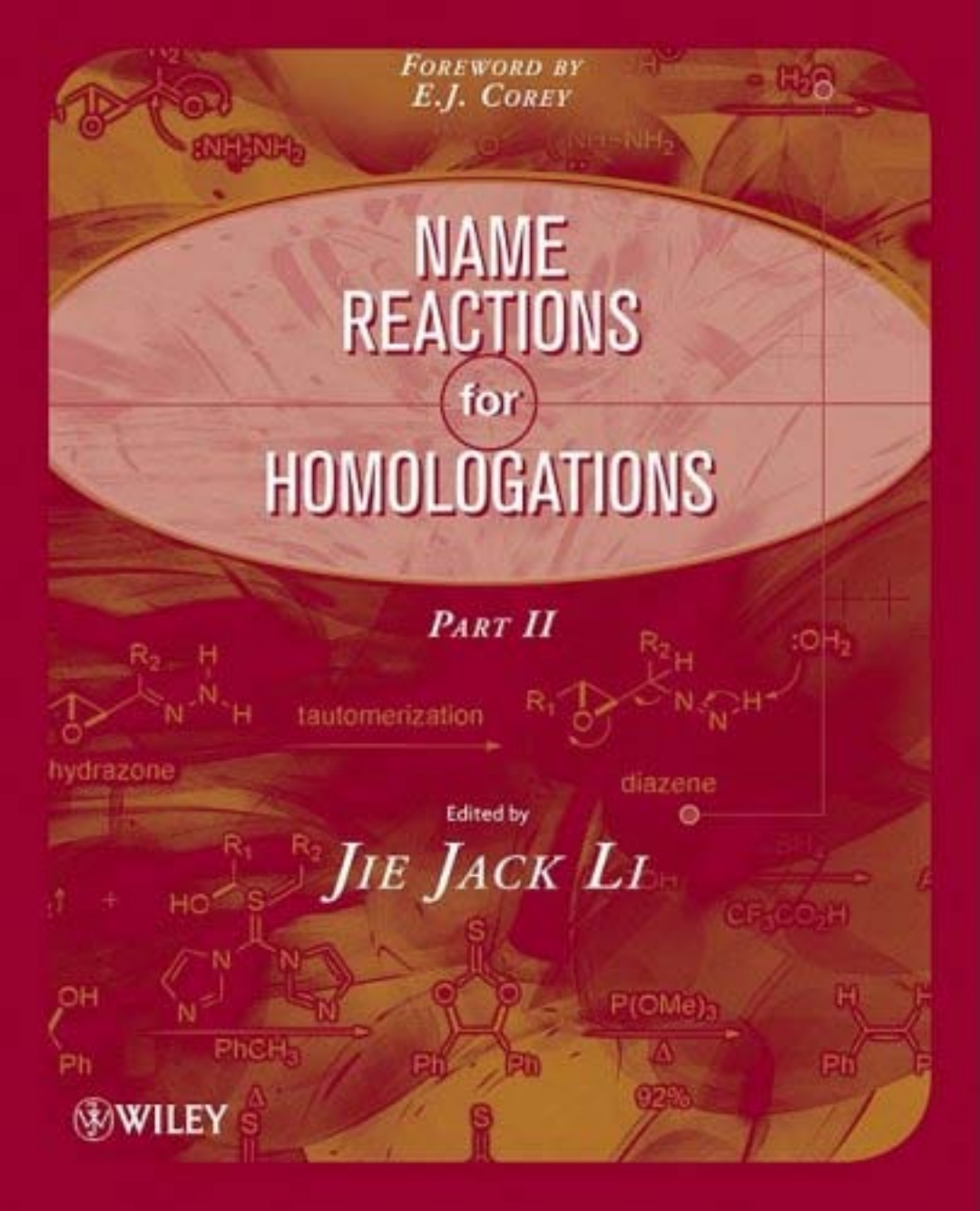
Foreword by
E.J. Corey
NAME
REACTIONS
for
HOMOLOGATIONS
Part II
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Name Reactions for Homologations
Part II

Name Reactions for Homologations

Part II

Edited by

Jie Jack Li

Bristol-Myers Squibb Company

Foreword by

E. J. Corey

Harvard University

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Dedicated to

Prof. E. J. Corey

On occasion of his eightieth birthday

Foreword

Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness waiting to be made. Then, there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a non-chemist. There is the staggering range of reagents, reaction conditions, catalysts, elements, and techniques that must be mobilized in order to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to that landscape at a rate that exceeds the ability of a normal person to keep up with it. In such a troubled setting any author, or group of authors, must be regarded as heroic if through their efforts, the task of the synthetic chemist is eased.

These two volumes on methods for the extension of carbon chains by the use of coupling reactions brings to the attention of practicing synthetic chemists and students of chemistry a wide array of tools for the synthesis of new and useful molecules. It is a valuable addition to the literature by any measure and surely will prove its merit in years to come. The new knowledge that arises with its help will be impressive and of great benefit to humankind.

E. J. Corey
October 1, 2008

Preface

This book is the fourth volume of the series *Comprehensive Name Reactions*, an ambitious project conceived by Prof. E. J. Corey of Harvard University in the summer of 2002. Volume 1, *Name Reactions in Heterocyclic Chemistry*, was published in 2005 and was warmly received by the organic chemistry community. Volume 2, *Name Reactions for Functional Group Transformations* was published in 2007. After publication of the current Volumes 3 and 4 on homologations in 2009, we plan to roll out Volume 5, *Name Reactions on Ring Formation* in 2010; and Volume 6, *Name Reactions in Heterocyclic Chemistry-2*, in 2011, respectively.

Continuing the traditions of the first two volumes, each name reaction in Volume 4 is also reviewed in seven sections:

1. *Description;*
2. *Historical Perspective;*
3. *Mechanism;*
4. *Variations and Improvements;*
5. *Synthetic Utility;*
6. *Experimental; and*
7. *References.*

I also introduced a symbol [R] to highlight review articles, book chapters, and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Prof. E. J. Corey. What he once told me — "*The desire to learn is the greatest gift from God*" — has been a true inspiration. Furthermore, it has been my great privilege and a pleasure to work with a collection of stellar contributing authors from both academia and industry. Some of them are world-renowned scholars in the field; some of them have worked intimately with the name reactions that they have reviewed; some of them even discovered the name reactions that they authored in this series. As a consequence, this book truly represents the state-of-the-art for *Name Reactions for Homologations*.

I welcome your critique.


Jack Li
October 1, 2008

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Name Reactions for Homologations
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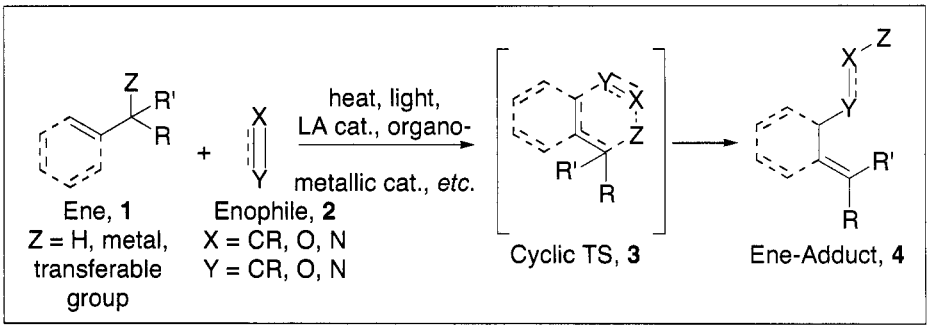
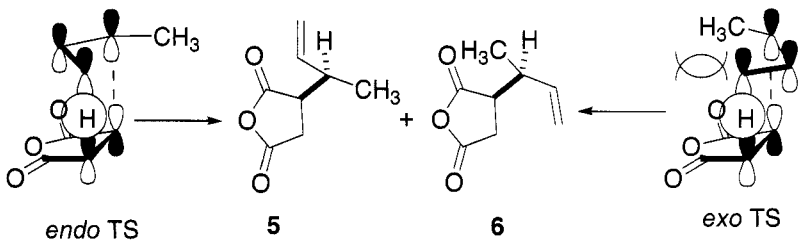
1.1.1 Alder–Ene Reaction

