insensitive to the solvents.

The results of the enyne bicyclization–carbonylation summarized in Table 1 and those of less successful experiments not included in Table 1, indicate the following. First, the Zr-promoted bicyclization reaction to produce zirconabicycles generally proceeds in ≥80% yields. Secondly, terminal alkynes have failed to undergo this reaction for reasons as yet unclear. The relatively high acidity of terminal alkynes appears to be responsible for the failure. On the other hand, various carbon groups, such as Me, Pr^n, $(CH_2)_2CH{=}CH_2$, CH_2SiMe_3, aryl, and alkenyl, as well as silyl and stannyl groups, can serve as satisfac-





(7)

tory substituents.[16,17] Thirdly, both five- and six-membered rings can be fused to the zirconacyclopentene or cyclopentenone moiety, although only a few examples of six-membered ring fusion have so far been obtained. Fourthly, a wide variety of carbon and heteroatom substituents can be accommodated, as judged by the examples given in equations (8) and (9).

The required highly carbon-substituted enynes, such as (**7**) and (**8**), are conveniently prepared by the Sakurai–Hosomi allylsilane conjugate addition,[18] followed by conversion of methyl ketones into silylated alkynes,[19] as shown in equation (10).[11]

Even oxygenated enynes, such as (**11**) and (**12**), react satisfactorily (equations 11–13).[20]

Fifthly, the bicyclization reaction of nitrogen-containing enynes, *i.e.* (**16**)–(**18**), not only proceeds satisfactorily but also reveals an intriguing and beneficial heteroatom effect.

The smooth cyclization of (**16**) to produce (**19**; equation 14) is somewhat surprising in the light of many unsuccessful attempts to effect a similar cyclization reaction of (**20**; equation 15).[16] The reactions of (**17**) and (**18**) are strictly stereospecific (equation 16).[16]

9.5.2.2 Synthetic Applications of the Zirconium-promoted Bicyclization of Enynes

It is clear from the results presented above that the Zr-promoted bicyclization of enynes is applicable to the synthesis of a wide variety of monocyclic, bicyclic and polycyclic compounds, including terpenoids. At present, however, the number of such applications is still very small.

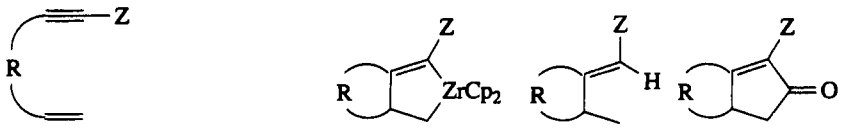
The stereodefined dienynes represented by (**22**) can now be readily prepared *via* either allylalumination[21] of 1,4-diynes, as in the synthesis of (**22a**) shown in equation (17),[15] or Cu-catalyzed allylmagnesiation of propargyl alcohols,[22] as shown in equation (18).[17]

After conversion of (**22**) into the corresponding Me_3Sn derivatives (**23**), the Zr-promoted bicyclization–carbonylation–iodinolysis of (**23**) gives (**24**) in good yields, as shown in equation (19).[23]

The formation of (**24**) is >98% stereoselective. Efforts are currently being made to apply this methodology to the synthesis of carbacyclin (**25**).[24] A model study indicates that the Pd-catalyzed cross-coupling reaction of alkenylzinc derivatives[25] is a promising method for the attachment of the so-called prostanoid ω-side chain, as shown in equation (20).

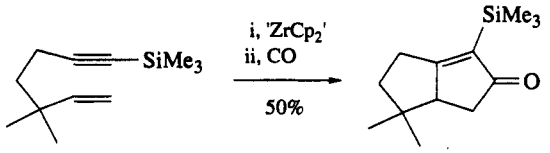
Another promising application is to use the Zr-promoted bicyclization of enynes for controlling the stereochemistry of aliphatic carbon centers, as exemplified by the synthesis of a key intermediate (**26**)[20] for invictolide (**27**) shown in Scheme 3.

Table 1 Zirconocene-promoted Bicyclization–Carbonylation of Enynes[a]

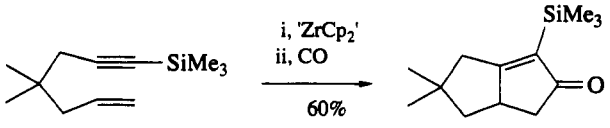


R	*Z*	*Procedure*[b]	*Yield*[c] *(%)*	*Yield*[d] *(%)*	*Yield*[e] *(%)*	*Ref.*
$(CH_2)_3$	TMS	A	95	75	65	11, 15
$(CH_2)_4$	TMS	B	90	87	60	11, 15
$(CH_2)_3$	$SnMe_3$	A[f]	92	60	63	15, 16
$(CH_2)_3$	Me	A	95	65	65	15, 16
$(CH_2)_3$	$(CH_2)_2CH{=}CH_2$	A	80	55	—	15, 16
$(CH_2)_3$	CH_2TMS	A[f]	90	—	55	15
$(CH_2)_3$	Ph	A[f]	90	70	55	15, 16
$(CH_2)_3$	CH=CHHex-(*E*)	A	80	75	50	15, 16
$(CH_2)_3$	g	A	—	80	—	15, 16
$(CH_2)_2CMe_2$	TMS	B	—	—	50	11, 15
$CH_2CMe_2CH_2$	TMS	B	—	—	60	11, 15
(*E*)-$MeCH{=}C(CH_2)_2$	TMS	B	—	—	55	11, 15
(*E*)-$Bu^nCH{=}C(CH_2)_2$	TMS	A	95	—	70	17
(*E*)-$Bu^n(Me)C{=}C(CH_2)_2$	TMS	A	92	—	73	17
(*Z*)-$Bu^n(Me)C{=}C(CH_2)_2$	TMS	A	93	—	65	17
$PhCH_2N(CH_2)_2$	TMS	A	85	—	66	15, 16
(16)		A	95	72	77	15, 16
(17)		A	92	62	—	15, 16
(18)		A	86	—	—	15, 16
h	Pr^n	A	—	94[i]	—	20
(12a)		B	—	70[j]	—	20
(12b)		B	—	k	—	20

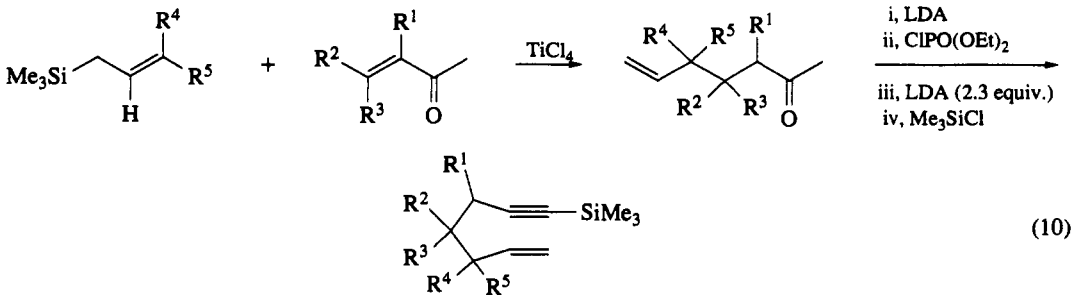
[a] Unless otherwise mentioned, the reaction is run in THF. [b] A = Cl_2ZrCp_2 + 2Bu^nLi; B = Cl_2ZrCp_2 + Mg + $HgCl_2$. [c] By ^1H NMR. [d] Isolated. [e] Isolated. [f] Benzene used as solvent. [g] Z = CH=CHCH $(OSiMe_2Bu^t)$n-C_5H_{11}. [h] R = $(CH_2)_2CH(OSiMe_2Bu^t)$. [i] A 2.5:1 mixture of **(13a)** and **(13b)**. [j] A 62:8 mixture of **(14a)** and **(14b)**. [k] This product is obtained as a by-product arising from **(12b)** in the reaction of a 74:26 mixture of **(12a)** and **(12b)**.



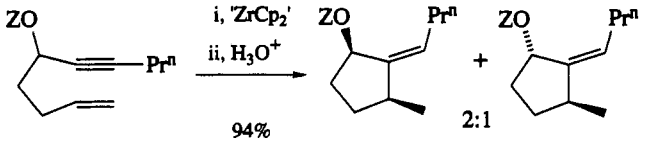
(7) (9) (8)



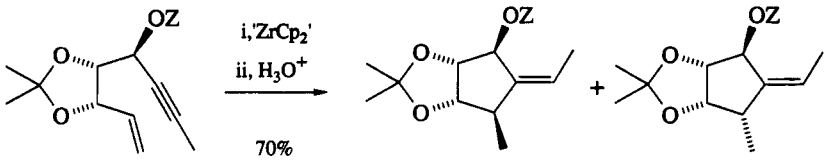
(8) (10) (9)



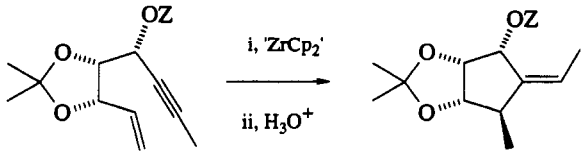
(10)



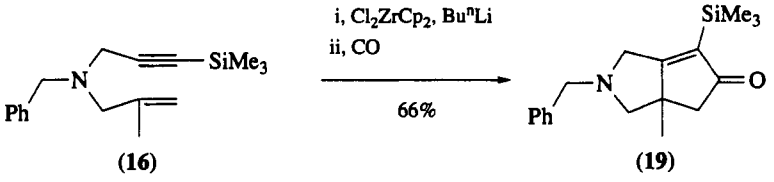
(11) Z = $SiMe_2Bu^t$ (13a) (13b) (11)



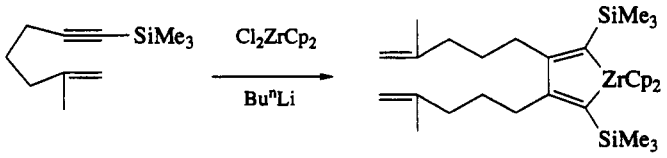
(12a) (14a) 62:8 (14b) (12)



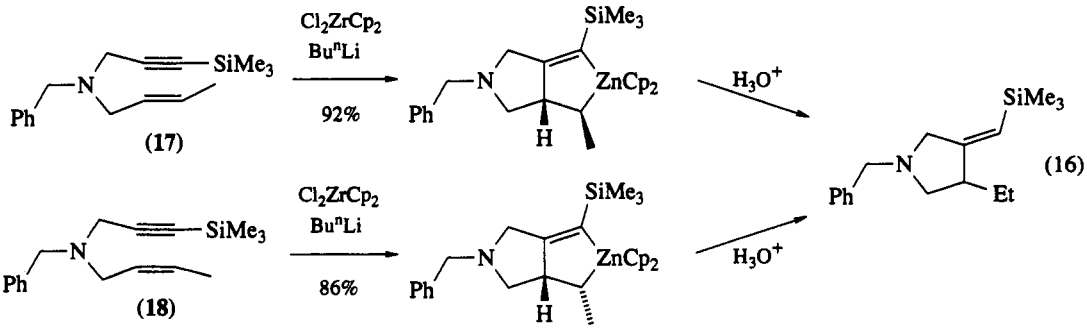
(12b) (15) Z = $SiMe_2Bu^t$ (13)



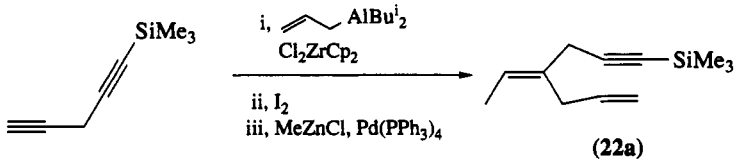
(16) (19) (14)



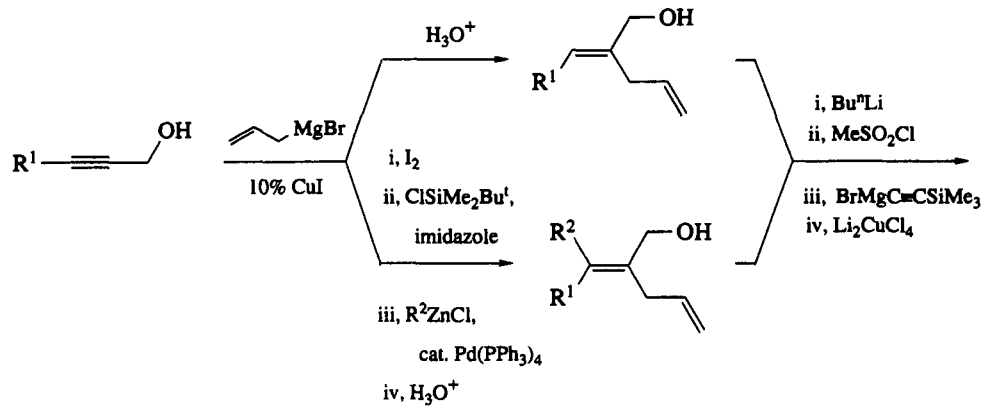
(20) (21) (15)

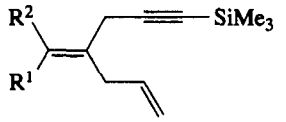


(17) (18) (16)



(22a) (17)

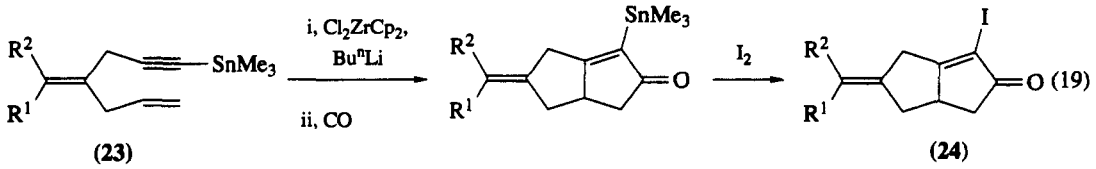




(22b) $R^1 = Bu^n$, $R^2 = H$
(22c) $R^1 = Bu^n$, $R^2 = Me$
(22d) $R^1 = Me$, $R^2 = Bu^n$

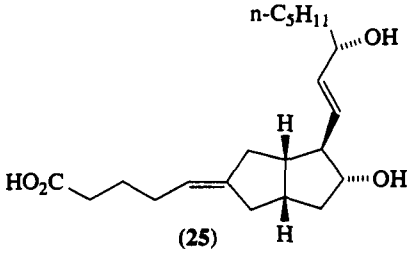
(18)

(22)

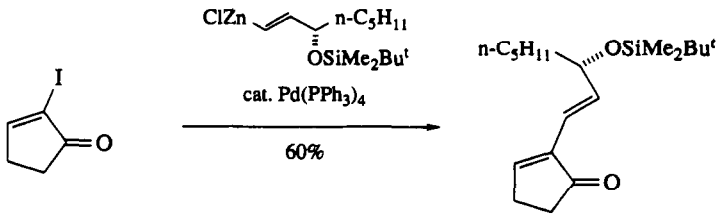


(19)

(23) (24)



(25)



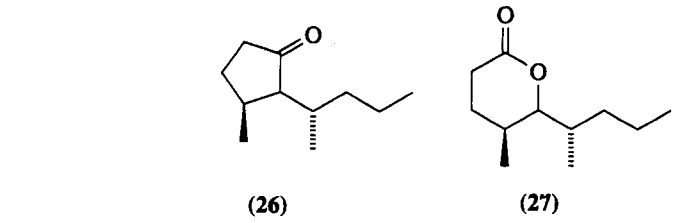
(20)

Although the product yields are very modest (40–50%), conversion of zirconacyclopentenes into the corresponding S-, Se- and Sn-containing cyclopentene derivatives has also been reported (equations 21 and 22).[20]

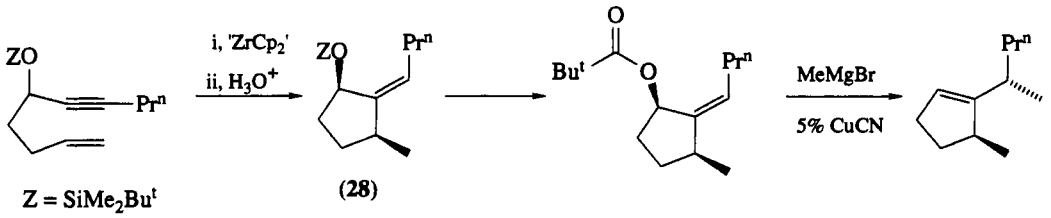
9.5.2.3 Bicyclization Promoted by Other Group IV Metals

Although the number of examples of the Ti-promoted bicyclization of enynes is very limited, the reaction appears to proceed satisfactorily in some favorable cases, as shown in equations (23) and (24).[20] The presumed titanacyclic intermediates do not appear to have been characterized.

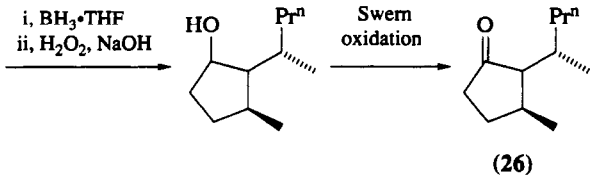
In more demanding cases, however, the Ti-promoted bicyclization reaction appears to be far inferior to the Zr-promoted reaction. For example, the reported yields of (**28**) for the Ti- and Zr-promoted reactions



(26) (27)

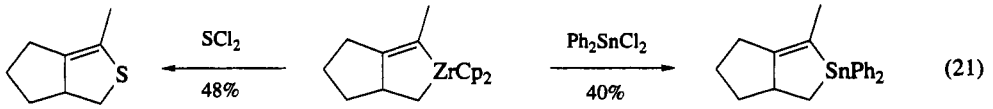


Z = $SiMe_2Bu^t$ (28)



(26)

Scheme 3



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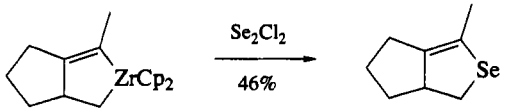
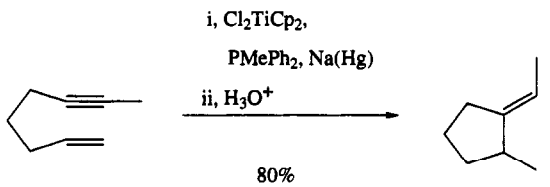
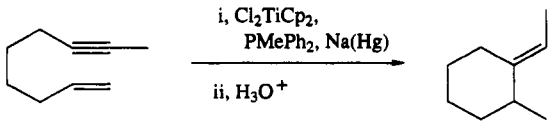


(22)



(23)

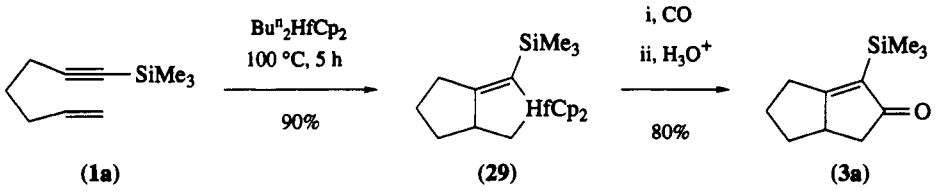


(24)

are 33 and 94%, respectively.[20] Furthermore, the use of a phosphine as a stabilizer appears to be essential for the Ti-promoted reaction,[15] thereby offsetting any economical advantage Ti might offer.