Timothy T. Curran

1.1.1.1 Description



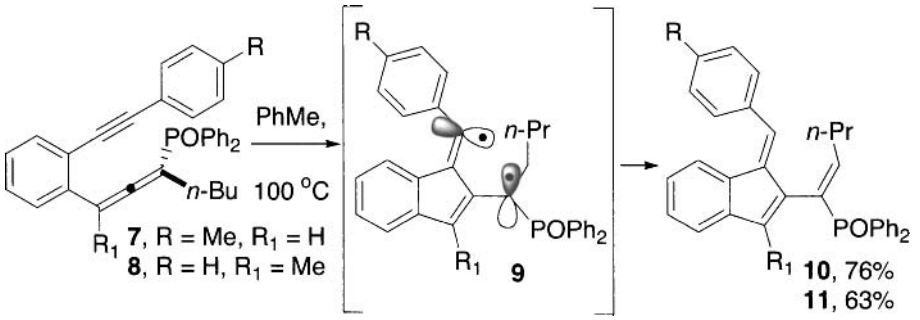
The Alder–Ene reaction is the indirect substitution addition of a compound containing a double or triple bond which also has an allylic, transferable group (typically a hydrogen–ene, **1**) with another multiple bond containing compound (enophile, **2**). The reaction leads to an allylic shift of one double bond and the transfer of the allylically-positioned, transferable group and formation of a new bond.



In the all carbon and hydrogen instance, the Alder–Ene reaction is considered to be concerted and is thermally allowed based on Woodward–Hoffman rules. Thus, the Alder–Ene reaction is proposed to be a six-electron process, like the Diels–Alder reaction, having transition states (*endo* and *exo*) analogous to the Diels–Alder reaction. However, the Alder–Ene reaction is easily modulated by steric effects as secondary electronic stabilizing effects have yet to be clearly identified. For example, Berson reported *cis*-2-butene reacted with maleic anhydride to provide about a 4:1 ratio of *endo*:*exo* adducts **5**:**6**, while *trans*-2-butene provided little selectivity at 43:57 ratio of **5**:**6**. In the reaction of maleic anhydride with *trans*-2-butene, the *exo*-TS encounters a steric interaction that the *endo*-TS does not. Steric effects are

observed for the thermal reaction of *cis*-2-butene and *trans*-2-butene with diethyl azodicarboxylate (DEAD) wherein the *trans*-compound reacts 3.7 times faster. These observations are steric in nature and lack electronic-stabilizing data for the *endo*-TS in comparison to the Diels–Alder reaction.[1,2]

Also, as shown in this example and similar to the Diels–Alder reaction, the "normal" or "traditional mode" of reaction is for the lowest unoccupied molecular orbital (LUMO) of the electron-deficient enophile to react with the highest occupied molecular orbital (HOMO) of the electron-rich ene. However, there are some carbon and hydrogen containing systems that have been proposed to proceed via radical or stepwise pathways. For example, allenyl alkynes **7** and **8** were thermally cyclized using PhMe under relatively mild conditions to provide **10** and **11** in good yield. The authors suggested a radical mechanism for this transformation via the fulvene biradical intermediate **9**.[3]

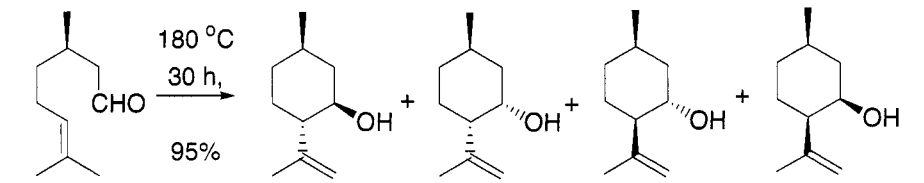


In addition, with the implementation of metals and the use of a variety of enophiles (RCHO, O_2, PTAD, RNO, SeO_2, R^3COR^4, benzyne, *etc.*), there is evidence for many of these reactions to be stepwise and oftentimes very difficult to distinguish concerted reactions from stepwise reactions. The broader definition of a radical, stepwise or concerted process of the Alder–Ene reaction will be utilized here.

1.1.1.2 Historical Perspective

Until recently, the Alder–Ene reaction was more underdeveloped than other pericyclic reactions like the Diels–Alder reaction. Alder's initial 1943 report on the study of the reaction that bears his name, described reactions of maleic anhydride with simple enes using an autoclave and temperatures in excess of 200 °C.[4] One of the reasons for the slow development may be attributed to the relatively harsh conditions used to promote the reaction thermally and the lack of high selectivity. While intramolecular reactions served to allow the

temperature for cyclization to be reduced in some instances, the reaction still lacked selectivity as illustrated in the thermal cyclization of β-citronellal (**12**) forming isopulegol **13** as the major product.[2]



12 β-citronellal

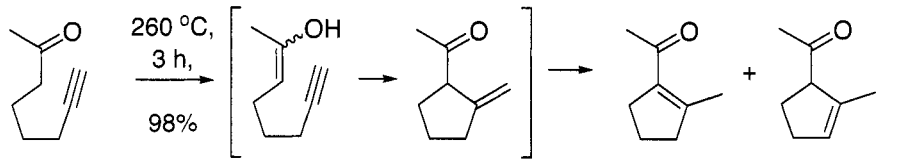
13 isopulegol 60%

14 neo-isopulegol 20%

15 iso-isopulegol 15%

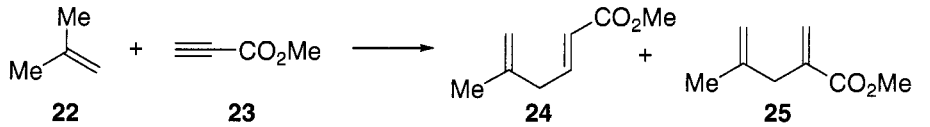
16 neoiso-isopulegol 5%

By the time of Hoffmann's first review on the subject in 1969, a variety of enophiles had been used including allenes, alkynes, benzyne, diazodicarboxylates, enones and enoates, ketones with and without electron-withdrawing groups (EWG), aldehydes, triazoline-dione (TAD), singlet oxygen ($^1O_2$), sulphur trioxide and selenium dioxide. Shortly after Hoffmann's review, a review describing enol formation for the ene component and intramolecular reaction with an enophile (Conia type ene reaction) appeared.[5] Subsequent to that review, Oppolzer and Snieckus reviewed the intramolecular Alder–Ene reaction.[6] They noted energetic differences between the intramolecular and intermolecular Alder–Ene reactions and suggested that the participation of non-activated enophiles in the intramolecular ene process is due to the less negative $\Delta S^{\ddagger}$ (–18 to –19 kcal/mol compared to the intermolecular case –36 to –45 kcal/mol) which compensates for the higher $\Delta H^{\ddagger}$ (31–32 kcal/mol for the intramolecular case and 18–22 kcal/mol for the intermolecular case). As shown, the reaction was typically thermally promoted under relatively harsh conditions, and mixtures of products were oftentimes reported.[2] The conversion of keto–alkyne **17** into an 85:15 mixture of **20**:**21** was reported in high yield at 260 °C via the enol intermediate **18** followed by ene reaction providing **19**. Alkene migration provided the two products.



17 **18** **19** **20** **21**

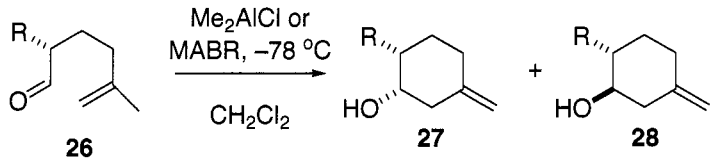
Similar to the Diels–Alder reaction, Lewis acid-catalyzed approaches were applied to intra- and intermolecular ene reactions, which served to diminish the temperatures required to promote the reaction and improved the selectivity. For example, reaction of 2-Me-2-propene with methyl propiolate provided a mixture of **24** and **25** at 220 °C, but proved higher yielding and more regioselective providing exclusively **24** when a Lewis acid was used.[1]



22 **23** **24** **25**

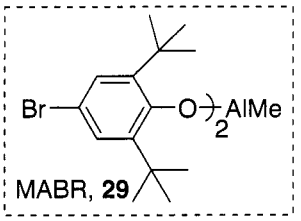
220 °C, 45%	93	7
$AlCl_3$, rt, 61%	100	0

With continued study of a variety of Lewis acids, not only was the selectivity improved but was frequently changed. Yamamoto and co-workers developed bis-phenoxy-methyl aluminum catalysts which proved to change the selectivity and provide high stereoselectivities for the Alder–Ene product.[7] In the instance cited, the stereoselectivity was changed due to use of the bulky Lewis acid MABR, **29** which provided mainly *trans*-**28.** In comparison, Me_2AlCl provided predominantly the *cis* product **27**.



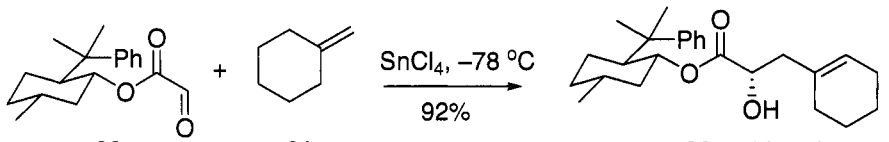
26 **27** **28**

R	Me_2AlCl Yield %, ratio **27**:**28**	MABR Yield %, ratio **27**:**28**
Me	65, 9:1	82, 1:32
i-Pr	70, 33:1	85, 1:17
Ph	95, 26:1	98, 1:62



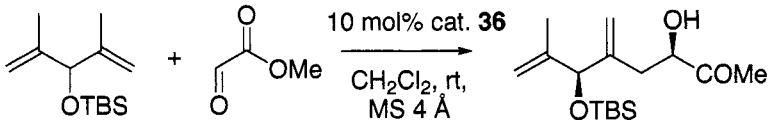
MABR, **29**

These reactions were, of course, limited to instances in which the enophile could be activated with a Lewis acid. Nevertheless, this was an excellent advancement toward promoting the utility of the Alder–Ene reaction and an asymmetric, Lewis acid-promoted ene reaction was reported by Whitesell using a chiral auxiliary.[8]



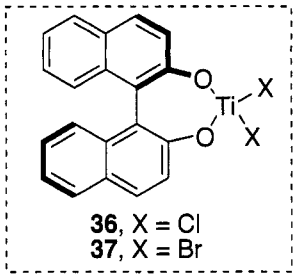
30 **31** **32**, > 99% *de*

The development and use of optically-enriched Lewis acids toward promoting the Alder–Ene reaction followed. This was elegantly applied to the desymmetrization of *meso*-bis-alkenes like **33** acting as the ene component with catalyst **36** and 4 Å molecular sieves in CH_2Cl_2. Not only were these binapthol-based titanium ligands used for desymmetrization, but catalyst **36** and **37** also proved general in promoting the intermolecular Alder–Ene reaction on a variety of enes with glyoxalate esters in 68–98% yields and 88–97% *ee*.[1]



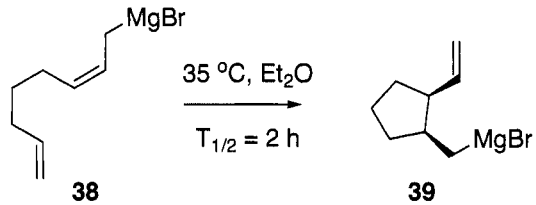
53%, > 99% *syn*, 99% *ee*

33 **34** **35**



36, X = Cl
37, X = Br

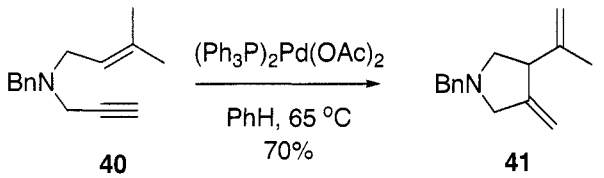
Metallo-Alder–Ene reactions have been reported in which the transferable group was an organometallic. One such example reported Grignard reagent **38** converting to **39** at room temperature.[9]



38 **39**

Catalytic transition-metals have more recently been utilized to promote reactions which provide formally the Alder–Ene product. Several

transition metals have successfully been applied to promoting this transformation. An early example of this reaction was catalyzed by palladium at a lower temperature than could be achieved thermally and provided **41** in good yield.[10]



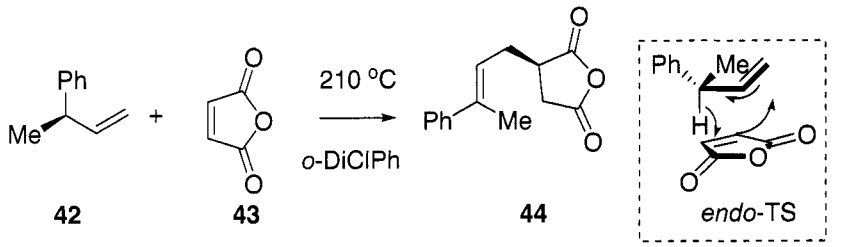
40 **41**

1.1.1.3 Mechanism

There has been much study and some argument on the mechanism of the Alder–Ene reaction. For carbon and hydrogen substrates, the reaction is typically accepted to be a six-electron, concerted process. For other substrates like oxalates, it has been suggested that the reaction is stepwise in particularly in Lewis acid-catalyzed reactions. Other enophiles like $^1O_2$, TAD or RNO are all suggested to go through a cyclic intermediate (peroxirane or aziridinium intermediate) and be stepwise. For the transition metal Alder–Ene reactions, a mechanism has been proposed and has been sufficient to explain product ratios. Overall, due to the complexity in discerning a particular mechanism which may be operable for certain types of reactants, it has been difficult to develop the Alder–Ene reaction.

Thermally-Promoted Reactions

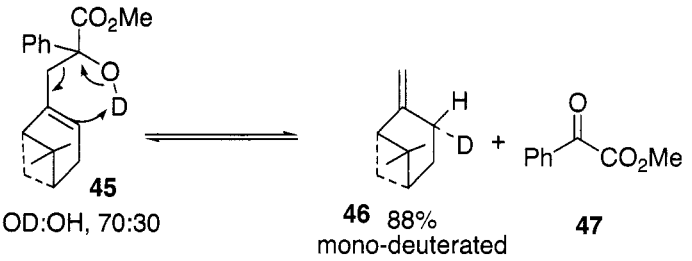
An early report suggesting a concerted or highly ordered transition state (TS) for the Alder–Ene reaction was described for the reaction of optically enriched 3-Ph-butene **42** and maleic anhydride **43**. In this reaction, optical activity was maintained in the product, and the optical rotation suggested a predominance of compound **44**. The *endo*-TS was suggested as the predominate conformation leading to product.[11]



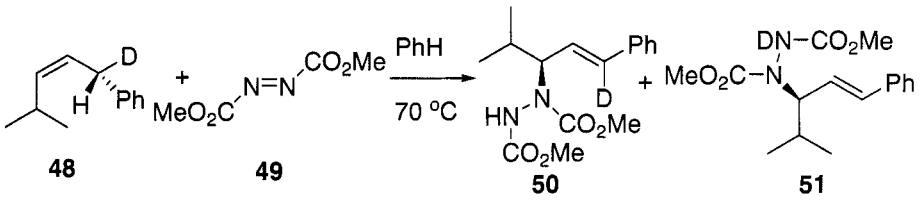
42 **43** **44**

Further evidence for a highly ordered transition state comes from the observation that entropies of activation (–125 to –170 J/mol•K) are comparable to that of the Diels–Alder reaction or other pericyclic processes.[12] Additionally, high pressure chemistry studied on Alder–Ene reactions with mesoxalate showed a large negative volume of activation (–36 to –48 mL/mol), similar to the Diels–Alder reaction. One would expect the biradical process to be about 10 mL/mol less than the pericyclic process.