Treatment of Cl_2HfCp_2 with 2 equiv. of Bu^nLi gives $Bu^n{}_2HfCp_2$ as a discrete product that is stable at 25 °C.[15] Its reaction with 7-(trimethylsilyl)-1,6-heptenyne (**1a**) is much slower than that of '$ZrCp_2$' but proceeds smoothly at 100 °C for 5 h to give the expected hafnabicycle (**29**) in 90% yield. Its carbonylation with 3 atm of CO at 25 °C for 2 h gives (**3a**) in 80% GLC yield based on (**1a**; equation 25).[15]

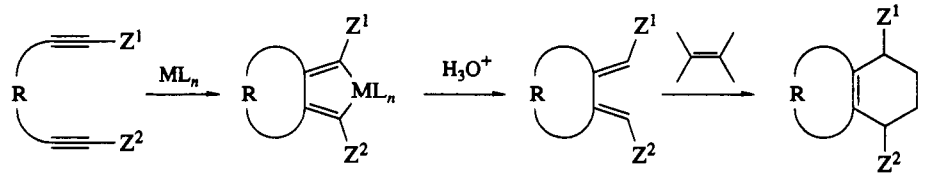
Although no advantage to the use of relatively expensive Hf has been noted so far, the higher stability of organohafnium intermediates relative to the corresponding Zr compounds promises to provide some significant synthetic advantages.



(1a) (29) (3a) (25)

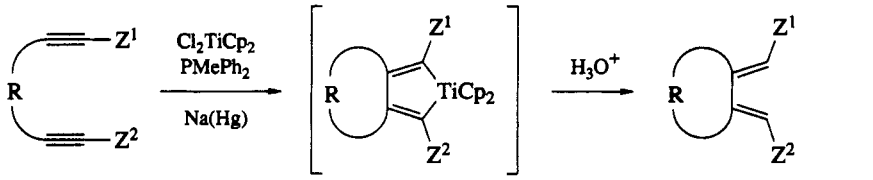
9.5.3 DIYNE BICYCLIZATION

Bicyclization of linear diynes (**30**) to produce bicyclic metallacyclopentadienes (**31**) followed by their conversion into *trans,trans*-1,2-bis(alkylidene)cycloalkanes (**32**) is a highly attractive synthetic operation primarily because (**32**) can now serve as the diene component in the Diels–Alder reaction (equation 26).



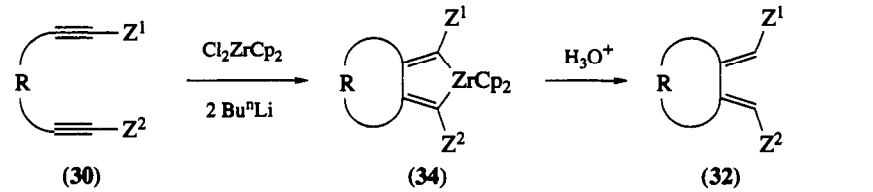
(30) (31) (32) (26)

The first generally applicable procedure for the conversion of (**30**) into (**32**) was developed with Cl_2TiCp_2,[26,27] as shown in equation (27).



(30) (33) (32) (27)

The titanabicycles (**33**) do not appear to have been fully characterized as such. Subsequently the corresponding Zr reaction was reported as an alternative procedure (equation 28).[14,15,27]



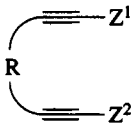
(30) (34) (32) (28)

In this case, some of the zirconabicycles (**34**) have been fully characterized. No attempts as yet appear to have been made to use Hf in the conversion of (**30**) into (**32**).

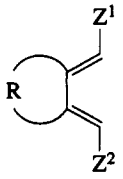
The experimental results summarized in Table 2 may permit the following generalizations. First, although both Ti and Zr are satisfactory in many cases, the Ti procedure is far more sensitive to steric and ring strains than the Zr procedure. Thus, the presence of one or more Pr^i, Bu^t, TMS and other sterically demanding groups causes a major decrease in product yield in the Ti reaction. Furthermore, the applicability of the Ti procedure is practically limited to the preparation of only five- and six-membered rings, while the Zr procedure can be used to synthesize four- to seven-membered rings. It is reasonable to state that the Zr procedure is, in general, either comparable or superior to the Ti procedure. So far, the superiority of the Ti procedure has been observed only in the reaction of 1,8-diethoxy-1,7-octadiyne.

The Diels–Alder reaction of the conjugated dienes (**32**) is well established. The following reaction sequence illustrates the potential synthetic utility of a combination of the bicyclization and the Diels–Alder reaction (equation 29).[27]

Table 2 Ti- or Zr-promoted Bicyclization–Protonolysis of Diynes



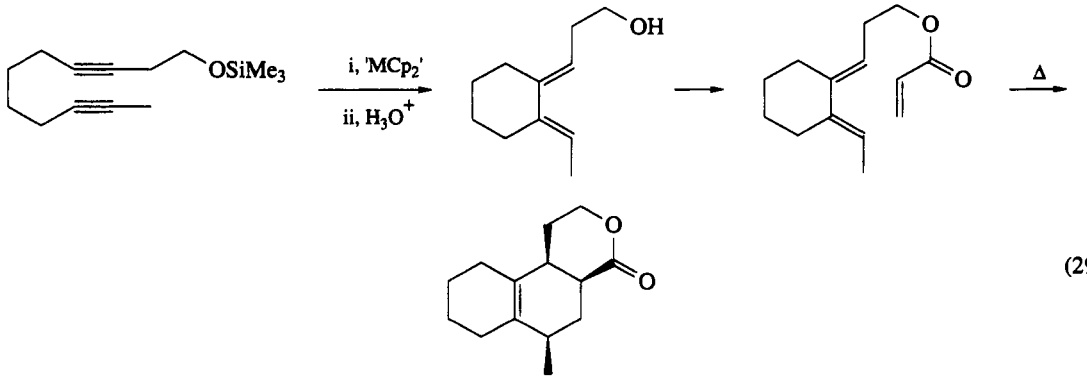
(30)



(32)

R	Z^1	Z^2	*Yield Using Ti (%)*[a]	*Yield Using Zr (%)*[b]	*Ref.*
$(CH_2)_2$	Me	Me	0	89	27
$(CH_2)_2$	Me	Bu^n	—	67 (76)	14
$(CH_2)_3$	Me	Me	78	70	27
$(CH_2)_3$	Et	Et		80 (85)	14
c	Me	Me	19	82	27
H_2COCH_2	Me	Me	72	—	27
H_2COCH_2	d	d	67	55	27
e	Me	$(CH_2)_2NH_2$	—	41	27
$(CH_2)_4$	Me	Me	89	70, 55 (84)	14, 27
$(CH_2)_4$	Et	Et	83	77	27
$(CH_2)_4$	Pr^i	Pr^i	16	67	27
$(CH_2)_4$	Bu^t	Bu^t	0	65	27
$(CH_2)_4$	Me	Pr^i	56	69	27
$(CH_2)_4$	Me	Bu^t	31	49	27
$(CH_2)_4$	Me	$(CH_2)_2OH$	79	63	27
$(CH_2)_4$	TMS	TMS	0	89 (97)	14, 27
$(CH_2)_4$	OEt	OEt	63	<16	27
f	Me	Me	—	60	27
$(CH_2)_5$	Me	Me	24	45, 40 (60)	14, 27
$(CH_2)_6$	Me	Me	0	<2	27

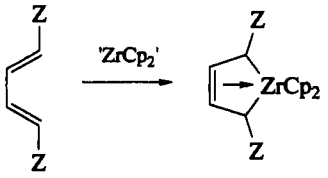
[a] Isolated. [b] Isolated. The numbers in parentheses are GLC yields. [c] R = $CH_2CH_2CH(OSiMe_2Bu^t)$. [d] $Z^1 = Z^2$ = 1,3-benzodioxol-5-yl. [e] R = $CH_2CH_2CH(OTMS)$. [f] R = 1,2-$(CH_2)_2C_6H_4$.



(29)

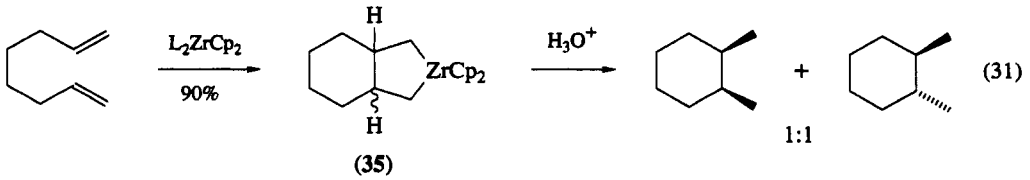
9.5.4 DIENE BICYCLIZATION

The double bonds in dienes can be isolated, conjugated, or cumulated. The reaction of conjugated dienes with '$ZrCp_2$' can give 1-zircona-3-cyclopentenes. This aspect of organozirconium compounds has been extensively studied and reviewed.[28–30] In fact, the conjugated diene–'$ZrCp_2$' reaction does not lead to the formation of bicyclic structures (equation 30). It instead gives monocyclic allylic zirconium derivatives exhibiting characteristics very different to those discussed above. For these reasons, the chemistry of the conjugated diene–'$ZrCp_2$' reaction is excluded from this review. Little or nothing is known about the cumulated diene–'$ZrCp_2$' reaction. The relatively high acidity of cumulenes may cause a difficulty similar to that observed with terminal alkynes.



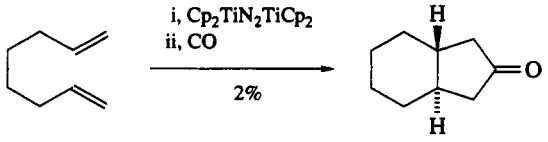
(30)

The reaction of 1,7-octadiene with Cp_2Zr–phosphine complexes generated by treatment of $Cp_2Zr(R)H$ with 2 equiv. of phosphine was briefly reported to give a 90% yield of the expected zirconabicycle (**35**; equation 31) as a 1:1 stereoisomeric mixture.[31] The nonstereoselectivity is rather disappointing, but this aspect may need to be reexamined in the light of more recent results in this area. No paper on the corresponding Hf reaction appears to have been published.



(35) (31)

Earlier, the corresponding reaction of '$TiCp_2$' was investigated under carbonylation conditions.[32] Although bicyclization may have occurred, the yield of 2-perhydroindanone was reported to be only 2% (equation 32). On the other hand, the reaction of Cl_2TiCp_2 with 1,2-bis(lithiomethyl)cyclohexane gave, after carbonylation, a 20% yield of the expected 2-perhydroindanone (equation 33).[32]



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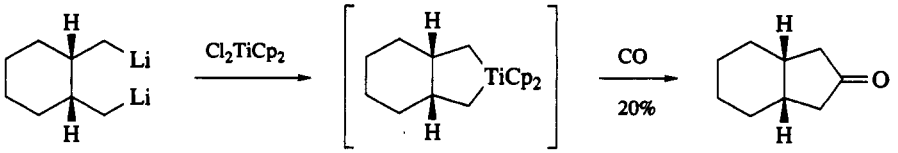


(33)

stereospecific

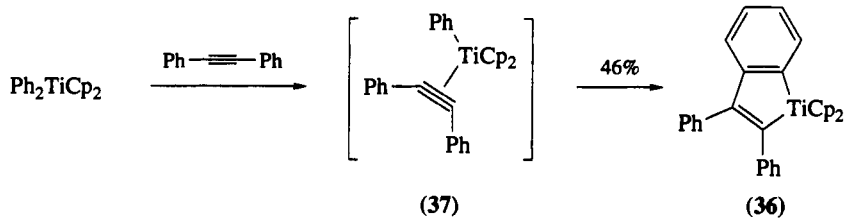
9.5.5 FORMATION AND REACTIONS OF THREE-MEMBERED AND FIVE-MEMBERED ZIRCONACYCLES

It has so far been assumed that treatment of Cl_2ZrCp with reducing agents, such as Mg and $HgCl_2$ or Bu^nLi, produces species that effectively act as $ZrCp_2$, *i.e.* '$ZrCp_2$'. Another key assumption has been that '$ZrCp_2$' interacts with alkynes and alkenes to produce zirconacyclopropenes and zirconacyclopropanes respectively, which then undergo cyclic carbometallation to afford five-membered zirconacycles. As such, these were only working hypotheses without sufficient experimental support. A few important aspects to be clarified are as follows. First, can three-membered zirconacycles actually be formed? Secondly, if they are indeed formed, how are they formed? Thirdly, can they serve as intermediates for five-membered zirconacycles? And how? Because of the current synthetic significance of organozirconium compounds in this area, this section deals mainly with zirconacycles.

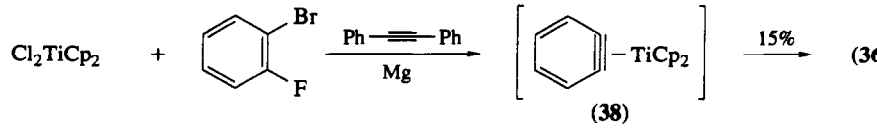
9.5.5.1 Formation of Zirconacyclopropenes and Zirconacyclopropanes

At the outset of the subsection, it should be emphasized that distinction between metallacyclopropenes and η^2-alkyne–metal complexes or that between metallacyclopropanes and η^2-alkene–metal complexes is largely a matter of semantics or convenience. Most or perhaps all of these species should probably be viewed as hybrids of three-membered metallacycles and π-complexes.

Prior to the development of the cyclization reactions discussed earlier, some three-membered metallacycles containing Group IV metals were known. In 1968, the thermal reaction of Ph_2TiCp_2 with PhC≡CPh producing (**36**; equation 34) was reported.[33] One of the presumed intermediates was (**37**). No experimental support was presented, and the mechanistic interpretation was probably erroneous in the light of what is now known. The same compound was later prepared by another method, and benzyne-titanocene complex (**38**; equation 35) was suggested as an intermediate.[34]

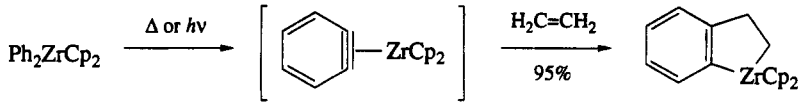


(37) (36) (34)



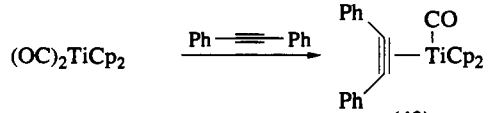
(38) (36) (35)

In an analogous manner, either thermolysis at 70 °C or photolysis of Ph_2ZrCp_2 was thought to generate benzyne–zirconocene (**39**; equation 36), but no direct evidence was provided.[35]



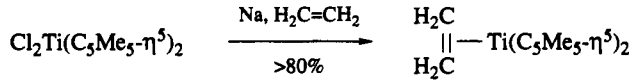
(39) (36)

Probably the first metallacyclopropene containing a Group IV metal that has been isolated and characterized is a diphenylacetylene–titanocene complex (**40**) prepared by the reaction of $(OC)_2TiCp_2$ with diphenylacetylene, as in equation (37).[36] Its structure was established primarily by X-ray crystallography.



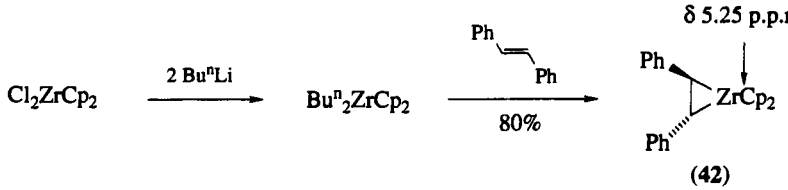
(40) (37)

In 1983, $(\eta^5\text{-}C_5Me_5)_2Ti(\eta^2\text{-}CH_2{=}CH_2)$ (**41**; equation 38) was prepared as the first example of metallacyclopropanes containing a Group IV metal, and its structure was established by X-ray analysis and other spectroscopic means.[37]



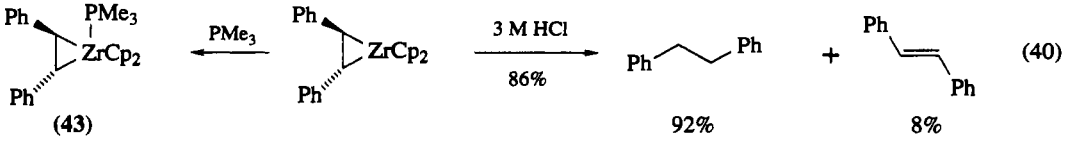
(41) (38)

Somewhat surprisingly, no report on the preparation of zirconacyclopropenes or zirconacyclopropanes as discrete, characterizable species and/or their full spectroscopic characterization was available until a few years ago. Probably, stilbene–zirconocene (**42**; equation 39) is the first example of such compounds spectroscopically characterized.[14]



(42) (39)

The compound (**42**) gives, on treatment with 3 M HCl, bibenzyl and stilbene in 79 and 7% yields, respectively, and reacts with PMe_3 to give a 1:1 complex (**43**; equation 40).[38]



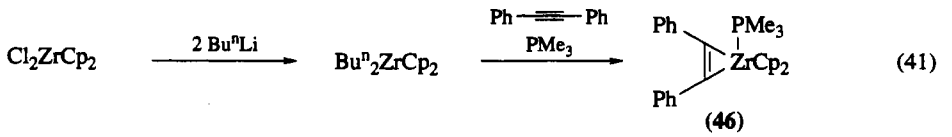
Since 1986, the following zirconacyclopropenes as well as one zirconacyclopropane, *i.e.* (**43**),[38] have been characterized by X-ray and other spectroscopic means. The compound (**44**)[39] represents a benzyne–zirconocene complex, and (**45**)[40] is an example of a cycloalkyne–zirconocene complex. Although these compounds are interesting and significant in their own right, they do not provide support for the formation of zirconacyclopropenes from alkynes and '$ZrCp_2$', because the alkyne components are generated *in situ* and have probably never been free.