A very interesting deuterium labelling study was done by Arnold and co-workers using pinene.[13] When compound **45** containing 100% OD label was allowed to partially react at 275 °C, it regenerated mono-deuterated β-pinene containing 88% of the mono-deuterated material **46**, other thermally rearranged products, and ester **47**. Furthermore, reaction of isolated **46** at 165 °C regenerated **45** in a 70:30 OD:OH mixture. This shows a reasonable degree of selectivity for the Alder–Ene reaction. During their study, it was also recognized that the ene reaction of **47** with β-pinene was not dependent on solvent polarity.



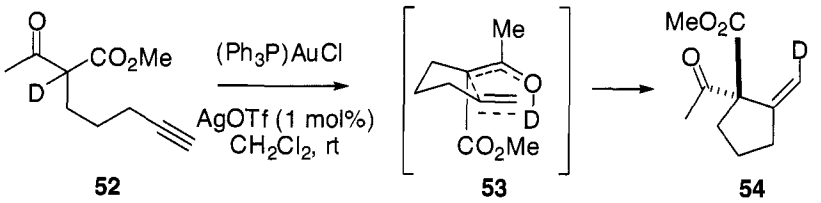
Use of azodicarboxylate as an enophile has also been investigated and results suggest that the reaction is not stepwise. On reaction of optically enriched **48** with methyl diazodicarboxylate **49**, a mixture of **50** and **51** was obtained. Both **50** and **51** were optically enriched and an isotope effect was observed (k_H/k_D ~3). Additionally, this ratio matches well with the ratio of enantiomers (also ~3) and thus the reaction is reported to proceed as a concerted mechanism with 94% transfer of chirality.[1,14]



The reaction of mesoxolate esters has been studied using both temperature and deuterium studies. While the authors concluded that

reaction of diethyloxomalonate with allyl benzene showed a temperature-independent isotope effect which supported a cyclic transition state, this has been challenged by others on theoretical grounds.

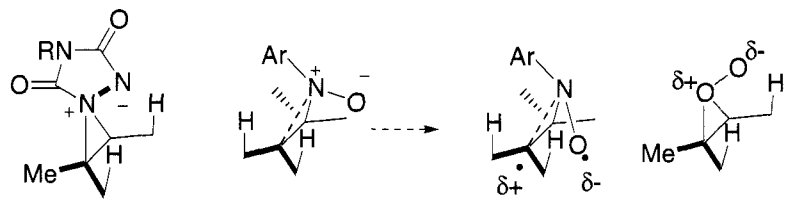
Conia-type reactions have recently been reported using gold catalysis.[15] Deuterium labelling experiments showed that the deutero-enol reacts with an Au–alkyne complex, illustrated by **53**, to provide the Alder–Ene product **54** with 90% of the D-incorporated *syn* to the keto-ester.



52 **53** **54**

Special Case Enophiles

As mentioned, TAD, nitroso and $^1O_2$ reactants have been shown to proceed through a 3-membered ring intermediate **55**, **56a,b**, and **57**, respectively.[16–18] These cyclic intermediates and the approach necessary to form them impacts the selectivity of the reaction. While all go through a 3-membered transition state, it has been suggested that the nitroso-Alder–Ene reaction proceeds through an aziridine intermediate **56a** converting to a polarized diradical **56b**. The polarized diradical **56b** was suggested to explain the relatively small kinetic isotope effect (KIE), thereby being the rate determining step in the process. Alternatively, others suggested that the aziridine intermediate **56a** proved sufficient to explain the observed isotope effects and regioselectivies of the reaction.

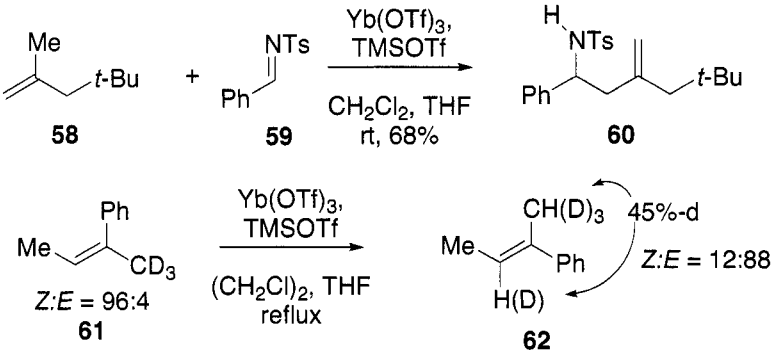


aziridine intermediate **55** | aziridine intermediate **56a** | polarized biradical **56b** | *peroxirane* intermediate **57**

Lewis Acid-Promoted Alder–Ene Reaction

The $SnCl_4$-promoted reaction of *cis*- and *trans*-2-butene with glyoxalate esters was suggested to be stepwise due to the observation that *cis*-2-butene

isomerized to *trans* prior to cyclization. More recently, this was shown in the use of $Yb(OTf)_3$ in TMSOTf.[19] While, these conditions are sufficient for the promotion of the Alder–Ene reaction of **58** and tosylimine **59** providing homoallyl–tosylamide **60**, deuterium experiments revealed scrambling of the olefinic hydrogens on **61** under slightly more rigorous conditions providing **62**.



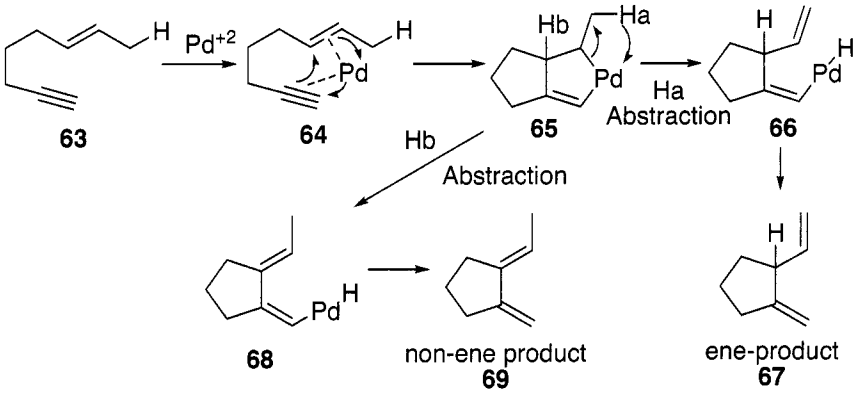
Computational, ^{2}H, and ^{13}C isotope effects on the reaction of 2-methyl-2-butene with formaldehyde catalyzed by Et_2AlCl support a stepwise mechanism with either the first or second step being rate-limiting.[20] A carbocationic process for the Lewis acid-catalyzed ene reaction may occur when the optimum geometry for a cyclic transition state is not accessible or the cationic intermediate is initially generated by the use of a strong Lewis acid.

Transition Metal-Catalyzed Alder–Ene Reaction

The use of transition metals to catalyze this process has been explored and pioneered by Trost, Oppolzer, Negishi, and others. Trost has proposed mechanisms and published scope and limitations on the reactions in which the selectivity is largely governed by sterics.[10,21,22] After formation of the metallocycle **65**, the course of the reaction is dependent upon the comparative, energetic accessibility of Hb in comparison to Ha. If the metallocycle **65** can get into a geometry in which syn elimination can occur, then competition is set-up between the β-hydride abstraction of Ha or Hb. Thus, reductive elimination of **66** or **68** leads to products **67** or **69**, respectively. A similar mechanism has been suggested for other metals shown to provide Alder–Ene products.

While the proposed mechanism for the transition-metal catalyzed Alder–Ene reaction is much different than the traditional Alder–Ene reaction, the overall transformation typically does produce an ene-type product.

Metals used to catalyze such a process have been Pd, Pt, Ni, Fe, Co, Ru, Ir, and Rh.

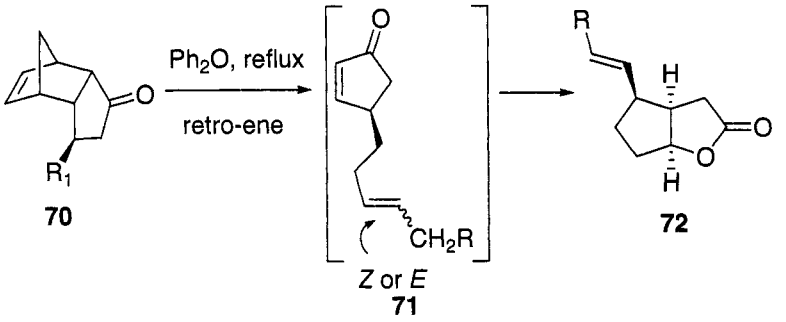


The mechanism of the Alder–Ene reaction is therefore considered to be duplicitous in that both concerted and stepwise processes may be operating in both the thermal and Lewis acid-catalyzed cases depending on the enophile and particular conditions. A concerted process should maximize allylic resonance by turning the axis of the breaking C–H bond parallel to the π-orbitals of the neighbouring alkene. The stepwise process may occur provided the optimum geometry of the TS is not accessible or if an intermediate radical, biradical or cation is formed and properly stabilized.[2] The transition metal-catalyzed reaction is mechanistically different, while formally providing the Alder–Ene product.

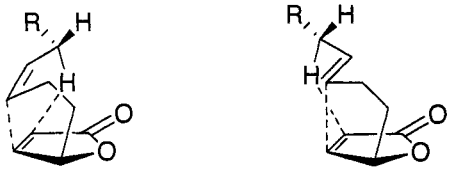
1.1.1.4 Regioselectivity and Stereoselectivity

The regioselectivity of the migrating group of the ene component in the Alder–Ene reaction is dependent upon a few factors: 1) the ability to adopt a proper conformation adequate for the reaction, 2) the steric accessibility of the migrating group, and 3) the electronic nature of the carbon containing the migrating group.

Intramolecular reactions provided the best examples for requiring the proper conformation for a successful Alder–Ene reaction to occur. Oftentimes, a chiral template has been used to induce chirality into the Alder–Ene reaction. Retro-Diels–Alder reaction formed **71**, which revealed the enophile, followed by cyclization to **72**. Notably, reactions with the *E*-alkenes were very slow and poor yielding, while the *Z*-alkenes which underwent reaction via the *exo*-TS led to product; the *E*-alkene required the *endo*-TS. The authors suggested that due to the highly strained *endo*-TS, the *Z*-alkenes reacted more smoothly.[23]

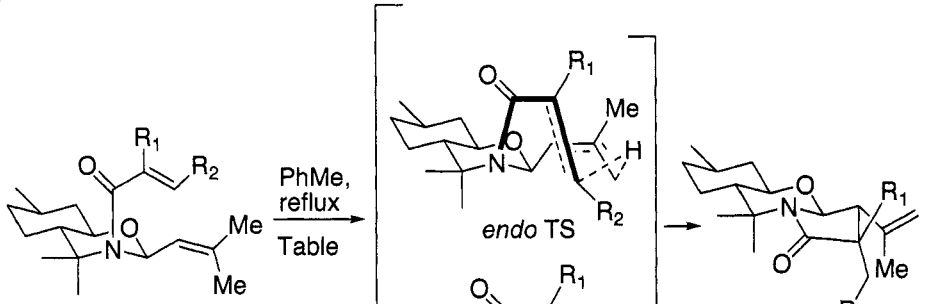


R_1	R	Ratio of **71**:**72**	Yield
Z-$(CH_2)_2$CH=CHCH$_3$	H	33:67	74%
E-$(CH_2)_2$CH=CHCH$_3$	H	56:44	43%
Z-$(CH_2)_2$CH=CHCH$_2$TMS	TMS	>1:<99	75%
E-$(CH_2)_2$CH=CHCH$_2$TMS	TMS	8:92	30%



preferred for *Z*-alkene
exo

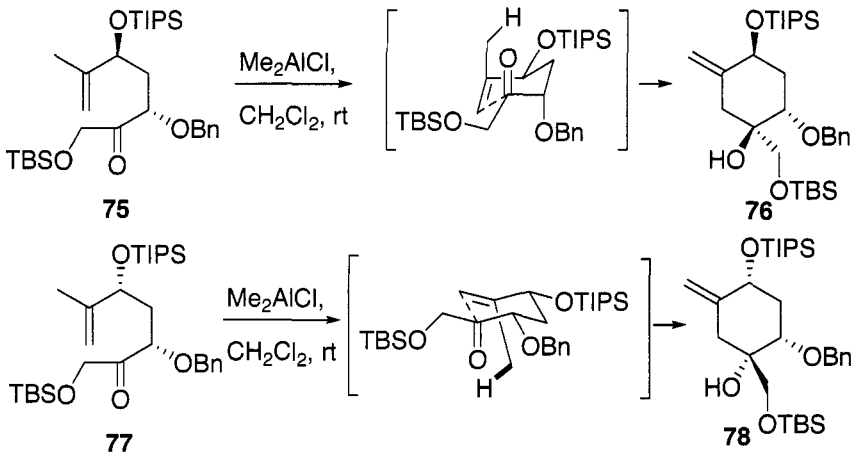
preferred for *E*-alkene
endo



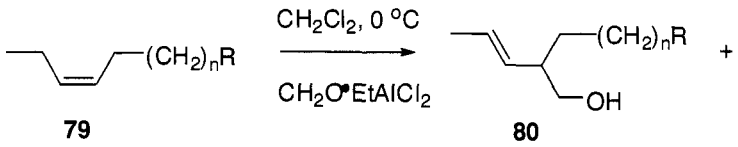
R_1	R_2	Time, h	Yield %
H	H	5	95
Me	H	10	92
H	Me	30	86

Perhydrobenzoxazine **73** was reported as being a chiral auxiliary used to control the stereoselectivity of a thermally induced Alder–Ene reaction. In this instance, both *endo*- or *exo*-transition states seemed plausible to provide the observed products. Both TS minimize non-bonding steric interactions and were used to explain the selectivity observed.[24] Ultimately, **74** was used to prepare *cis*-3,4-disubstituted pyrrolidines. For the conversion of **73** into **74**, it should be noted that the enophile was the α,β-unsaturated amide and that the new C–C bond formed was alpha to the carbonyl. This appeared counter-intuitive for a LUMO enophile controlled reaction.