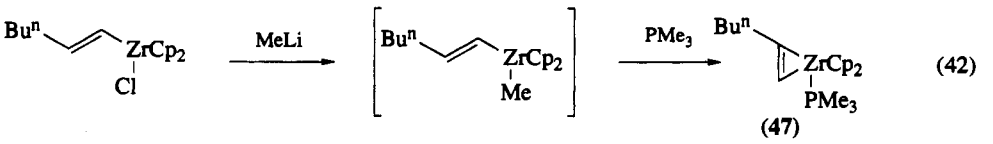
The first isolated and fully characterized zirconacyclopropene prepared by the reaction of free alkyne and '$ZrCp_2$' is (**46**; equation 41; Figure 1).[41] Independently and simultaneously, another X-ray structure of an acyclic alkyne–zirconocene (**47**) prepared as shown in equation (42) was also published.[42] The first X-ray structure of a zirconacyclopropane derivative is shown in Figure 2.[38]

It has now been established that both zirconacyclopropenes and zirconacyclopropanes can be prepared as discrete and fully characterizable species. More relevant to the present discussion is that these species can be generated by the reaction of free alkynes or alkenes with '$ZrCp_2$', as shown in equations (39) and (41). Another useful piece of information is that the formation of (**46**) from diphenylacetylene according to equation (41) is about 150 times as fast as that of (**43**) from (*E*)-stilbene under the same conditions, indicating that, in comparable situations, alkynes are far more reactive than alkenes towards '$ZrCp_2$'. Little definitive information is currently available on the formation of related three-membered hafnacycles.

The second question to be answered is how three-membered zirconacycles are formed. This will no doubt depend on the starting compounds, the reagents and the reaction conditions. A reasonably clear mechanistic scheme has emerged for the reactions of '$ZrCp_2$' derived from Cl_2ZrCp_2 and Bu^nLi.[14,15] Treatment of Cl_2ZrCp_2 with 2 equiv. of Bu^nLi at –78 °C gives $Bu^n{}_2ZrCp_2$ in nearly quantitative yield. Although the compound is too unstable to fully identify as such, it has been characterized by NMR. Its treatment with 2 equiv. of iodine gives Bu^nI in excellent yield. Furthermore, the corresponding reaction of Cl_2HfCp_2 gives $Bu^n{}_2HfCp_2$, which is stable at 25 °C and readily characterizable. Treatment of $Bu^n{}_2ZrCp_2$ with 2 equiv. of PMe_3 gives a relatively stable complex, which was initially and erroneously identified as $Cp_2Zr(PMe_3)_2$ on the basis of a triplet-like ^1H NMR signal for the Cp group.[14] The original simplistic view was as shown in equation (43).

An alternate structure (**48**) was suggested.[42] Reexamination has established that it is a *ca.* 90:10 mixture of (**49**) and (**48**).[15] It now is likely that '$ZrCp_2$' generated *in situ* from Cl_2ZrCp_2 and $2Bu^nLi$ is (**50**). It is also likely that (**50**) is formed directly from $Bu^n{}_2ZrCp_2$, as shown in equation (44).





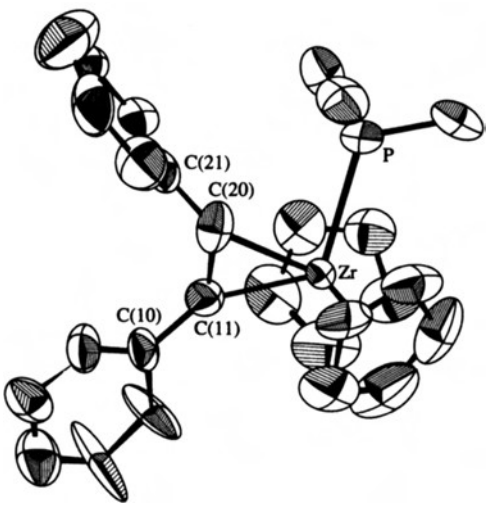


Figure 1 Molecular structure and atom labeling scheme for $Cp_2Zr(PhC{\equiv}CPh)(PMe_3)$ (**46**). Selected bond lengths and angles are as follows: Zr—C(10) = 2.20(4) (Å); Zr—C(20) = 2.25(4); Zr—P = 2.70(1); C(10)—C(20) = 1.36(6); C(10)—Zr—C(20) = 36(1)°; Zr—C(10)—C(20) = 74(2); Zr—C(20)—C(10) = 70(2); C(11)—C(10)—C(20) = 134(4); C(10)—C(20)—C(21) = 133(4)

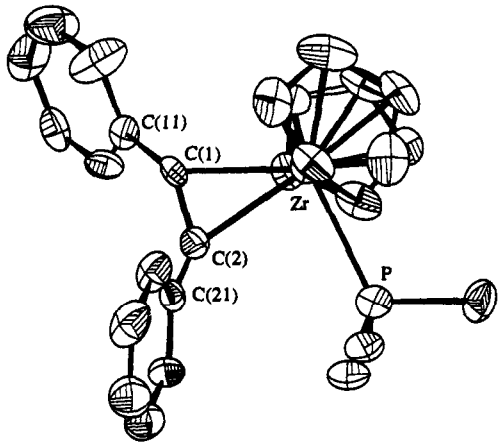
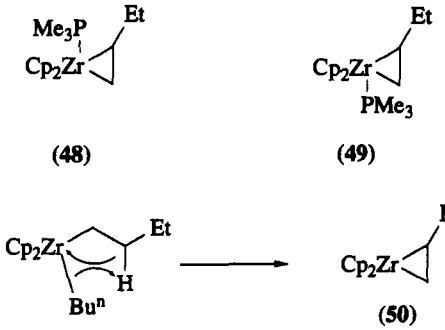


Figure 2 Molecular structure and atom labeling scheme for $Cp_2Zr(PhCH{=}CHPh)(PMe_3)$(**43**). Selected bond lengths (Å) and angles are as follows: Zr—P = 2.715(5); Zr—Cl = 2.361(15); Zr—C(2) = 2.426(15); C(1)—C(2) = 1.376(21); C(1)—C(11) = 1.509(22); C(2)—C(21) = 1.495(22); C(1)—Zr—C(2) = 33.4(5)°; C(11)—C(1)—C(2) = 127.2(14); C(21)—C(2)—C(1) = 122.8(14); P—Zr—C(2) = 75.9(9); Zr—C(2)—C(1) = 70.7(9); P—Zr—C(1) = 114.5(4); P—Zr—C(2) = 81.3(4); Zr—C(1)—C(11) = 123.5(1); Zr—C(2)—C(21) = 125.2(10)

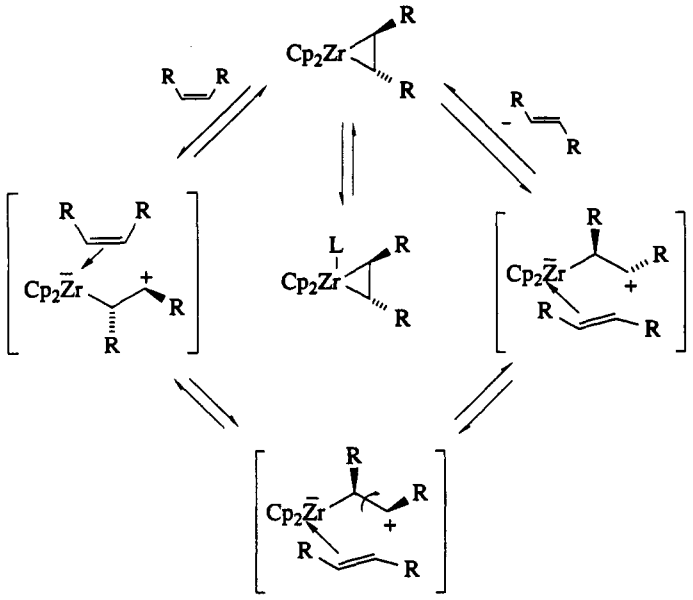
(43)



(48) (49)

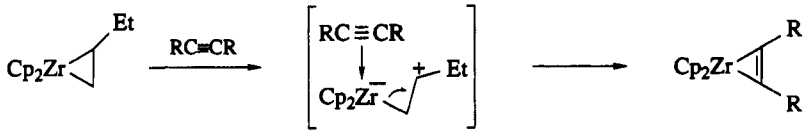
(44)

Further investigation of alkene ligand exchange processes has revealed a novel semiassociative–semidissociative mechanism for alkene ligand exchange shown in Scheme 4. The salient feature of the mechanism is that, in an associative process, an alkene ligand partially dissociates to generate a dipolar species in which C and Zr are positively and negatively polarized, respectively.[43]



Scheme 4

The conclusions summarized in Scheme 4 are based on the following. First, the reaction of $Bu^n_2ZrCp_2$ with either (*E*)- or (*Z*)-stilbene gives exclusively the (*E*)-stilbene–zirconocene complex (**42**). (*Z*)-Stilbene is isomerized to the (*E*)-isomer under the catalytic influence of '$ZrCp_2$'. Secondly, whereas the complexation and/or isomerization processes are retarded by electron-donating phosphines, an electron-donating substituent, *e.g.* Me, in the *para* position of stilbene accelerates these processes, the ρ value being *ca.* −2.9. Thirdly, the proposed mechanism is in accord with simple molecular orbital considerations. Although yet to be further clarified, the reaction of an alkyne with (**50**), a formal d^0, 16-electron species, probably proceeds in a similar manner (equation 45).



(45)

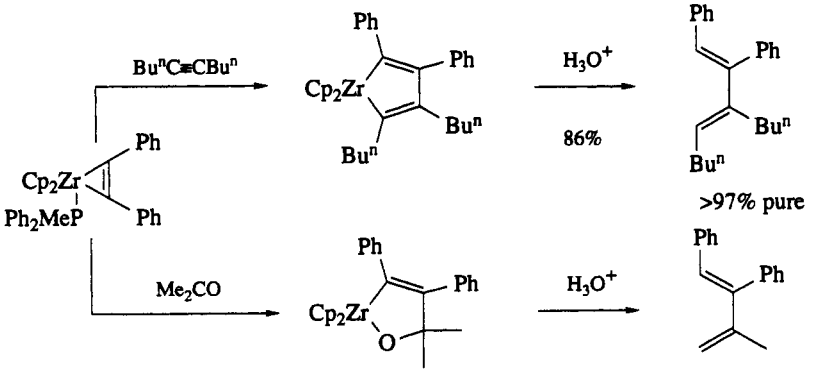
9.5.5.2 Formation of Zirconacyclopentadienes, Zirconacyclopentenes and Zirconacyclopentanes *via* Three-membered Zirconacycles

Earlier studies of the preparation of five-membered zirconacycles either do not discuss the intermediacy of three-membered zirconacycles or merely suggest their intermediacy. Such studies include those on the formation of zirconacyclopentadienes,[9,10,14,26,27] zirconacyclopentenes,[11,16,20,44–46] and zirconacyclopentanes.[31,35]

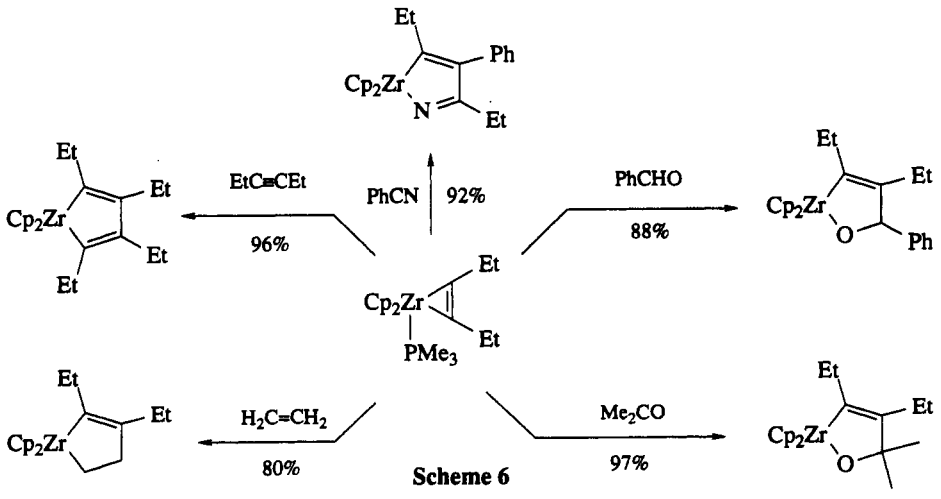
The recent availability of well-defined zirconacyclopropenes[39–42] and zirconacyclopropanes[14,15,38,43] has permitted investigation of their conversion into five-membered zirconacycles. In general, zirconacyclopropenes readily undergo coupling with alkynes, alkenes, nitriles, aldehydes and ketones to produce the corresponding five-membered zirconacycles. Some representative results involving zirconacyclopropenes corresponding to acyclic alkynes,[41,42] cyclic alkynes[40] and benzynes[39] are shown in Schemes 5–9. These results show some remarkable pair selectivity and regioselectivity.

The precise mechanisms of the conversion of zirconacyclopropenes into five-membered zirconacycles are still unclear. For the reactions of alkynes and alkenes, a concerted carbometallation mechanism earlier proposed[1] appears to be plausible, but remains only a reasonable working hypothesis. One useful piece of information is that the reaction of an *in situ* generated benzyne–zirconocene complex with stilbene is stereospecific, as shown in equation (46),[45] suggesting that, in contrast to the formation of some three-membered zirconacycles, this and other related reactions may be concerted.

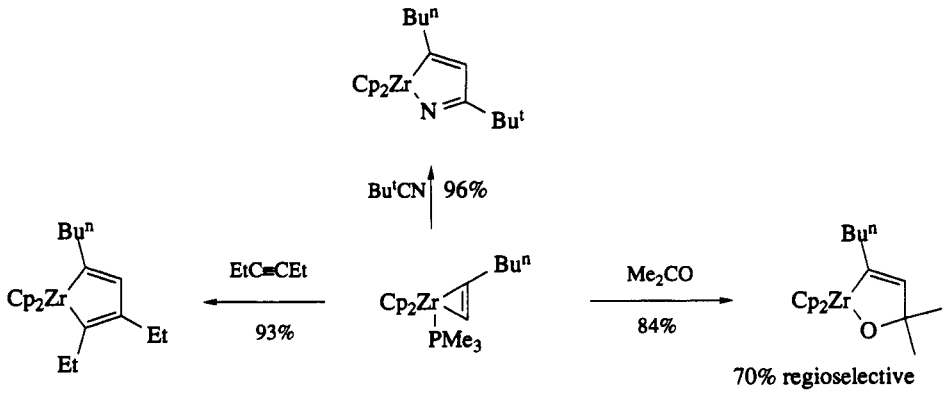
With the information available at present, the following mechanistic scheme may be proposed for the bicyclization of (**1a**) with '$ZrCp_2$' generated *in situ* by treating Cl_2ZrCp_2 with Bu^nLi. The reaction of Cl_2ZrCp_2 with 2 equiv. of Bu^nLi initially produces at –78 °C $Bu^n{}_2ZrCp_2$ which, in the presence of (**1a**), decomposes to generate 1-butene–zirconocene (**50**) as '$ZrCp_2$'. Interaction of (**50**) with (**1a**) initially produces, most likely *via* a semiassociative–semidissociative mechanism (Scheme 4), an intermediate repre-