An intramolecular cyclization of an ene with a Lewis acid-activated carbonyl also took advantage of low-energy conformers to obtain high selectivity in the reaction. The optically-enriched ketones **75** and **77** underwent Lewis acid promoted cyclization via a "chair–chair" transition state, which minimized steric interactions and provided quantitative yield of the optically-enriched alcohols **76** and **78**, respectively. In this instance, the OTIPS group served as a conformational anchor to result in the stereoselectivity in the cyclization.[25]

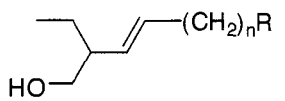


A study conducted with a range of butenes and pentenes with diethyl azodicarboxylate showed that hydrogen on primary carbons was abstracted more readily than secondary and much faster than tertiary hydrogens.[2] An electron-withdrawing group (EWG) on the carbon with the migrating group diminishes the transferability of the group. The EWG could merely be a heteroatom or a group. Snider published this observation in a study on the reaction of *cis*-alkenes with formaldehyde and $EtAlCl_2$. The observed product ratio was claimed to be due to formation of the carbenium ion furthest from the EWG.[26] Notably, the inductive effect drops off as carbons were added for the addition of formaldehyde to alkene **79**.



79 80

R (n)	Yield %	ratio **80:81**
OH (1)	43	100:0
OAc (1)	59	100:0
OH (2)	63	80:20
OAc (2)	64	82:18
OH (3)	50	67:33
H (3)	75	44:56

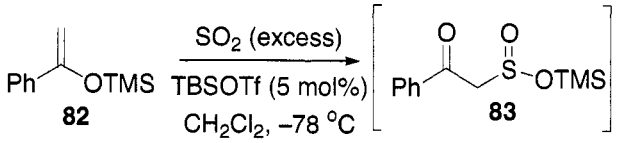


81

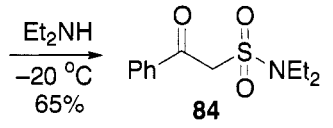
Selectivity of Certain Enophiles

Ene reactions using $Me_2Si{=}C(TMS)_2$, $Me_2Sn{=}C(TMS)_2$, and $Me_2Ge{=}C(TMS)_2$ as enophiles have been reported with the more reactive being sila-ethene. These ene reactions were proposed to be concerted. In all cases, when reacted with propene, a C–Si, C–Sn or C–Ge bond formed, and the carbon bearing the two TMS groups forms a C–H bond.[27] Likewise, reaction with SeO_2 takes place via an Alder–Ene reaction.[28]

Some Alder–Ene products remain quite reactive; therefore, trapping of the initial product may be required. Alder–Ene reactions of SO_2 have been reported with subsequent trapping of the sulfinate ester with an amine to provide sulfonamides. In this case, the TMS group serves as the transferring group, but **83** was not suitable for isolation, and the amide **84** was prepared in good yield for this Conia-type Alder–Ene reaction.[29]



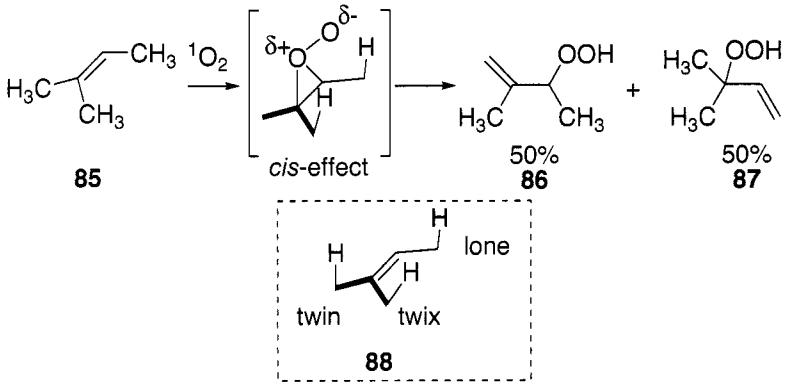
82 83



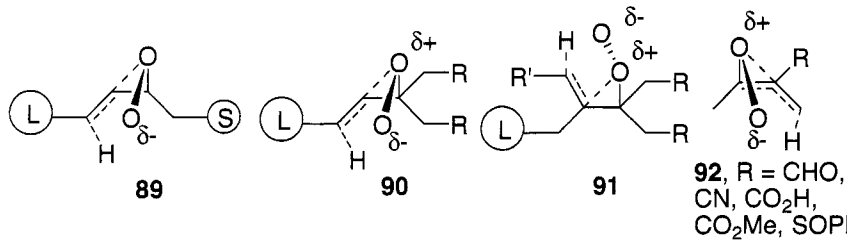
84

As mentioned in the mechanistic section, TAD, $^1O_2$, and RNO reactions have been shown to be special enophiles. Reactions using these enophiles have been well studied and characterized. For example, $^1O_2$ manifests a "*cis*-effect," which is characterized by H-abstraction from the more substituted side of the alkene, forming a 1:1 mixture of **86** and **87**. Furthermore, the hydrogen removed displays a preference for removal from the lone carbon as shown in structure **88**.[16,30] Most of the explanations for the transition state are consistent with the idea that the two allylic hydrogens stabilize the transition state.

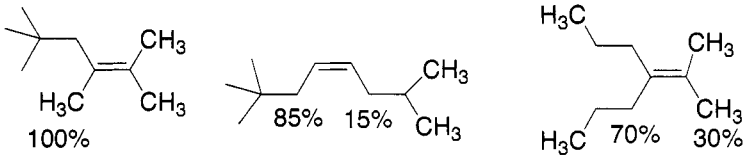
Models have been developed to explain the selectivity displayed between which of the two alkyl groups, twix or lone, will undergo H-abstraction in the $^1O_2$ reaction. Typically, steric effects impact the selectivity unless there is an EWG attached to one of the two *cis*-allylic carbons.



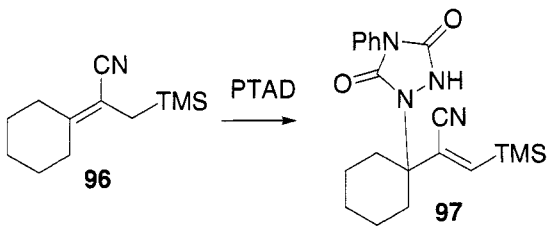
Several models of selectivity are shown. Models **89–91** depict the peroxide bond being formed away from the large, sterically encumbering group. When an EWG is attached directly to the alkene (e.g., **92**), there is a driving force to form the double bond in conjugation with the EWG. There may be steric interactions to consider as well as electronic repulsion or attraction of the perepoxide with other functionality.



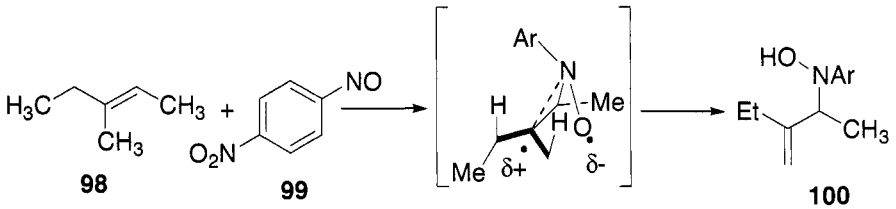
Reactions using phenyl or methyl triazolinediones (PTAD or MTAD) have also been rigorously studied. TAD has been shown to have a "gem-preference" for H-abstraction, which is H-abstraction from one of the two geminal carbons which is attached the larger substituent with the new C–N bond formed away from the large substituent. Examples of selectivity for PTAD reactions are shown in structures **93–95.** H-abstraction occurred close to the larger substituent with C–N bond formation away from the larger group.[16]



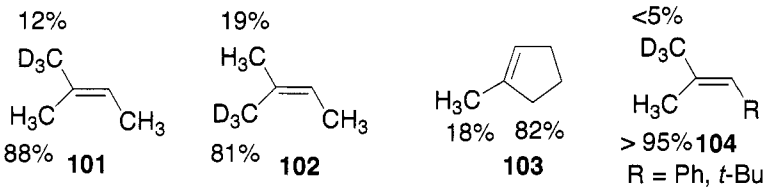
Of course, there are always exceptions to the rule as reported for the conversion of **96** into **97** using PTAD, in which the only product was **97**. The inversion of regioselectivity was rationalized by positive charge build-up in the transition state.



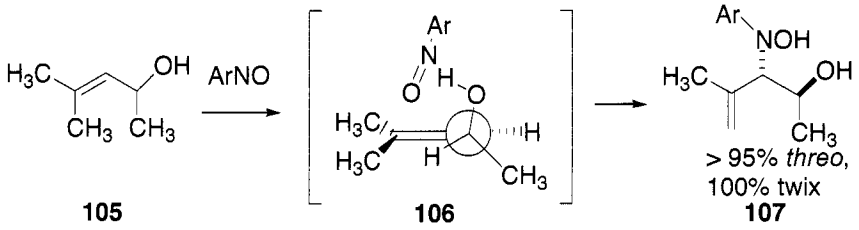
Nitroso compounds and their reaction with alkenes have been very well characterized. Reactions of aryl or acyl nitroso compounds have demonstrated synthetic utility. Interestingly, reaction of aryl nitroso compounds did not display analogous selectivity to TAD nor $^1O_2$ but instead displayed a selectivity of its own. Reaction of *p*-nitro-nitrosobenzene manifested a selectivity for abstraction from the twix group (see **88**). An example of this was the conversion of **98** into **100**, the only compound reported to form.[30]



This twix selectivity was exhibited in reactants as shown (**101–104**). This has been dubbed the "skew effect" and was rationalized in terms of steric interactions in the possible transition states.[17]



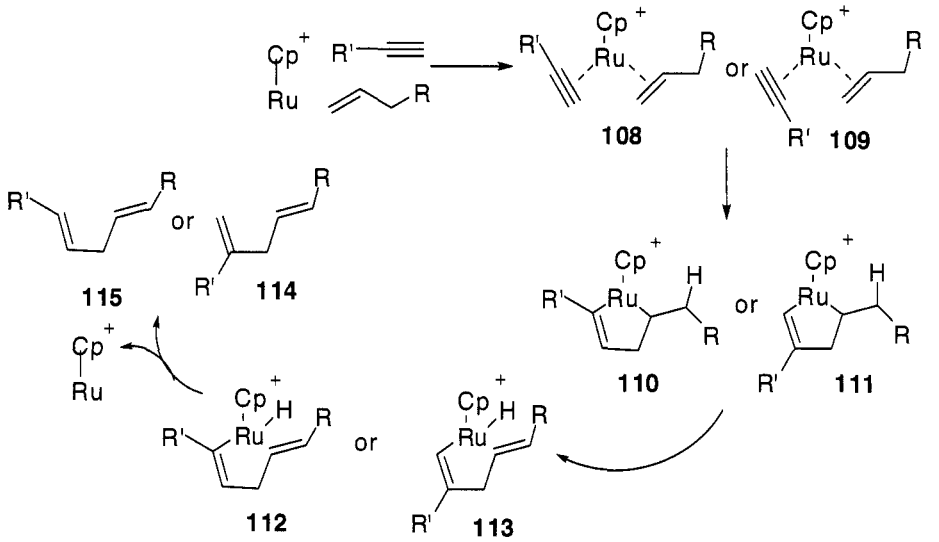
The selectivity of the nitroso-Alder–Ene reaction has been recognized as having a hydrogen bonding or hydroxyl directing effect as demonstrated in the selectivity for the conversion of **105** into **107**. Transition state **106** in which the hydroxyl group serves to stabilize the transition state by hydrogen bonding to the incoming nitroso group. For this reaction, a solvent effect has also been reported which impacted selectivity; thus, protic sources can serve to stablize the transition state.[17]



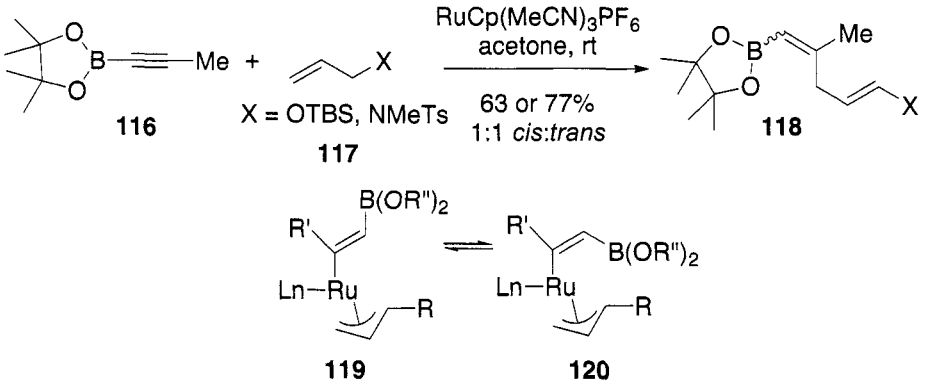
Selectivity of Metallo-Catalyzed Alder–Ene Reaction

Transition metal catalyzed reactions, providing a formal Alder–Ene product, have a unique mechanism and selectivity when compared to the traditional Alder–Ene reaction product. There has been a debate in explaining the initial step, whether a π-allyl complex was formed from the ene reaction components, or merely complexation of each reacting component and metallocycle formation. For the Ru-catalyzed reaction, Trost and coworkers[22] reported that the below description rationalized the observed selectivity. Coordination followed by carbocyclization provides either **110** or **111**. Carbometallations normally prefer to attach at the less substituted terminus of the alkyne, favoring initial formation of **109** leading to **111**. However, steric effects between the two bonding carbons may disfavor such a mode and therefore **108** may be preferred due to steric effects which would form carbocycle **110**. So, as R′ increases in size, one would expect that more

of the carbocycle **110** leading to linear product **115**, which is observed. This mechanism is quite similar to the Pd-promoted reaction as described earlier.



Recent studies published by Lee and coworkers[31] did not think that the mechanism here explained the lack of *cis/trans* selectivity of the formed vinyl boronate. The authors suggested a π-allyl equilibrating intermediate **119** and **120** rather than a similar equilibrating intermediate from **112**. Regardless of the mechanism, the boronate example shows the power of the transformation in generating the functionalized linear product **118**.



1.1.1.5 Variations and Improvements

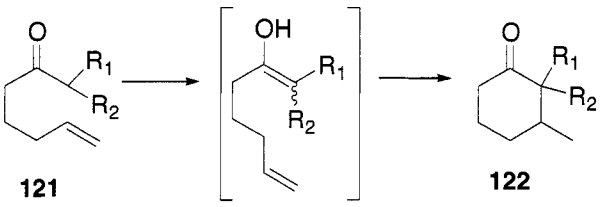
Variations in promoting the Alder–Ene reaction have been broadly mentioned in the examples above. In general, the reaction may be promoted

thermally, un der high pressure, with light (hν in the case of $^1O_2$), Lewis acid, or catalyzed by transition metals, or Lewis acids. There are variations on the thermal theme; explicitly, reactions can be done in solvents, in the neat liquid phase, or in the vapor-phase. Asymmetric catalysis in many of the above areas has been studied. Lowering the temperature of the Alder–Ene reaction was key to the improvement of the reaction; this allowed more sensitive functionality and improvements in selectivity of the reaction to be realized.