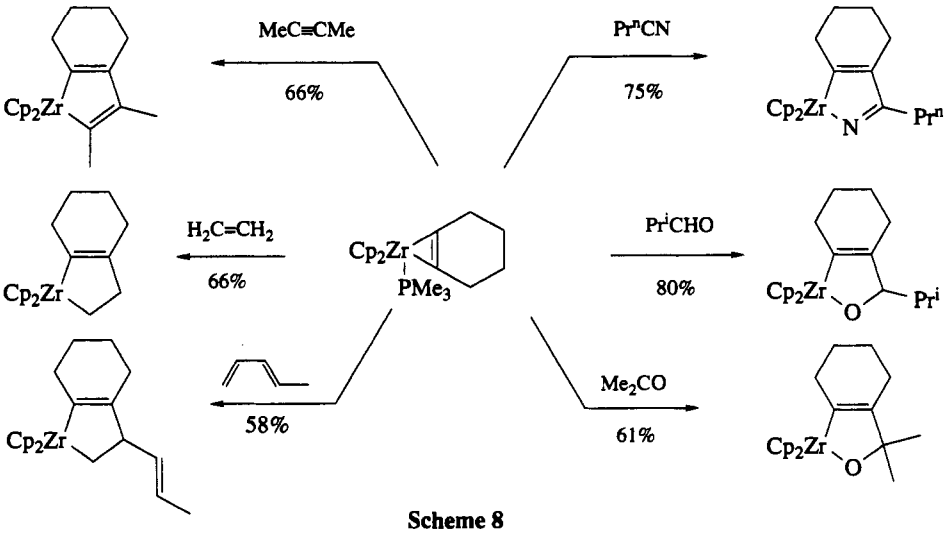
Scheme 5



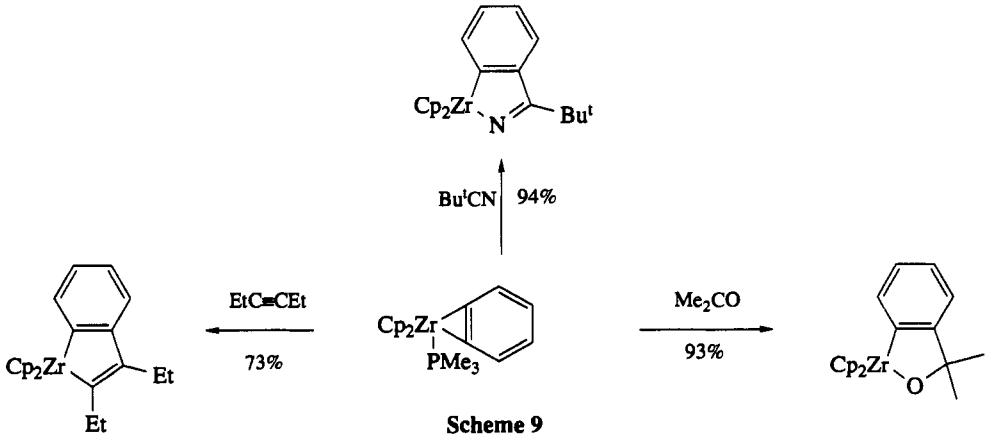
Scheme 6



Scheme 7



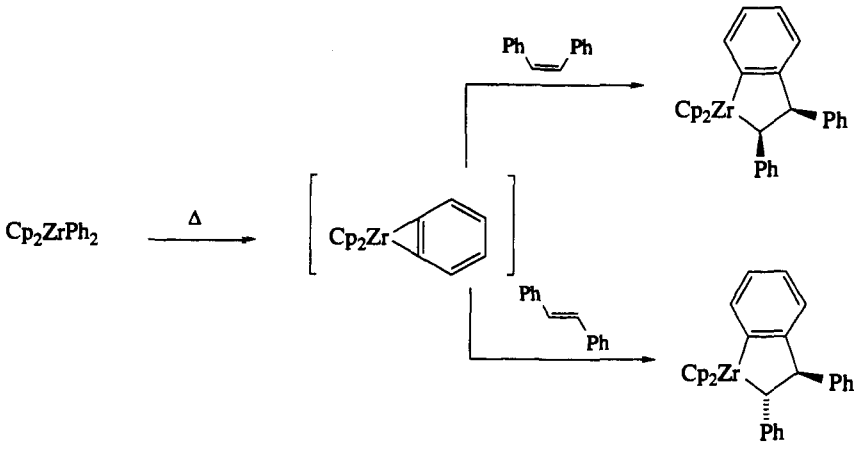
Scheme 8



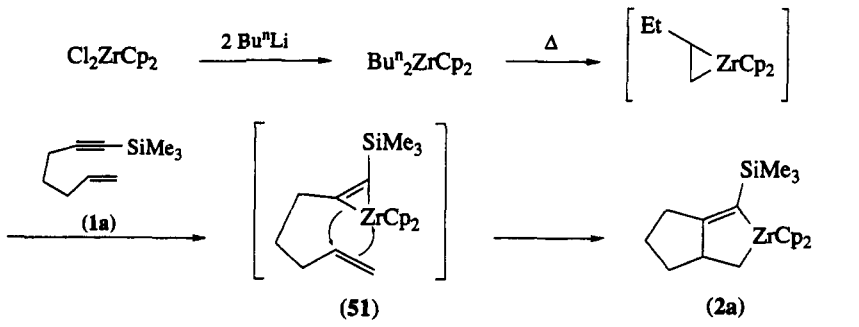
Scheme 9

sented by (**51**), which then undergoes concerted intramolecular carbozirconation to give (**2a**), as depicted in equation (47).

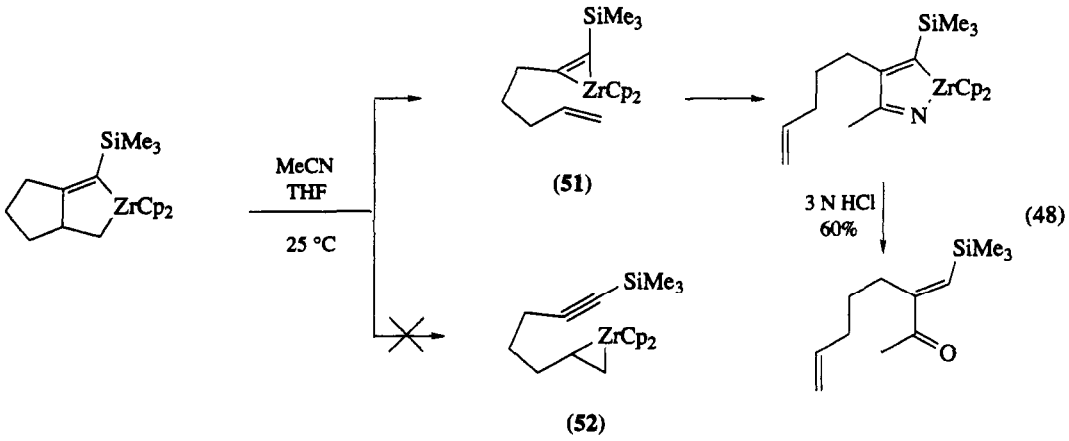
Formation of (**51**) rather than the zirconacyclopropane derivative (**52**) is reasonable in the light of the considerably higher reactivity of alkynes relative to alkenes. Furthermore, the following intriguing results not only reveal some remarkable reactivity of five-membered zirconacycles but also support the intermediacy of (**51**) rather than (**52**; equation 48).[15]



(46)

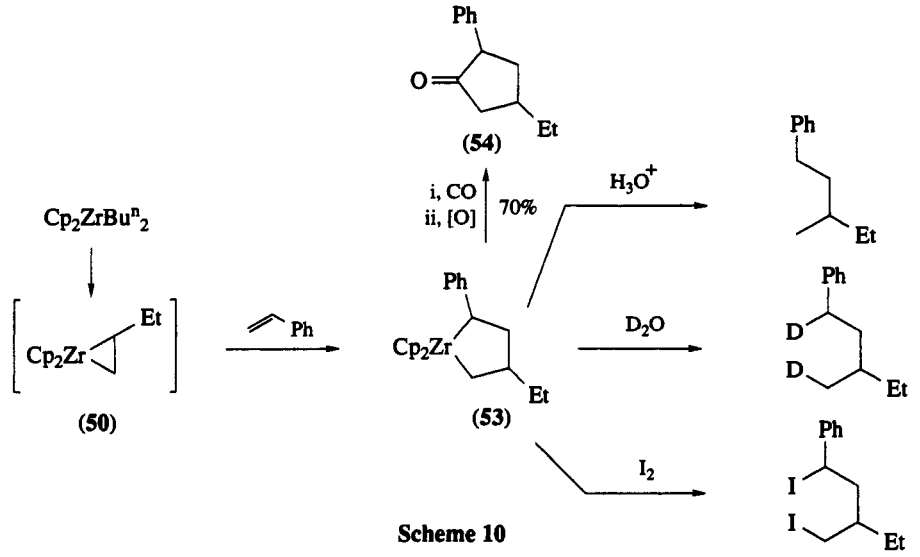


(47)



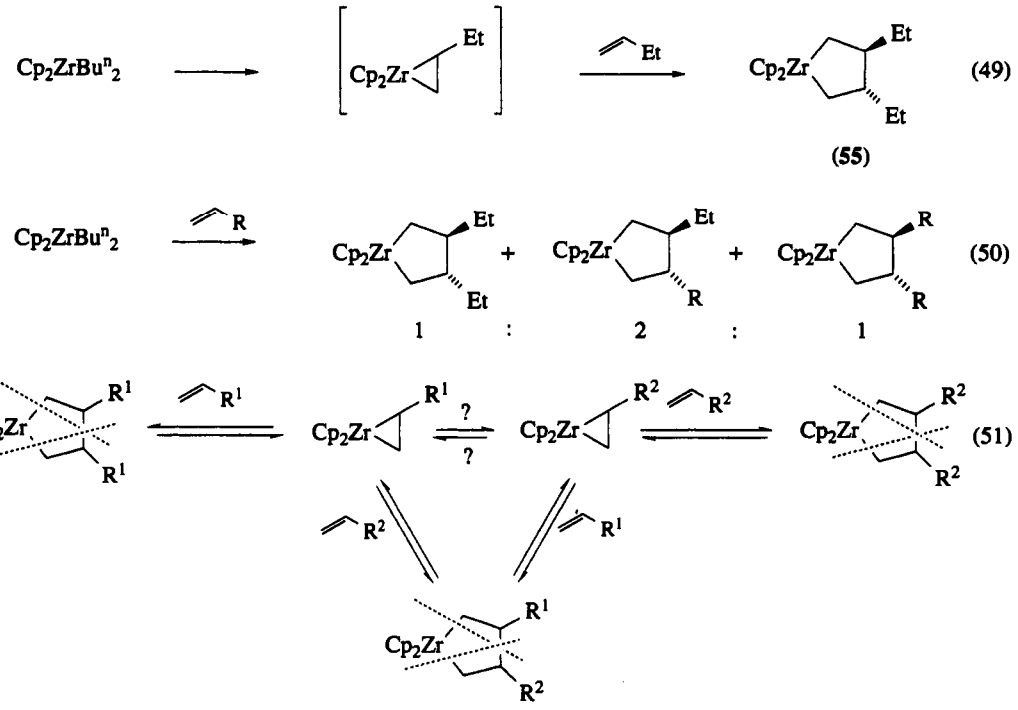
(48)

The reactions of zirconacyclopropanes with alkenes and alkynes are somewhat more capricious and unpredictable than those of zirconacyclopropenes. Zirconacyclopropanes display both σ- and π-reactivities even toward compounds of the same class. For example, the reaction of 1-butene–zirconocene (**50**) with stilbene gives stilbene–zirconocene (**42**) *via* alkene displacement (π-reactivity), as shown in equation (39). On the other hand, the corresponding reaction with styrene gives exclusively a zirconacyclopentane derivative (**53**), displaying a high pair selectivity and a high and intriguing regioselectivity, as shown in Scheme 10.[47] Protonolysis, deuterolysis and iodinolysis cleanly give the expected products in good yields, and carbonylation provides (**54**) in 70% yield, after oxidation of the corresponding cyclopentanol formed as a minor by-product of (**54**).[47] The isolated product (**54**) is a 5:1 mixture of two possible diastereomers. Since (**54**) is readily epimerizable, this ratio may not represent the stereoselectivity of the cyclization step. Regardless of the precise stereochemistry of the reaction, the pair-selective and regioselective alkyl–alkene coupling and carbonylation reactions can provide potentially attractive synthetic tools.

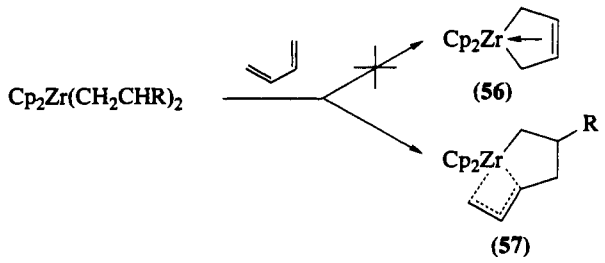


Scheme 10

Interestingly, the reaction of $Cp_2ZrBu^n_2$ with 1-butene cleanly and selectively gives (**55**).[47] At present, the difference in regiochemistry between Scheme 10 and equation (49) cannot readily be explained. Presumably, placement of alkyl substituents in the 3- and 4-positions of the zirconacyclopentane ring is favored by steric factors, whereas additional electronic factors, such as formation of the benzyl cation rather than alkyl cations, may favor placement of aryl substituents in the 2- or 5-position. This point, however, needs to be further investigated. Unfortunately, the reaction of (**50**) with other terminal alkenes containing alkyl substituents is not pair selective, giving essentially statistical mixtures of three cyclic products, even though the reaction is highly regioselective and apparently stereoselective, favoring the *trans* relationship between the two substituents (equation 50).[47] These results suggest that the formation of zirconacyclopentanes from zirconacyclopropanes is readily reversible (equation 51), as in the cases of zirconacyclopentenes shown in equation (48).

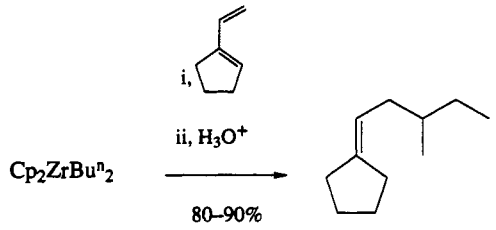


The reaction of $Cp_2ZrBu^n_2$ with conjugated dienes produces previously reported zirconacycles[28–30] of the type represented by (**57**; equation 52). A wide variety of substituents can, in principle, be readily incorporated in Cp_2ZrR_2, and a wide variety of conjugated dienes appear to participate in the reaction. Consequently, this provides a convenient alternative to the previously developed procedures.[28–30]

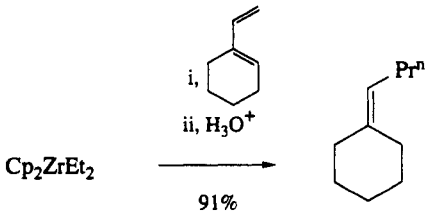


(52)

One application of the reaction shown in equation (52) is the conversion of cyclic, conjugated dienes into exocyclic alkenes. Although the stereochemistry of the reaction needs to be established, the cyclization–protonolysis sequence may provide a convenient route to stereodefined exocyclic alkenes, as suggested by the examples given in equations (53) and (54).[48] These reactions are all at least 90–95% regioselective, as judged by ^{13}C NMR.



(53)



(54)

9.5.6 CONCLUSION

The results presented above indicate that the Zr-promoted bicyclization reactions of enynes and diynes constitute novel and attractive synthetic methods. The corresponding reaction of dienes remains to be developed. Somewhat unexpectedly, the reactions of monoalkynes and monoalkenes can, in many cases, be highly pair selective and regioselective. Many aspects of these reactions also need to be further developed. Besides being attractive from the viewpoint of organic synthesis, the chemistry of '$ZrCp_2$' provides a number of novel structural and mechanistic features that broaden the horizon of organometallic chemistry.

Many unaccomplished and yet highly necessary tasks remain. The scope and limitations as well as mechanistic details of most of the reactions discussed above need to be further delineated. More extensive and challenging applications of the newly developed reactions to the synthesis of natural products and other complex organic molecules must also be carried out. In addition, other less routine but highly desirable aspects should also be explored. These include asymmetric cyclization and catalytic procedures for cyclization–carbonylation.

In general, the corresponding organotitanium reactions appear to be more prone to steric hindrance and other strain factors. In principle, this may be overcome by various approaches, such as stabilization by suitable ligands. Nonetheless, it appears at present that, on balance, advantages of using the Ti reactions may be observed only in a limited number of cases. On the other hand, organohafnium compounds appear to be generally more stable or less reactive than the corresponding organozirconium compounds,

even though they appear to participate in most of the corresponding reactions. This and the higher cost of Hf relative to that of Zr makes Hf less attractive than Zr. However, the greater thermal stability of organohafnium compounds may prove to be advantageous in some cases where the instability of organozirconium compounds may be the cause for difficulties.

As is clear from the introductory discussion, most, if not all, of the *d*-block transition metals are expected to participate in reactions that are related to those discussed here. In addition to the Co-based methodology[8] mentioned earlier, some related reactions of Pd and Ni[49–56] are known. Also related are the cyclization reactions of metal–carbene complexes containing Cr, Mo, W and other transition metals with alkynes and alkenes[57] and a recently reported Nb- or Ta-promoted diyne–alkyne cyclization reaction,[58] which appears to be closely related to a number of previously developed alkyne cyclotrimerization reactions, such as those catalyzed by Co.[59] Investigations of reactions involving other transition metals may prove to be important especially from the viewpoint of developing asymmetric and catalytic procedures.

The author wishes to thank his coworkers whose names appear in the references section, especially S. J. Holmes, F. E. Cederbaum, D. S. Swanson, T. Takahashi, and C. J. Rousset.

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9.6
Metal-catalyzed Cycloaddition of Small Ring Compounds

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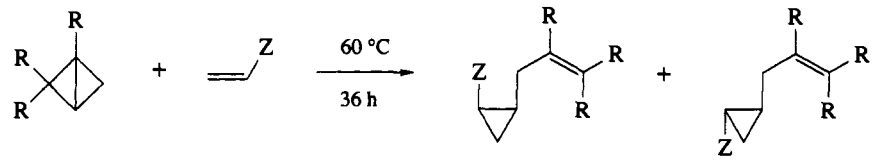
9.6.1 INTRODUCTION

Highly strained carbon–carbon double bonds and even carbon–carbon σ-bonds of small ring compounds interact readily with transition metal complexes. Such perturbation activates them to enter into intra- and inter-molecular cycloadditions with cleavage of carbon–carbon σ-bonds.[1]

9.6.2 TRANSITION METAL CATALYZED REACTIONS OF BICYCLO[1.1.0]BUTANES: SYNTHESIS OF ALLYLCYCLOPROPANES

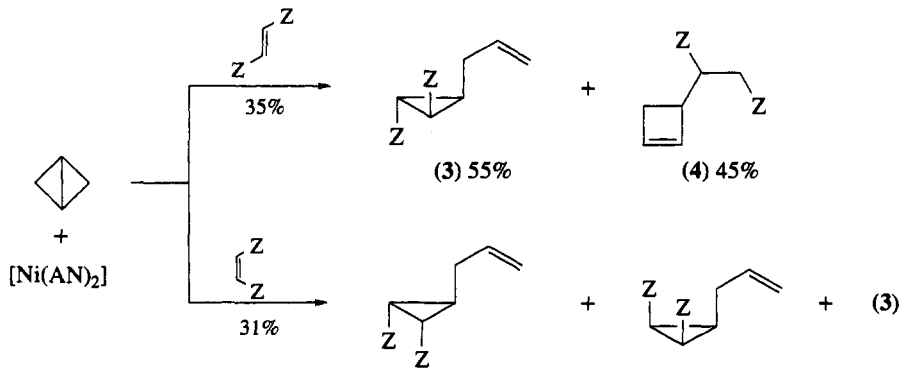
Bicyclo[1.1.0]butanes (**1**; equation 1),[2] the smallest bicyclic hydrocarbons, are highly strained but stable at ambient temperature. Under the influence of a catalytic amount of a nickel(0) complex, however, they undergo cleavage of the central bond and one of the four peripheral bonds and enter into cycloaddition reactions with electron deficient alkenes to afford allylcyclopropane derivatives. Reaction of

bicyclo[1.1.0]butane (**1a**) and methyl acrylate catalyzed by $[Ni(AN)_2]$ (AN = acrylonitrile) affords methyl 2-allylcyclopropanecarboxylates (**2a**) in quantitative yield (*cis:trans* = 65:35).[3] Similarly, allylcyclopropanes are obtained in good yields by use of (**1b**), 1-methoxycarbonylbicyclo[1.1.0]butane, 1-cyanobicyclo[1.1.0]butane, *etc.*[3a] The reactions of (**1a**) with 2,3-*cis*-dideuterated methyl acrylate and with dimethyl fumarate and dimethyl maleate indicate that the overall process proceeds with excellent stereospecificity and with retention of configuration in the alkenic reaction partner (equation 2).



(1) (1)

(1)	$Z = CO_2Me$	*cis*-(2)	*trans*-(2)
a: R = H	quantitative	65 :	35
b: R = Me	70%	65 :	35



(2)

$Z = CO_2Me$

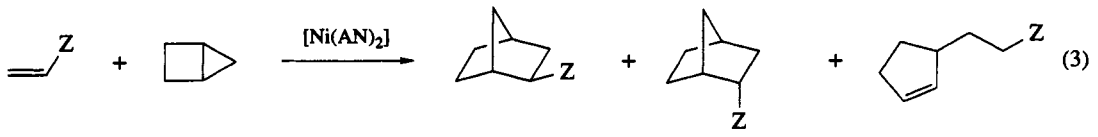
This coupling reaction can be formally viewed as a metal-assisted intramolecular retrocarbene addition of bicyclobutanes, followed by intermolecular cycloaddition of the resulting allylcarbene–nickel complexes to alkenes.

Methoxycarbonylcyclopropane derivatives are also obtained in 38% yield (*cis:trans* = 30:8) by the reaction of 1-methylbicyclo[1.1.0]butane with methyl acrylate in the presence of a catalytic amount of $[\{RhCl(norbornadiene)\}_2]$, in addition to 2-methyl-1,3-butadiene (37%) and 2,7-dimethyl-1,4,7-octatriene (25%).[4]

9.6.3 TRANSITION METAL CATALYZED REACTIONS OF BICYCLO[2.1.0]PENTANES: SYNTHESIS OF BICYCLO[2.2.1]HEPTANES

Bicyclo[2.1.0]pentane (**7**; equation 3) readily undergoes a cycloaddition across carbon–carbon double bonds in the presence of nickel(0) complexes.[5] The mode is formally analyzed as a thermally forbidden [2 + 2] process[6] and is in striking contrast to that of the lower homolog, bicyclo[1.1.0]butane, which suffers cleavage of two σ-bonds and affords formal allylcarbene addition products.[7] When a solution of bicyclo[2.1.0]pentane (**7**) and $[Ni(AN)_2]$ in excess methyl acrylate is heated at 40 °C for 36 h under a nitrogen atmosphere, the stereoisomeric cycloadducts *exo*- and *endo*-2-methoxycarbonylbicyclo[2.2.1]heptane (**8a**) and (**9a**) (50:50 ratio) are produced in 66% combined yield, in addition to the monocyclic product methyl 3-(cyclopent-2-enyl)propionate (**10a**; 22%). Reaction of (**7**) with acrylonitrile affords the corresponding adducts (**8b**), (**9b**) and (**10b**).

In contrast to the purely thermal cycloaddition which occurs in a nonstereospecific manner with respect to alkenes in low yield, nickel(0) catalysis results in a highly stereospecific cycloaddition, as demonstrated by the reactions between (**11**; equation 4) and dimethyl fumarate or dimethyl maleate.

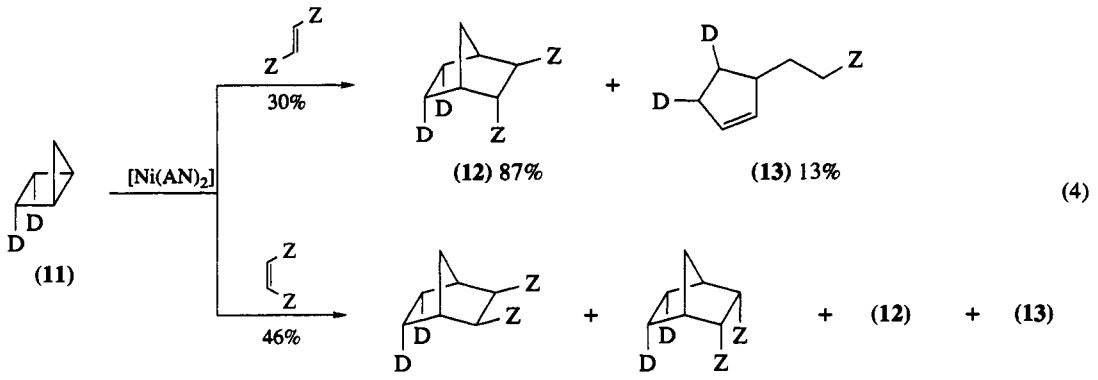


(3)

(7) (8) (9) (10)

a: Z = CO_2Me	40 °C/36 h	66%	50:50	22%
b: Z = CN	70 °C/36 h	75%	62:38	16%

Interestingly, the purely thermal cycloaddition occurs with inversion of the configurations at C-1 and C-4 of (**11**), while the nickel(0)-catalyzed reaction proceeds with retention of configuration at these carbons.



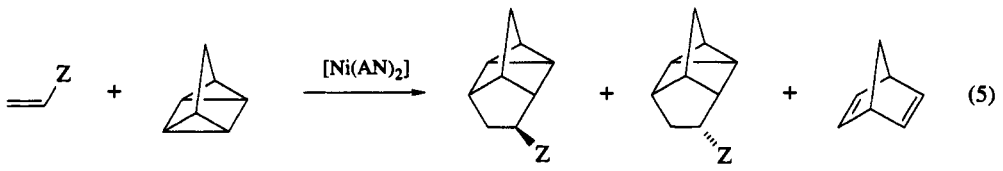
(4)

(**12**) 87% (**13**) 13%

$Z = CO_2Me$ (**14**) 61% (**15**) 5% 4% 30%

9.6.4 TRANSITION METAL CATALYZED REACTIONS OF OTHER STRAINED POLYCYCLIC HYDROCARBONS

Quadricyclane (**16**; equation 5) reacts with electron deficient alkenes in the presence of [Ni(acrylonitrile)$_2$] to afford the cycloadducts (**17a**) and (**17b**) in moderate yields, along with some norbornadiene.[8] This catalytic cycloaddition proceeds in a highly stereospecific manner with retention of alkene configuration. The same compounds are obtained using norbornadiene in place of (**16**) under similar catalytic conditions. In the absence of transition metals, though under rather forcing conditions, quadricyclane (**16**) reacts with electron deficient alkenes in a concerted [2 + 2 + 2] manner to give tricyclo[4.2.1.$0^{2,5}$]non-7-enes.[9]

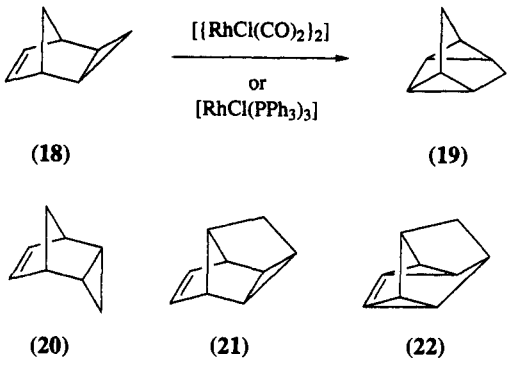


(5)

(**16**) (**17a**) (**17b**)

Z = CN	20 °C/48 h	50%	49:51	30%
CO_2Me		58%	40:60	–

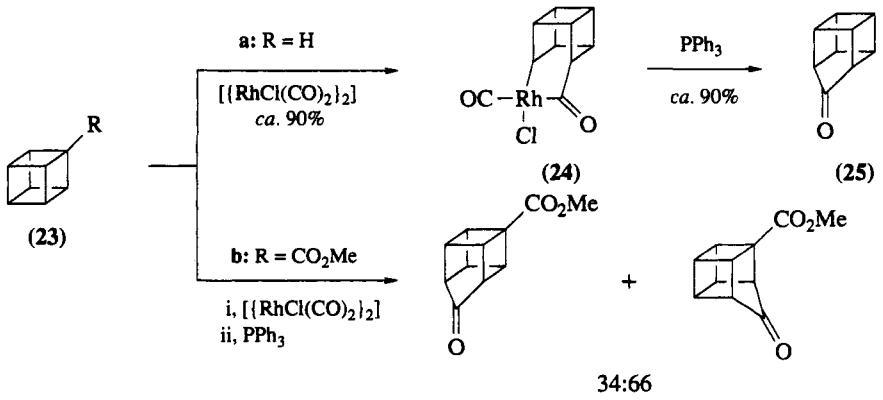
exo-Tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**18**; equation 6) as either neat liquid or solution in $CDCl_3$, is converted quantitatively into tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane (**19**) in the presence of 10 mol % of [{RhCl(CO)$_2$}$_2$] at room temperature.[10] This reaction is also promoted by [RhCl(PPh_3)$_3$] at elevated temperature. In the latter reaction, a metallacyclic intermediate has been proposed.[11] Failure of the *endo* isomer (**20**) to undergo a similar reaction shows that the *exo* arrangement of the fused cyclopropane ring in (**18**) is prerequisite for the occurrence of the valence isomerization. Tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]non-8-ene (**21**), a compound closely related to (**18**), is not converted to (**22**) in the presence of [{RhCl(CO)$_2$}$_2$] at room temperature for two days or with [RhCl(PPh_3)$_3$] at 170 °C for three days.[12]



(18) (19) (6)

(20) (21) (22)

Rhodium(I) complexes are efficient catalysts for the valence isomerizations of cubane (**23a**; equation 7) and its derivatives to the corresponding *syn*-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-dienes. When a stoichiometric amount of [{RhCl(CO)$_2$}$_2$] is added to a chloroform solution of cubane, the organorhodium compound (**24**) is obtained in about 90% yield. Treatment of (**24**) with a stoichiometric amount of triphenylphosphine gives, in about 90% yield, the polycyclic ketone (**25**) together with a small amount (5–10%) of cyclooctatetraene.[13] A similar reaction is also reported for the methoxycarbonyl derivative (**23b**).



(7)

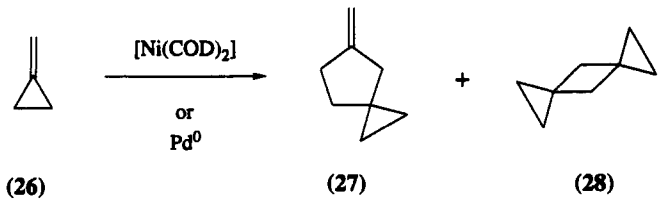
9.6.5 TRANSITION METAL CATALYZED REACTIONS OF METHYLENECYCLOPROPANES: SYNTHESIS OF METHYLENECYCLOPENTANES

Although methylenecyclopropanes[14] are highly strained molecules, they are stable at ambient temperature. At elevated temperature they undergo [2 + 2]-type reaction with alkenes[15] such as butadiene and maleic anhydride and [3 + 2] reaction with tetracyanoethylene.[16] The latter reaction involves a trimethylenemethane diradical intermediate. For catalytic transformations of methylenecyclopropanes, nickel(0) and palladium(0) complexes have been used successfully.

In the presence of [Ni(COD)$_2$], methylenecyclopropane (**26**; equation 8) cyclodimerizes at temperatures as low as –15 °C to give (**27**), (**28**) and small amounts of higher oligomers.[17] When [Ni(COD)$_2$] is used as a catalyst with electron deficient alkenes (*e.g.* dialkyl fumarate or maleic anhydride) as additives, cyclopentane derivative (**27**) is obtained as a major product (60–65% yield), along with (**28**) (1–4%), 1,3-dimethylenecyclohexane (1–12%) and oligomers (<25%).[18] Reaction of (**26**) using nickel(0) compounds, modified by trialkylphosphines, as catalysts gives a complex mixture which consists of open chain and cyclic $C_{12}H_{18}$ hydrocarbons in up to 95% combined yield.[19] Palladium(0) complexes prepared *in situ* from triisopropylphosphine and [Pd(DBA)$_2$], or from triisopropylphosphine, diethylaluminum ethoxide and [Pd(acac)$_2$], catalyze the dimerization of (**26**) to (**27**) in high yield and with high selectivity.[20]

Synthetically useful [3 + 2] cycloadditions of (**26**) and alkenes to give methylenecyclopentanes have been attained in the presence of a catalytic amount of nickel(0) or palladium(0) complexes.

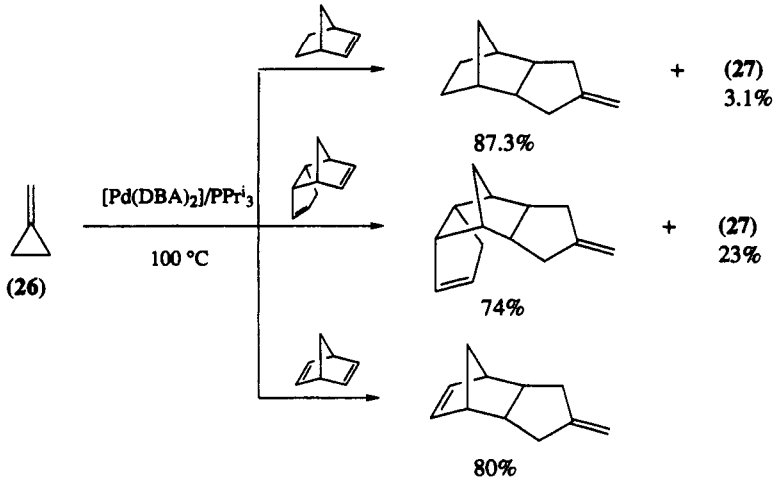
[Pd(DBA)$_2$]/PPr$^i_3$ (equation 9) catalyzes the cycloaddition of (**26**) with strained alkenes to give the corresponding methylenecyclopentanes.[20] The codimer, methylenecyclopentane, is also obtained in 20% yield from the reaction of (**26**) with ethylene, along with (**27**) in 64% yield, in the presence of [Pd(acac)$_2$]/PPr$^i_3$/Et$_2$AlOEt.



(8)

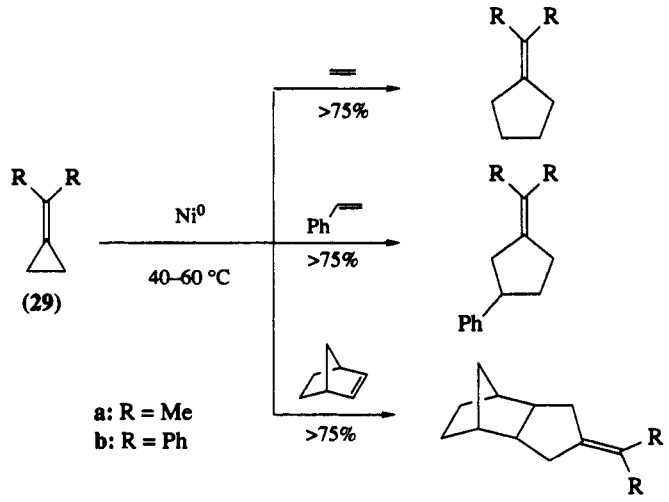
(26) (27) (28)

$[Ni(COD)_2]$	50%; (27):(28) = 80:20
$[Ni(COD)_2]$/dibutyl fumarate	68%; (27):(28) = 94:6
$[Ni(COD)_2]$/maleic anhydride	67%; (27):(28) = 98:2
$[Pd(DBA)_2]/PPr^i_3$	100%; selectivity of (27) = 91%
$[Pd(acac)_2]/PPr^i_3/Et_2AlOEt$	100%; selectivity of (27) = 94%
$[Pd(PPh_3)_4]$	4%; selectivity of (27) =100%



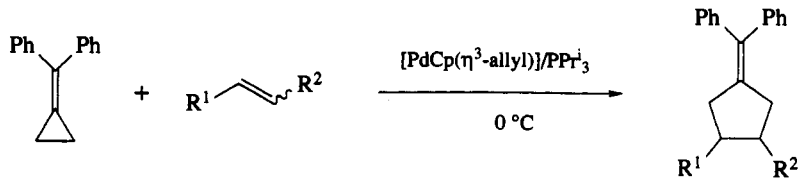
(9)

When isopropylidenecyclopropane (**29a**; equation 10) or diphenylmethylenecyclopropane (**29b**) is used, the codimerizations with alkenes such as ethylene, styrene or norbornene giving alkylidenecyclopentanes are achieved under mild conditions in more than 75% yields.[21]



(10)

(Diphenylmethylene)cyclopentane derivatives (**30**; equation 11) are also obtained by the reaction of (**29b**) with simple alkenes in the presence of [PdCp(η^3-allyl)] and triisopropylphosphine.[22]



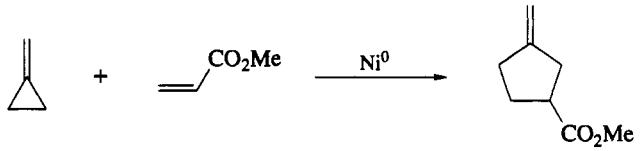
(11)

(29b) (30)

R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
H	H	83	H	Ph	88
H	Me	83	H	$CH{=}CH_2$	48
H	Et	86	$-CH_2CH_2-$		61

1-Methylene-2-vinylcyclopropane is cyclodimerized by palladium(0)/PPr^i_3 systems to give carbocycles such as 5-methylene-3-vinylallylidenecyclohexane (41%) and 3-methyleneallylidenecyclooct-5-ene (13%). Codimerization of 1-methylene-2-vinylcyclopropane with norbornene is also catalyzed by $[Pd(DBA)_2]/PPr^i_3$ to afford 4-allylidenetricyclo[5.2.1.$0^{2,6}$]decane (55%) and 4-methylene-3-vinyltricyclo[5.2.1.$0^{2,6}$]decane (17%).[23]

Compound (**26**) reacts with methyl acrylate in the presence of nickel(0) complexes (*e.g.* [Ni(acrylonitrile)$_2$],[24] [Ni(COD)$_2$][25]) under mild conditions to give 3-methoxycarbonylmethylenecyclopentane (**31**; equation 12) in high yields (>82%). Use of methyl vinyl ketone or acrylonitrile as the substrate also gives rise to the corresponding methylenecyclopentane.[24a] Cycloadditions of 2-methyl- or 2,2-dimethyl-methylenecyclopropanes with $CH_2{=}CHZ$ (Z = electron-withdrawing group) give 4-substituted 2-methyl- or 2,2-dimethyl-methylenecyclopentanes (30–60%), while 2,2,3,3-tetramethylmethylenecyclopropane gives no cycloadducts on reaction with electron deficient alkenes.[22]



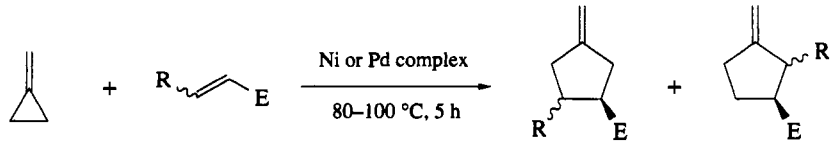
(12)

(**26**) (**31**) >82%

The complexes [Ni(acrylonitrile)$_2$][24b] and [Ni(COD)$_2$][25] catalyze [3 + 2] cycloadditions of (**26**) with electron deficient 1,2-disubstituted alkenes to afford 2,3- or 3,4-disubstituted methylenecyclopentanes such as (**32**) and (**33**). Similar reactions have been reported by use of tertiary phosphine complexes of nickel(0)[26] and palladium(0)[27] (equation 13 and Table 1). The reaction proceeds regioselectively to give (**32**) or (**33**) depending on both the alkene structure and catalytic system. Reactions catalyzed by phosphine–palladium(0) complexes afford only products of the type (**32**), *via* selective cleavage of the C(2)—C(3) bond of (**26**).

Cycloadditions of isopropylidenecyclopropane (**29a**) or diphenylmethylenecyclopropane (**29b**) with electron deficient alkenes are catalyzed by [Ni(acrylonitrile)$_2$][24a] or triarylphosphite–nickel(0) compounds (Table 2)[28] to give alkylidenecyclopentane derivatives (**34**) and (**35**) in high yields (equation 14).

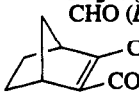
2-(Trimethylsilyl)methylenecyclopropane (**36**; equation 15) is usable instead of methylenecyclopropane in reactions with electron deficient alkenes involving [PdCp(η^3-allyl)]/PPr^i_3, giving silylated methylenecyclopentanes (**37**) and (**38**) in good yields and with better selectivities than those obtained from unsubstituted methylenecyclopropane (**26**). The trimethylsilyl group can be easily removed by protonolysis with trifluoroacetic acid.[29]



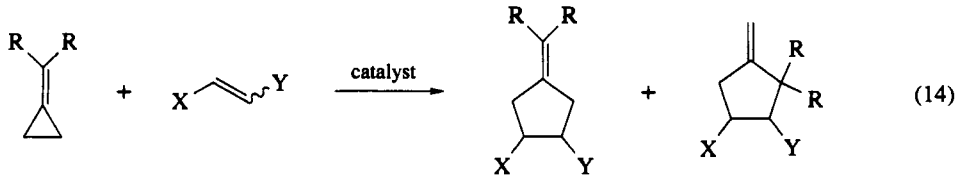
(13)

(**26**) (**32**) (**33**)

Table 1 Reactions of Methylenecyclopropane and Electron Deficient Alkenes in the Presence of Nickel(0) or Palladium Complexes

R	*E*	*Catalyst*[a]	*Yield (%)*	*Composition (%)* *Cis-(32)*	*Trans-(32)*	*Cis-(33)*	*Trans-(33)*	*Ref.*
H	CO_2Me	A	55					26
H	CO_2Me	B	92					25
H	CO_2Me	C	87.5					27b
Me	CO_2Me (*E*)	A	55			22	78	26
Me	CO_2Me (*E*)	B	43			0	100	25
Pr	CO_2Me (*E*)	A	50			27	73	26
$(CH_2)CO_2Me$	CO_2Me (*E*)	A	49			28	72	26
CO_2Et	CO_2Et (*Z*)	A	42	25	75			26
CO_2Et	CO_2Et (*Z*)	D	78.2	23	77			27b
CO_2Me	CO_2Me (*Z*)	B	78			90	10	25
CO_2Et	CO_2Et (*E*)	A	72	4	96			26
CO_2Et	CO_2Et (*E*)	C	89.2	4	96			27b
CO_2Et	CO_2Et (*E*)	E	79.0	4	96			27b
Me	CHO (*E*)	A	54			9	91	26
		A	62	100				26

[a] A, $[Ni(COD)_2]/PPh_3$; B, $[Ni(COD)_2]$; C, $[PdCp(\eta^3\text{-allyl})]/PPr^i_3$; D, $[PdCp(\eta^3\text{-allyl})]/P(OEt)_3$; E, $[Pd(DBA)_2]/PPr^i_3$.



(14)

(29) (34) (35)

a: R = Me
b: R = Ph

catalyst A, $[Ni(COT)_2]/P(OAr)_3$
catalyst B, $[Ni(COD)_2]/P(OAr)_3$

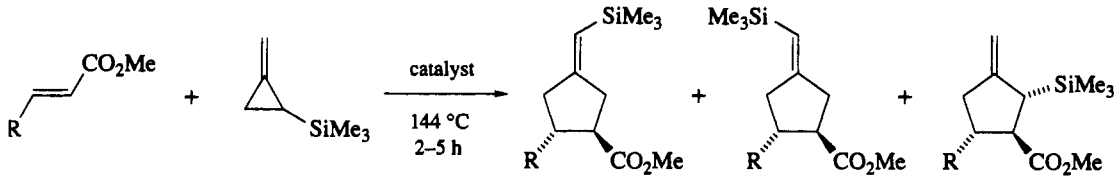
Table 2 Reactions of Alkylidenecyclopropanes with Electron Deficient Alkenes in the Presence of Nickel(0) Complexes[28]

(29)	*R*	*X*	*Y*	*Catalyst*[a]	*Temp (°C)*	*Time(h)*	*Yield (%)* *(34)*	*(35) (X, Y)*
b	Ph	H	CO_2Me	A	50	8	79	
a	Me	H	CO_2Me	B	100	5	81	14 (CO_2Me, H)
b	Ph	Me	CO_2Me (*E*)	B	120	5	75 (*trans*)	
a	Me	Me	CO_2Me (*E*)	B	110	5	14 (*trans*)	46 (*trans*) (Me, CO_2Me)
b	Ph	CO_2Et	CO_2Et (*E*)	B	100	3	98 (*trans*)	
a	Me	CO_2Et	CO_2Et (*E*)	B	120	5	56 (*trans*)	34 (*trans*)
b	Ph	CO_2Et	CO_2Et (*Z*)	B	120	5	28 (*cis*) 69 (*trans*)	
a	Me	CO_2Et	CO_2Et (*Z*)	B	130	10	57 (*trans*)	23 (*trans*)
b	Ph	H	CN	A	120	5	82	
a	Me	H	CN	A	120	5	47	4 (H,CN)

[a] A, $[Ni(COT)_2]/P(OAr)_3$; B, $[Ni(COD)_2]/P(OAr)_3$.

The nickel(0)-catalyzed codimerizations of methylenecyclopropane (**26**) or 2,2-dimethylmethylenecyclopropane with the chiral derivatives of acrylic acid lead to optically active 3-methylenecyclopentanecarboxylic esters or amides (**39**; equation 16) in good yields (Table 3). When (–)-camphorsultam acrylate is used, 3-methylenecyclopentanecarboxylic amides are obtained in up to 98% *de*.[30]

The seven-membered ring product (**49**; equation 17) is obtained as a mixture of the *trans* and *cis* isomers (82:18) in 67% yield from the reaction of (**26**) with dimethyl muconate (**48**) in the presence of a



(36) (*Z*)-(37) (*E*)-(37) (38)

catalyst: [PdCp(η^3-allyl)]/PPr^i_3 (15)

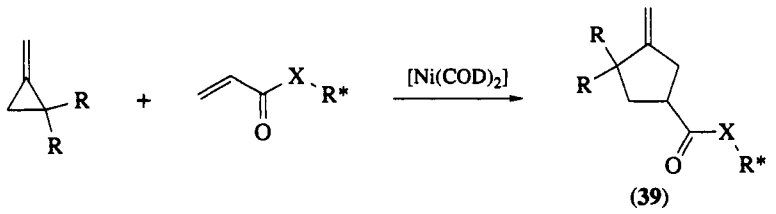
R = H	78%	53	:	47	:	0
R = Me	79%	57	:	43	:	0
R = CO_2Me	87%	0	:	90	:	10

palladium(0) catalyst.[13] On the other hand, methyl 2,4-pentadienoate reacts with (**26**) only at the terminal C=C bond, giving methyl 3-(3-methylenecyclopentyl)prop-2-enoate in poor yield (25%).[31]

Bicyclic ketones are prepared by cycloadditions of methylenecyclopropanes with cyclic α,β-unsaturated carbonyl compounds. *cis*-Bicyclo[3.3.0]octan-2-ones (**50**), (**51**) and (**52**) are obtained in good yields by phosphine–nickel(0)-catalyzed cross coupling reactions of 2-cyclopentenone with methylenecyclopropanes in the presence of 0.1–1 equiv. of triethylborane as a Lewis acid (equations 18 and 19 and Table 4).[32]

(Diphenylmethylene)cyclopropane (**29b**) reacts with α,β-unsaturated cyclic ketones in the presence of [PdCp(η^3-allyl)] and triisopropylphosphine to afford compounds (**53**) in moderate to high yields (equation 20).[22]

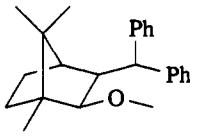
When 2-(trimethylsilyl)methylenecyclopropane (**36**; equation 21) is allowed to react with cyclic unsaturated ketones in the presence of [PdCp(η^3-allyl)]/PPr^i_3, silylated methylenecyclopentanes (**54**) and (**55**) are produced in good yields and with better selectivities than those obtained from unsubstituted methylenecyclopropane. The trimethylsilyl group can easily be removed.[29]



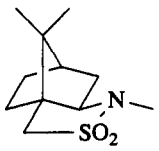
(16)

(39)

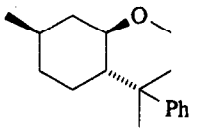
R*–X–:



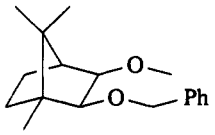
(1*R*,2*R*,3*S*)-(**40**)



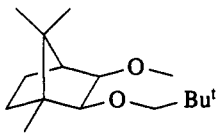
(7*S*)-(**41**)



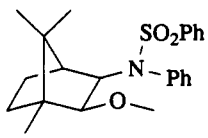
(1*R*,2*S*,5*R*)-(**42**)



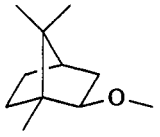
(1*R*,2*S*,3*R*)-(**43**)



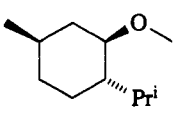
(1*R*,2*S*,3*R*)-(**44**)



(1*R*,2*S*,3*R*)-(**45**)



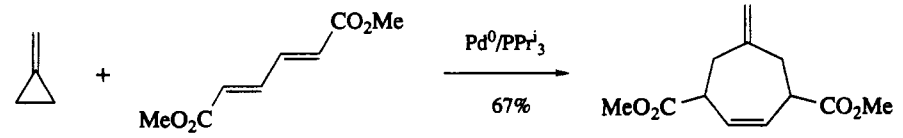
(1*R*,2*R*,4*R*)-(**46**)



(1*R*,2*S*,5*R*)-(**47**)

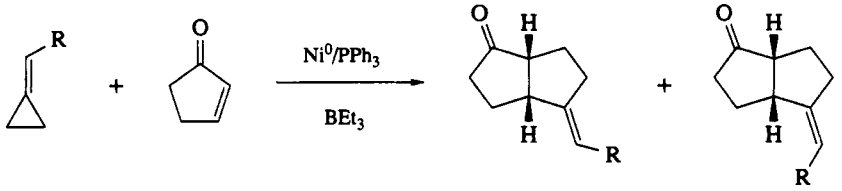
Table 3 Cycloadditions of Methylenecyclopropanes with Chiral Acrylic Acid Derivatives, Catalyzed by $[Ni(COD)_2]$[30]

R	*R*—X—*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*De (%)*	*Configuration at C-1*
H	(**40**)	–20	24	93	80	(*S*)
Me	(**40**)	20	20	63	25	—
H	(**41**)	20	16	79	83	(*S*)
H	(**41**)	0	20	80	86	(*S*)
H	(**41**)	–20	16	72	91	(*S*)
H	(**41**)	–35	24	76	86	(*S*)
Me	(**41**)	0	20	86	98	(*S*)
H	(**42**)	–20	24	59	78	(*R*)
Me	(**42**)	20	14	55	55	—
H	(**43**)	–20	72	85	30	—
H	(**44**)	20	72	47	46	—
H	(**45**)	–20	72	38	68	(*S*)
H	(**46**)	25	7	92	3	—
H	(**47**)	–20	72	78	26	—



(17)

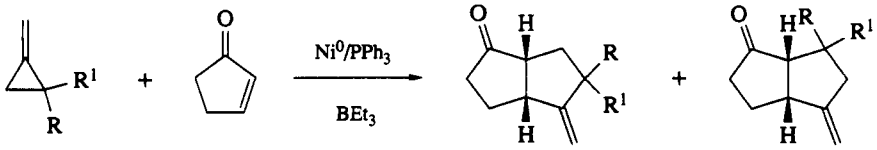
(**26**) (**48**) (**49**)



(18)

(*E*)-(**50**) (*Z*)-(**50**)

R	*Yield (%)*			
H	50			
n-C_5H_{11}	68	85	:	15
Ph	72	100	:	0

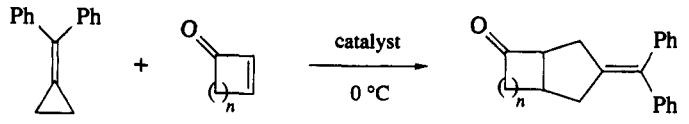


(19)

(**51**) (**52**)

Table 4 Cycloadditions of Methylenecyclopropanes with 2-Cyclopentenone, Catalyzed by a PPh_3–Ni^0–BEt_3 System[32]

R	R^1	*Yield (%)*	*Isomer ratio*			
			Endo-(**51**)	*Exo-*(**51**)	*Endo-*(**52**)	*Exo-*(**52**)
Me	H	73	63	37	61	39
Ph	H	75				
$SiMe_3$	H	50	68	32		
Me	Me	37				

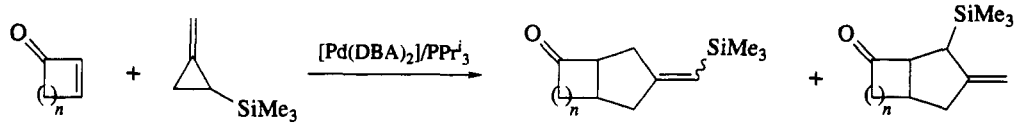


(20)

(29b) (53)

catalyst [PdCp(η^3-allyl)]/PPr^i_3

$n = 2$, 97%
$n = 3$, 76% *cis:trans* = 74:26
$n = 4$, 80% *cis:trans* = 16:84

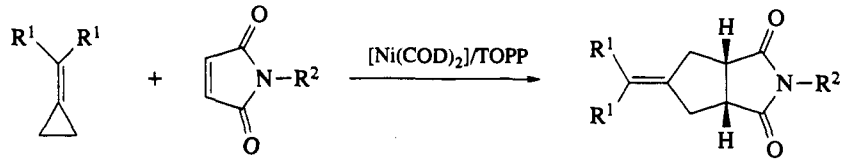


(21)

(36) (54) (55)

$n = 2$	144 °C	5 h	81%	72% (*cis*, *(Z):(E)* = 5:2)	28%
$n = 3$	110 °C	15 h	31%	68% (4 isomers)	32%
$n = 4$	144 °C	5 h	71%	72% (*trans*, *(Z):(E)* = 5:3)	28%

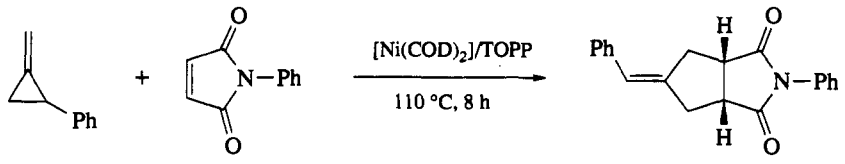
Nickel(0)-catalyzed [3 + 2] cycloadditions of methylenecyclopropanes with *N*-substituted maleimides (**56**; equation 22) lead almost exclusively to 5-alkylidenehexahydro-1*H*-cyclopenta[*c*]pyrrolo-1,3-diones (**57**) and (**58**; equation 23). A similar reaction occurs in the presence of a palladium(0) catalyst, but with lower selectivity. Unsubstituted maleimide and maleic anhydride do not undergo this cycloaddition. Ozonolysis of (**57**) and (**58**) into the corresponding ketone derivatives (62–78% yield) followed by reduction of both carbonyl groups gives 1*H*-cyclopenta[*c*]pyrroles, which are of interest with regard to their pharmacological activity (98% yield).[33]



(22)

(56) (57)

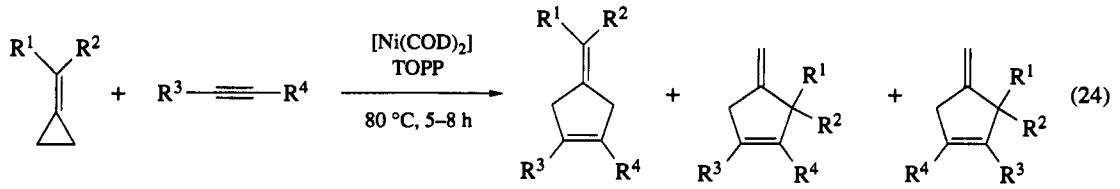
R^1	R^2	*Catalyst ratio*	*Conditions*	*Yield (%)*
H	Ph	$[Ni(COD)_2]$/TOPP = 1:1	70 °C/20 h	12
Me	Ph	$[Ni(COD)_2]$/TOPP = 1:1.5	120 °C/5 h	90
Me	Ph	$[Ni(COD)_2]$/TOPP = 1:4	120 °C/14 h	84 (isolated)
Me	Me	$[Ni(COD)_2]$/TOPP = 1:4.5	120 °C/10 h	93
Ph	Ph	$[Ni(COD)_2]$/TOPP = 1:2	120 °C/2 h	83 (isolated)



(23)

(58) 82%

Additions of methylenecyclopropanes to alkynes (**59**; equation 24) give 4-methylene-1-cyclopentenes (**60**), (**61**) and (**62**) in the presence of phosphite-coordinated nickel(0) catalysts (Table 5). Alkynylsilanes are particularly suitable for these codimerizations. In the reactions with 1-alkynes or dialkylalkynes, oligomerization of the alkynes cannot be avoided. When alkynes with electron-attracting substituents are used, cyclotrimerization is so rapid that cross addition no longer occurs.[34]



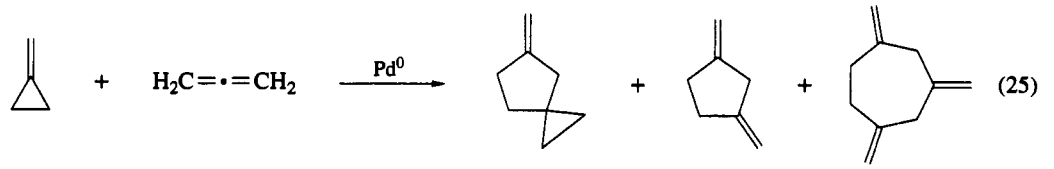
(59) (60) (61) (62)

TOPP = $P(OC_6H_4Ph\text{-}o)_3$

Table 5 Cycloadditions of Methylenecyclopropanes with Alkynes, Catalyzed by TOPP–$[Ni(COD)_2]$[34]

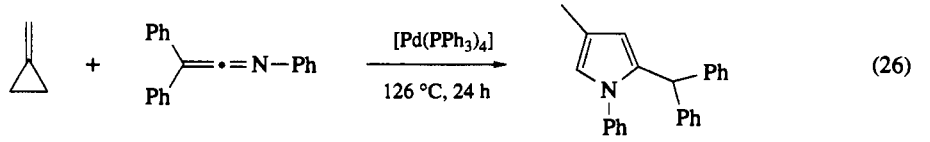
R^1	R^2	R^3	R^4	*Yield (%)*	*Composition (%)* (60)	(61)	(62)
H	Ph	$SiMe_3$	$SiMe_3$	41		100	
Me	Me	$SiMe_3$	$SiMe_3$	50		100	
Ph	Ph	$SiMe_3$	$SiMe_3$	71	48	52	
H	n-C_5H_{11}	Me	$SiMe_3$	82	12	63	25
Me	Me	Et	$SiMe_3$	88		85	15
Ph	Ph	Et	$SiMe_3$	92	60	24	16
H	H	CH_2OSiMe_3	$SiMe_3$	59			
Me	Me	CH_2OSiMe_3	$SiMe_3$	82	6	60	34
Ph	Ph	CH_2OSiMe_3	$SiMe_3$	90	53	2	45
H	H	CO_2Me	$SiMe_3$	72			
H	n-C_5H_{11}	CO_2Me	$SiMe_3$	65	25	22	53
Me	Me	CO_2Me	$SiMe_3$	64	41	21	38
Ph	Ph	CO_2Me	$SiMe_3$	63	100		
Me	Me	Me	Me	66	6	94	
Ph	Ph	Me	Me	95	6	94	
Ph	Ph	CH_2OSiMe_3	CH_2OSiMe_3	86	57	43	

In the co-oligomerization of methylenecyclopropane (**26**) with allene (**63**; equation 25) on a palladium(0) catalyst, prepared *in situ* from $[Pd(acac)_2]$, triisopropylphosphine and diethylaluminum ethoxide, or from $[Pd(DBA)_2]$ and triisopropylphosphine, cyclic hydrocarbons such as 2-methylenespiro[2.4]heptane (**27**), 1,3-dimethylenecyclopentane (**64**) and 1,3,5-trimethylenecycloheptane (**65**) are formed.[35]

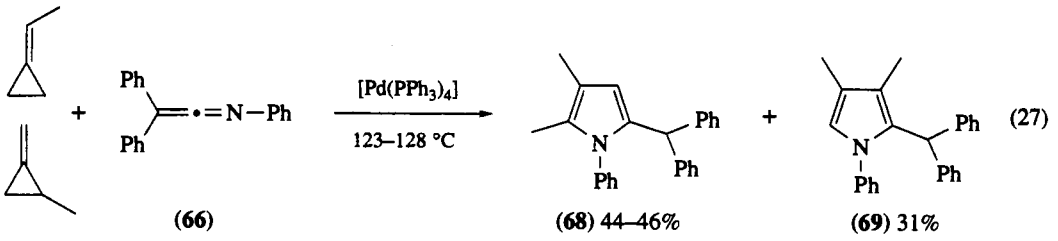


(26) (63)	(27)	(64)	(65)
$[Pd(acac)_2]/PPr^i_3/Et_2AlOEt$	23%	40%	10%
$[Pd(DBA)_2]/PPr^i_3$	38%	14%	25%

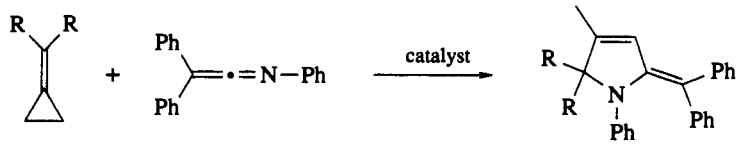
$[Pd(PPh_3)_4]$- or $(PhO)_3P/[Ni(COD)_2]$-catalyzed [3 + 2] cycloadditions of methylenecyclopropanes with ketenimines (**66**) lead selectively to pyrroles (**67**; equation 26), (**68**) and (**69** (equation 27), or α-methylene-Δ^3-pyrrolines (**70**; equation 28) depending on the substituents of the imino group and the methylenecyclopropanes. Diphenylketene-*N*-methylimine reacts with (**26**) to give 1-methylimino-3-methyl-5,5-diphenylcyclopent-2-ene in 38% yield.[36]



(26) (66) (67) 96%



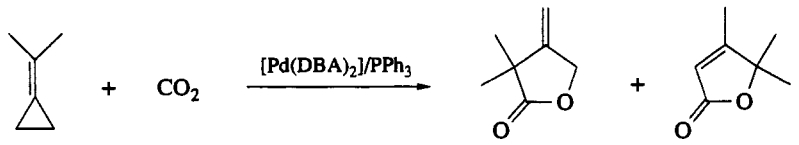
(66) (68) 44–46% (69) 31% (27)



(66) (70) (28)

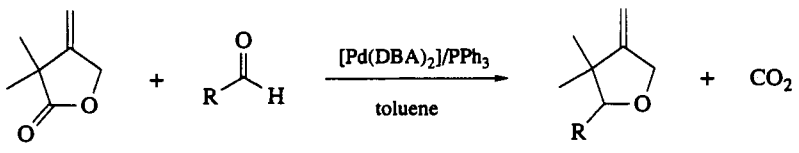
R = Me	$[Pd(PPh_3)_4]$	123 °C/30 h	93%
	$[Ni(COD)_2]$/TOPP	70 °C/7 h	93%
R–R = $-(CH_2)_5-$	$[Pd(PPh_3)_4]$	127 °C/30 h	91%
	$[Ni(COD)_2]$/TOPP	70 °C/5 h	94%

Palladium(0)–phosphine complexes catalyze the reaction of methylenecyclopropanes and CO_2 with opening of the three-membered ring to give γ-lactones.[37] When isopropylidenecyclopropane is treated in benzene with CO_2 (40 atm) at 126 °C for 20 h in the presence of a catalytic amount of $[Pd(DBA)_2]/PPh_3$, lactone (**71**; equation 29) is formed in 69% yield accompanied by 3,4,4-trimethyl-2-buten-4-olide (**72**) in 8% yield. Cyclopropylidenecyclohexane and butylidenecyclopropane also react with CO_2 to give the corresponding lactones and butenolides in moderate yields. With methylenecyclopropane (**26**) as substrate, further alkylation of 3-methyl-2-buten-4-olide proceeds under the same catalytic conditions to give cotrimer, cotetramer, copentamer, *etc.*, while 2,2-dimethylmethylenecyclopropane and *cis*-2,3-dimethylmethylenecyclopropane do not react under similar conditions.



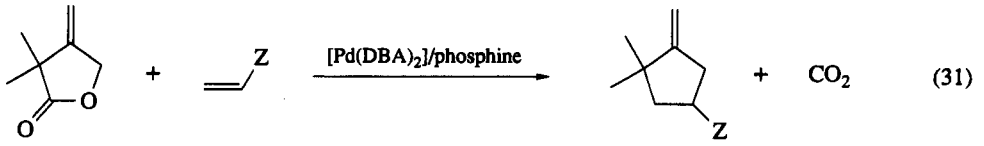
(71) (72) (29)

Lactone (**71**; equation 30) undergoes cycloaddition to aromatic and aliphatic aldehydes in the presence of a catalytic amount of a palladium(0) complex to give 3-methylenetetrahydrofuran derivatives (**73**) with the liberation of carbon dioxide. α,β-Unsaturated carbonyl compounds also react with (**71**) to give (**35**) (equation 31 and Table 6).[38]



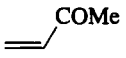
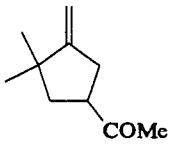
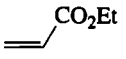
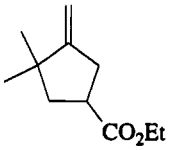
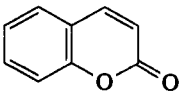
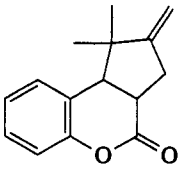
(71) (73) (30)

R	*Conversion (%)*	*Yield (%)*
Ph	100	100
1-Np	72	69
CH=CHPh	25	16
1-furyl	69	67



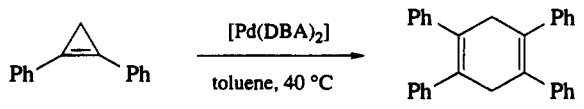
(71) Z = electron-withdrawing group (35) (31)

Table 6 Reaction of (71) with α,β-Unsaturated Carbonyl Compounds Catalyzed by Phosphine–$[Pd(DBA)_2]$[38]

Substrate	*Phosphine*	*Product*	*Yield (%)*
	DPPE		25
	PPh_3		38
	PPh_3 DPPE		66 92

9.6.6 TRANSITION METAL CATALYZED REACTIONS OF CYCLOPROPENES: SYNTHESIS OF VINYLCYCLOPROPANES

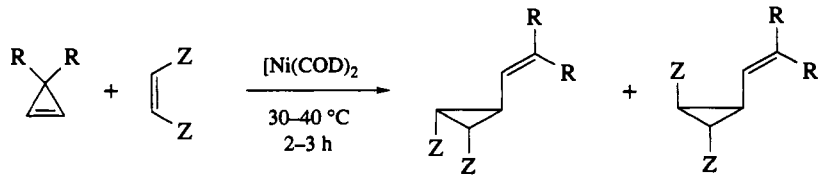
Cyclopropenes are highly strained and thus very reactive molecules. Cyclopropene itself tends to polymerize even below 0 °C and 1-methylcyclopropene dimerizes within minutes at room temperature *via* an ene reaction. In contrast, 3,3-dimethylcyclopropene does not undergo an ene reaction even at 100 °C, but it readily oligomerizes under the influence of nickel(0)[39] or cyclodimerizes to 3,3,6,6-tetramethyltricyclo[3.1.0.$0^{2,4}$]hexane (80% yield) in the presence of palladium(0).[40] 1,2-Diphenylcyclopropene is converted to 1,2,4,5-tetraphenylcyclohexa-1,4-diene in the presence of palladium(0) in high yield (equation 32).[14]



95% (32)

When electron deficient alkenes are added to cyclopropene derivatives (**74**; equation 33) and (**77**; equation 34) in the presence of $[Ni(COD)_2]$, vinylcyclopropanes are formed in good yields.[41] For example, dialkyl fumarate or maleate reacts with 3,3-dimethylcyclopropene in the presence of $[Ni(COD)_2]$ to give 2,3-bis(alkoxycarbonyl)-1-(2-methyl-1-propenyl)cyclopropanes (**75**), (**76**), (**78**) and (**79**), in which alkene stereochemistry is chiefly retained, in 50–73% yields. Reaction of methyl acrylate with 3,3-dimethylcyclopropene results in the formation of several products, while reaction of methyl acrylate with 3,3-diphenylcyclopropene gives vinylcyclopropane derivatives (**80**; equation 35) in 85% yield. Under similar conditions, methyl crotonate reacts with (**74a**) to give (**82**) in low yield (equation 36).[41] Catalysis with nickel(0)/PR_3,[42] $[Ni(CO)_4]$,[43] $[Pd(DBA)_2]$[44] or $[Pd(DBA)_2]/PPr^i_3$[31] gives mainly

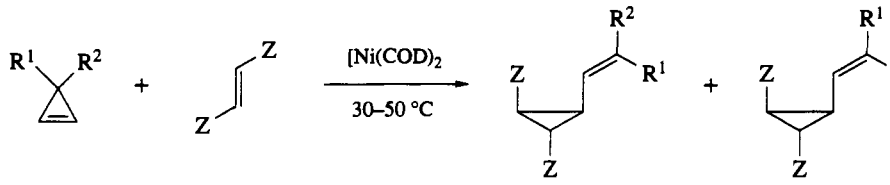
homooligomers and mixed oligomers with a small amount of 1:1 cycloadducts. In these cycloaddition reactions, vinylcarbene–metal complexes are formed at first by the reaction of cyclopropene with low valent metals. The carbene complexes then react with alkenes to give vinylcyclopropane derivatives.



(33)

(74) $Z = CO_2Me$ (75) (76)

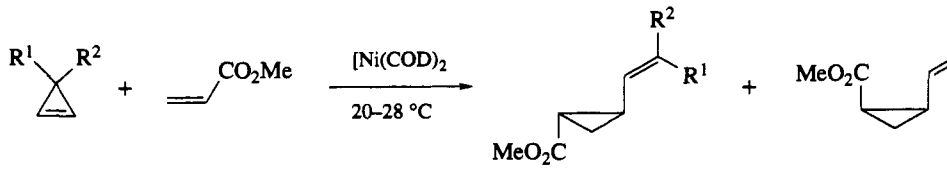
a:	R = Me	60%	97	:	3	
b:	R = Ph	65%	79	:	21	



(34)

(77) $Z = CO_2R^3$ (78) (79)

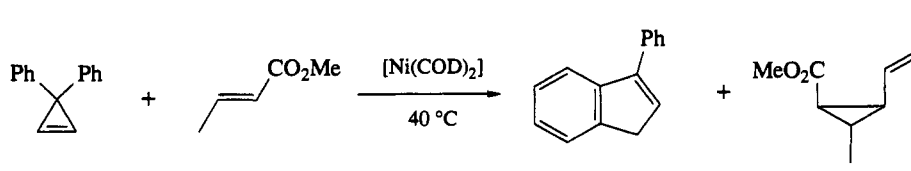
$R^1 = R^2 = R^3 = Me$	50%	
$R^1 = R^2 = Me$, $R^3 = Et$	73%	
$R^1 = Me$, $R^2 = Ph$, $R^3 = Et$	84%	*(E):(Z)* = 89.5:10.5
$R^1 = R^2 = Ph$, $R^3 = Et$	87%	



(35)

(77) *trans*-(80) *cis*-(80)

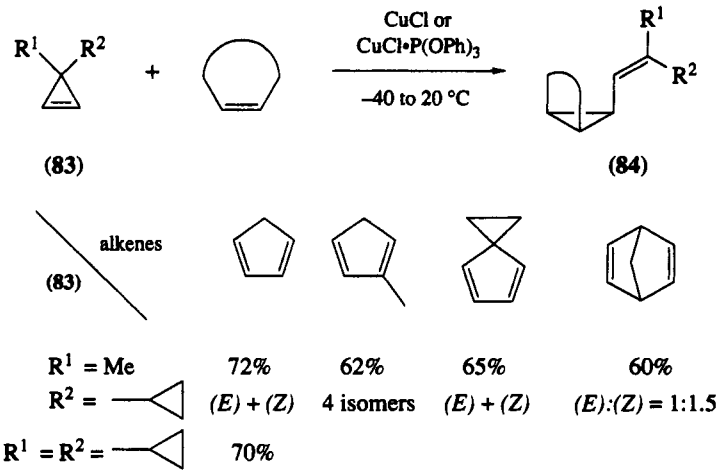
$R^1 = R^2 = Me$	39%	51		:	49	
$R^1 = Me$, $R^2 = Ph$	51%	64	*(E):(Z)* = 51:49	:	36	*(E):(Z)* = 92:8
$R^1 = R^2 = Ph$	85%	86		:	14	



(36)

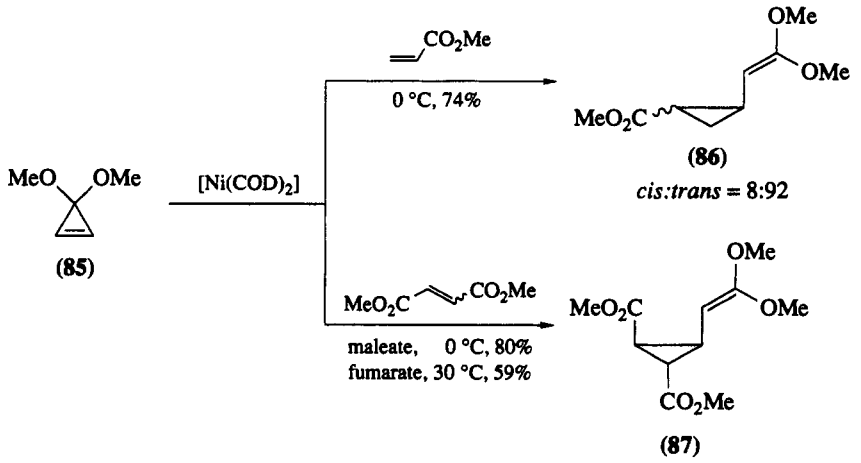
(74a) (81) 26% (82) 16%

Vinylcarbene is also regarded as an intermediate in the catalytic isomerization of cyclopropene in the presence of $[CuCl\{P(OPh)_3\}]$.[45] 3-Methyl-3-cyclopropylcyclopropene (**83a**) and 3,3-dicyclopropylcyclopropene (**83b**) react with cyclopentene derivatives under the influence of $CuCl/P(OPh)_3$ to yield *endo*-vinylcyclopropane derivatives (**84**; equation 37) in 55–72% yields. 3-Methoxycarbonyl-1-propylcyclopropene also reacts with norbornadiene in the presence of CuCl to give the corresponding vinylcarbene adducts in 60% yield.



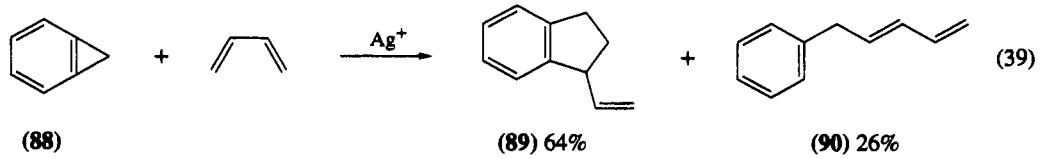
(37)

In the presence of $[Ni(COD)_2]$, 3,3-dimethoxycyclopropene (**85**; equation 38) reacts with methylacrylate, dimethyl fumarate and dimethyl maleate to give the corresponding vinylcyclopropanes (**86**) and (**87**), respectively.[46]

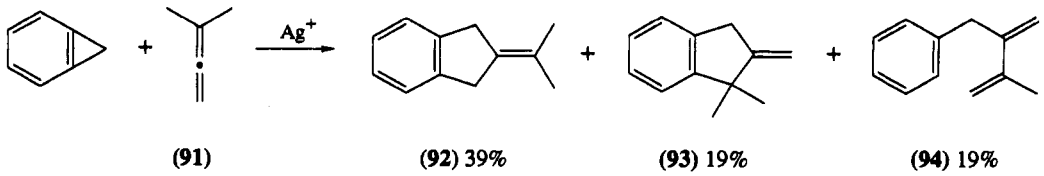


(38)

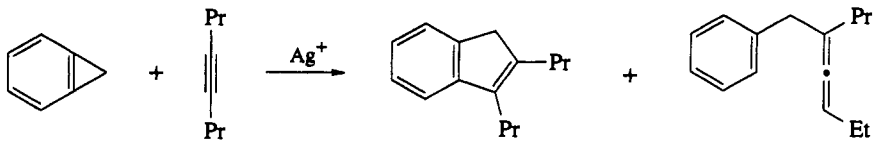
Benzocyclopropene (**88**) and naphtho[*b*]cyclopropene react with various alkenic substrates to give cycloaddition products in the presence of silver ion.[47] Reaction of (**88**; equation 39) with butadiene assisted by 1 mol % of $AgBF_4$ in benzene (0 °C, 30 min) gives (**89**) and (**90**). Dimethylallene (**91**; equation 40) and oct-4-yne (**95**; equation 41) also react readily with (**88**) in the presence of silver ion to give the corresponding cycloaddition products (**92**), (**93**) and (**96**), together with acyclic products (**94**) and (**97**).



(39)



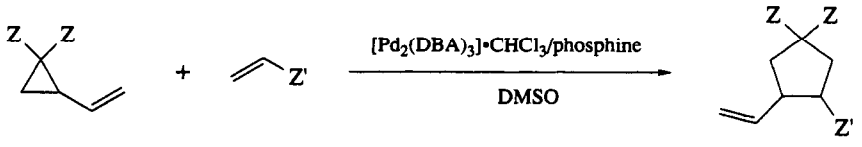
(40)



(95) (96) 25% (97) 14% (41)

9.6.7 TRANSITION METAL CATALYZED REACTIONS OF VINYLCYCLOPROPANES: SYNTHESIS OF CYCLOPENTANE DERIVATIVES

Vinylcyclopentane derivatives (**99**) are prepared from the palladium(0)-catalyzed cycloaddition reaction of vinylcyclopropane (**98**), bearing two electron-withdrawing groups, with electron deficient alkenes (equation 42 and Table 7).[48] The reaction can be formally envisaged as a 1,3-dipolar cycloaddition.



(42)

(98) (99)

Z, Z' = electron withdrawing group

9.6.8 TRANSITION METAL CATALYZED REACTIONS OF CYCLOPROPANONES AND RELATED COMPOUNDS

Heterocyclic spirans are prepared by $[Ni(CO)_4]$-promoted tandem cycloaddition of diphenylcyclopropanone (**100**) to isothiocyanates (**101**; equation 43) or to carbon disulfide (**105**; equation 44). When an equimolar mixture of (**100**), (**101**) and $[Ni(CO)_4]$ is allowed to react in DMF at 65–70 °C, two heterocyclic spirans, pyrrolin-2-one-5-spiro-5′-thiolen-4′-one (**102**), and (**103**), are formed in addition to the pyrroline derivative (**104**). Similarly, carbon disulfide (**105**), reacts with (**100**) to give thiolen-2-one-5-spiro-5′-thiolen-4′-one (**106**) along with a small amount of 1:1 cycloadduct (**107**).[49]

1-Ethoxy-1-trimethylsiloxycyclopropane (**108**; equation 45) is a stable and distillable liquid and is available in good yield by reductive silylation of ethyl 3-chloropropanoate.[50] Compound (**108**) smoothly reacts below 0 °C with aliphatic aldehydes in the presence of a slight excess of $TiCl_4$ giving γ-lactones (**109**) in high yield, while reaction with aromatic aldehydes gives linear adducts.[51] The reaction of 1-isopropoxy-1-siloxycyclopropane (**110**; equation 46) with $TiCl_4$ gives crystalline 3-trichlorotitanium propionate (**111**) in 82% yield. When complex (**111**) is treated with half an equivalent of a tetraalkoxytitanium complex and then with ketones, γ-lactones (**112**) are obtained in high yields.[52]

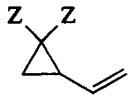
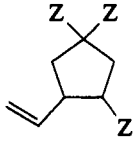
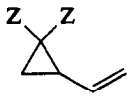
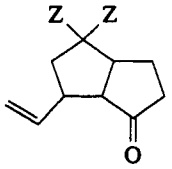
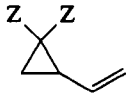
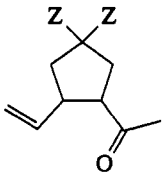
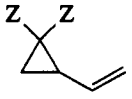
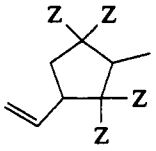
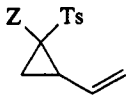
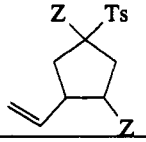
The addition of a carbonyl compound to methyl 2-siloxycyclopropanecarboxylate (**113**; equation 47) in the presence of a stoichiometric amount of $TiCl_4$ affords a mixture of hydroxyalkylation products (**114**) and (**115**), which are versatile starting materials for highly substituted tetrahydrofurans, dihydrofurans, and γ-butyrolactones.[53]

9.6.9 TRANSITION METAL CATALYZED REACTION OF CYCLOPROPENONES

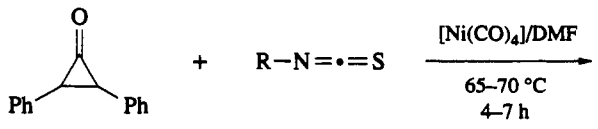
Tetrasubstituted 1,4-benzoquinones (**117**) are formed by the $[Ni(COD)_2]$-catalyzed dimerization of 2,3-disubstituted cyclopropenones (**116**; equation 48) (R = Ph, 51%; R = Pr, 43%; R—R = —$(CH_2)_5$—, 18% yield).[54]

Reactions of diphenylcyclopropenone with ketenes (**118**; equation 49) in the presence of a catalytic amount of $[Ni(CO)_4]$ afford 1:1 cycloadducts, cyclopentene-1,2-diones (**119**) and -1,3-diones (**120**), in more than 80% yields. The yields of the products are significantly affected by variation of the solvent used in the reaction, and DMF is the solvent of choice.[55]

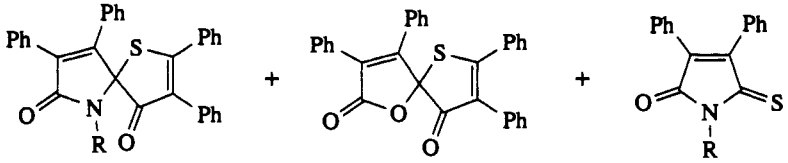
Table 7 Reactions of Vinylcyclopropanes and α,β-Unsaturated Carbonyl Compounds Catalyzed by Palladium(0) Complexes [48]

Substrates [a]	*Phosphine*	*Temperature* (°C)	*Time* (h)	*Product*	*Yield* (%)
	DPPE	80	2		84
	PBu^n_3	30	1		87
	PBu^n_3	30	1		66
	PBu^n_3	30	3		89
	PBu^n_3	30	3		77

[a] Z = CO_2Me.



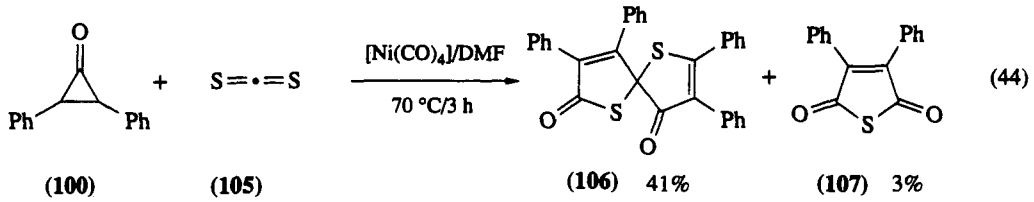
(100) (101)



(102) (103) (104)

	(102)	(103)	(104)
R = Ph	30%	17%	6%
R = COPh	50%	–	–

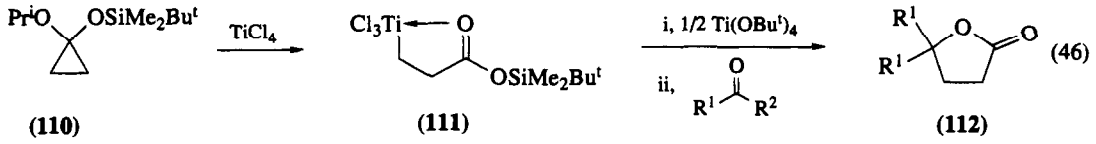
(43)



(100) (105) (106) 41% (107) 3% (44)

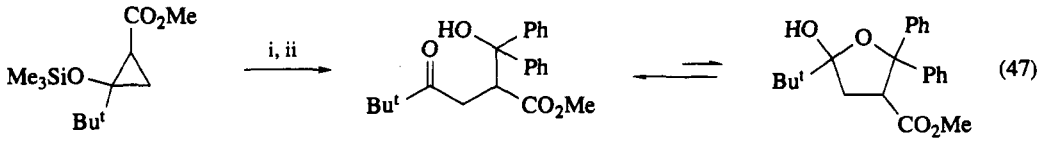
(108) (109) (45)

R = Pr 77%
R = C_8H_{17} 81%



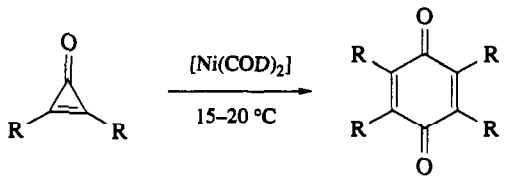
(110) (111) (112) (46)

R^1 = Me, R^2 = Ph 20 °C 1 h 93%
R^1–R^2 = –$(CH_2)_5$– 20 °C 18 h 84%



(113) (114) (115) (47)

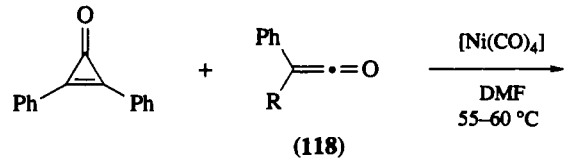
i, Ph_2C=O, $TiCl_4$, –78 to 20 °C, CH_2Cl_2; ii, H_2O, 95% yield



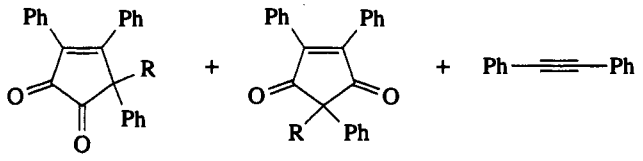
(116) (117) (48)

9.6.10 TRANSITION METAL CATALYZED REACTIONS OF CYCLOBUTENEDIONES: SYNTHESIS OF QUINONES

Benzocyclobutenedione (**121**) and cyclobutenedione (**125**) react with the low valent cobalt complex $[CoCl(PPh_3)_3]$ to form phthaloylcobalt (**122**; equation 50) and maleoylcobalt complexes, respectively. Subsequent treatment of (**122**) (L = PPh_3) with one equivalent of dimethylglyoxime (DMG) in pyridine provides a route to the dimethylglyoxime variant (**123**) in high yields. From the phthaloylcobalt complex (**123**), naphthoquinones (**124**) are prepared in high yield simply by heating (**123**) to 80 °C in the presence of an alkyne and a mild Lewis acid such as $CoCl_2 \cdot 6H_2O$. Similarly, benzoquinones (**126**; equation 51) are obtained from (**125**). Effective reaction rates were only achieved at room temperature in the presence of a strong Lewis acid such as $SnCl_4$ or $Zn(OSO_2CF_3)_2$.[56] Complex (**122**) also reacts directly with alkynes on treatment with $AgBF_4$ in MeCN, but more forcing conditions (110 °C, 20–40 h) are necessary for reasonable reaction rates compared to that of the reaction of (**123**). Iron compounds can also be used for this transformation and the phthaloyltetracarbonyliron complex produces naphthoquinones simply on



(118)

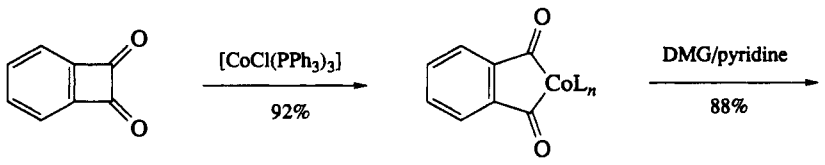


(119) (120) (49)

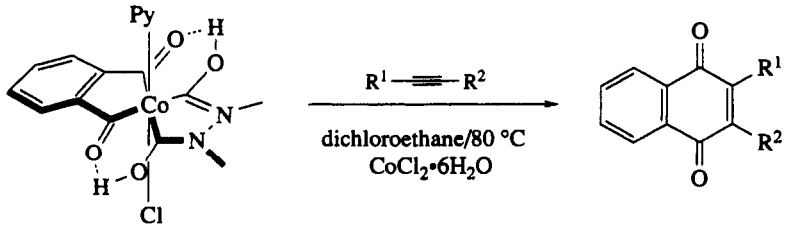
R	*Solvent*		*Yield* (%)	
Ph	DMF	85.9	trace	4.8
Ph	THF	11.0	8.5%	24.1
Et	DMF	85.3	trace	5.8

heating in MeCN in the presence of alkynes (100 °C, 6 h). Similar or even better results are obtained by using iron complexes instead of cobalt compounds. Sterically demanding alkynes, however, give significantly higher yields of the naphthoquinone products using cobalt instead of iron.

Nanaomycin A (**128**), an antibiotic pyranonaphthoquinone, has been synthesized *via* this route starting from (**127**).[57] This method has also been applied to the synthesis of royleanone (**129**), an abietanoid diterpene quinone possessing antitumor cytotoxicity, in which the highly substituted quinone skeleton has been efficiently constructed by using the maleoylcobalt complex.[58]

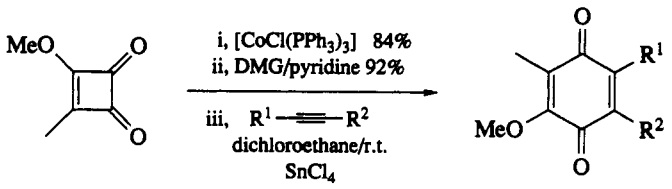


(121) (122)



(123) (124) (50)

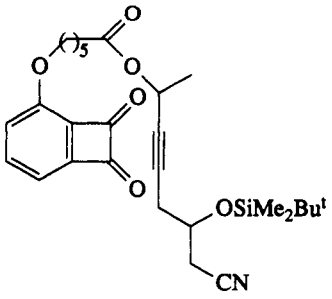
R^1	R^2	*Yield* (%)	R^1	R^2	*Yield* (%)
Bu	H	87	Et	OEt	85
Me	CO_2Et	99	Me	$CH_2CH{=}CMe_2$	94



(51)

(125) (126)

R^1	R^2	*Yield* (%)	*Regioisomer ratio*
Bu	H	65	10:1
Me	CO_2Me	62	20:1
$CH_2SiMe_2Bu^t$	Me	51	20:1
$(CH_2)_2N(CH_2Ph)(COCO_2Et)$	H	65	7:1



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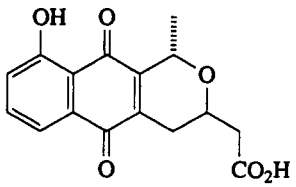
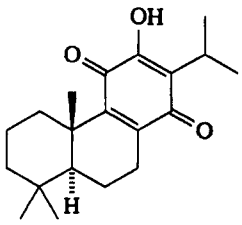


(128) Nanaomycin A



(129) Royleanone

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Author Index

This Author Index comprises an alphabetical listing of the names of over 7000 authors cited in the references listed in the bibliographies which appear at the end of each chapter in this volume.

Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

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The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

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