Thermal Alder–Ene Reactions

Early keys to the thermally promoted Alder–Ene reaction were to use both liquid and vapor-phases to promote the reactions. Liquid phase was done by simply heating the neat compound or dissolving in a solvent then heating or using a sealed tube. Vapor-phase techniques were done using static vapor-phase or a gas flow process that required special equipment.[5]

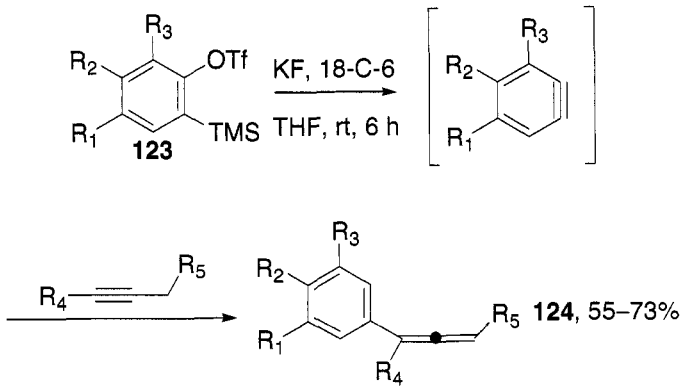
For the Conia-type Alder–Ene reaction, placing groups α- to the carbonyl apparently promoted enolization and served to allow the reaction to occur at lower temperatures and without vapor-phase equipment. At lower temperatures, for shorter time periods, better yields were realized as shown for the conversion of **121** into **122** with various alpha substituents.



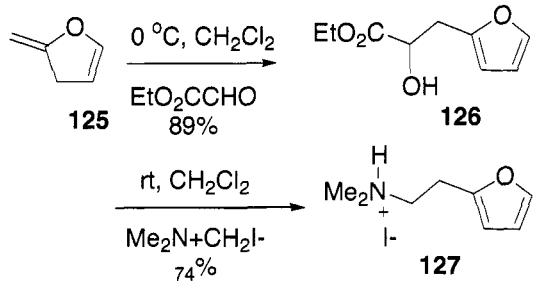
121 **122**

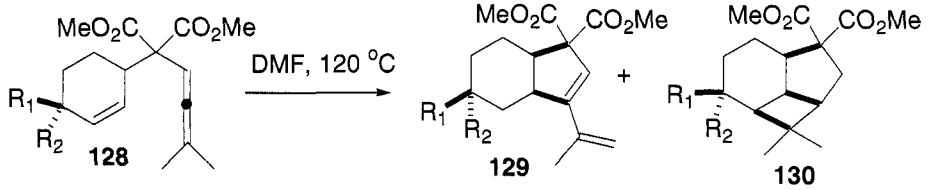
380 °C, 16 h	$R_1 = R_2 = H$, 35%
350 °C, 4 h	$R_1 = R_2 = Me$, 80%
300 °C, 2 h	$R_1 = Ph$, $R_2 = H$, 90%

Activating the enophile using EWG(s) also would facilitate the Alder–Ene reaction. Additionally, using electron-deficient enophiles also promoted the reaction. For example, benzyne proved to be a highly activated enophile as shown in the conversion of **123** into **124**.[32] Benzyne was generated at rt in the presence of the ene component (here an alkyne) to form allenes. Deuterium-labelling experiments supported the Alder–Ene process.



Highly reactive ene components, which allow the reaction to occur at lower temperature, have also been reported. Ene **125** generated by Kishner reduction of the 2-furylhydrazone proved to be a very powerful ene component reacting separately with ethyl glyoxalate at 0 °C without Lewis acid and with Eschenmoser's salt at rt providing **126** and **127**, respectively, in high yield.[33]

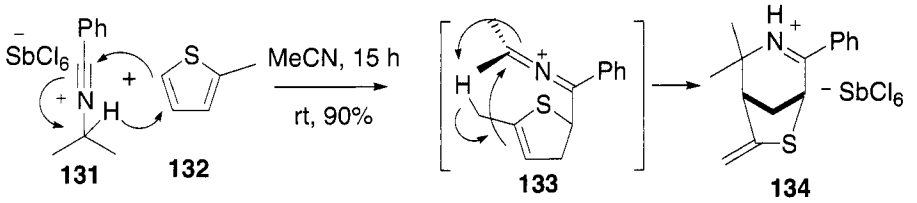




	Time	Ratio of **129:130**	Yield %
$R_1 = R_2 = H$	24	9:1	84
$R_1 = R_2 = Me$	108	95:5	86
$R_1 = H$, $R_2 = t\text{-}BuCO_2$-	24	90:10	82
$R_1 = PhCO_2$-, $R_2 = H$	24	81:19	72

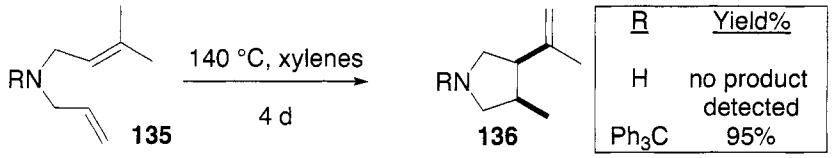
Bäckvall and co-workers recently reported a solvent effect which promoted the Alder–Ene reaction to occur at a relatively mild temperature for the unactivated, all-carbon system.[34] At 120 °C in DMF, the cyclization of the terminal allenic double bond with simple alkenes occurred intramolecularly. While a by-product was formed, no activator was utilized. Other solvents were screened as well as ionic liquids and were found inferior to DMF in facilitating the reaction. One limitation observed was that only 5-membered rings were formed and the ene portion had to be an allene which contained two terminal methyl groups. Such requirements for reaction suggested something more than merely a solvent effect.

An inverse electron demand Alder–Ene reaction has been reported in which a nitrilium ion acts as the ene and an arene as enophile.[35] The reaction occurred at room temperature and was proposed to be a double Alder–Ene reaction. The first step provided compound **133,** which could undergo a stepwise addition of the vinyl sulphide to the azonia–allene followed by elimination or alternatively, a second concerted Alder–Ene type mechanism was suggested. The heterobicycle **134** was isolated in 90% yield.



131 **132** **133** **134**

Sammes has reported a steric acceleration of the Alder–Ene reaction similar to a Thorpe–Ingold effect which brings the two reacting components into close proximity; thus, promoting the reaction.[36] For the conversion of **135** into **136**, while the *N*-trityl compound undergoes reaction in 95% yield to provide **136**, the N–H compound shows no sign of cyclization product **136** under the same conditions.



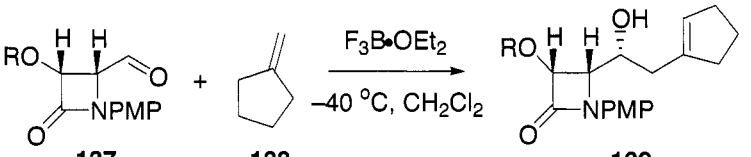
135 **136**

Lewis Acid Catalysis

As previously mentioned, Lewis acid activation of a carbonyl to lower the energy of the LUMO can facilitate the Alder–Ene reaction. There are several examples using a variety of Lewis acids. Lewis acids derived from Al, B, In,

Sc, Cr, Cu, Yb, silyl triflates, and others, have been reported to successfully promote the reaction.

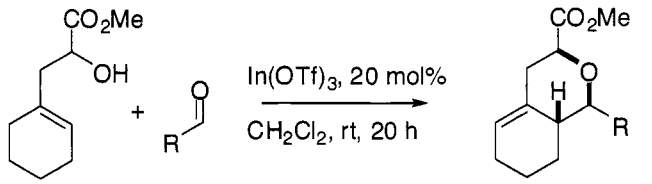
The BF_3-promoted reaction of **137** provided **139** in high yield and stereoselectivity. The *p*-methoxyphenyl protecting group of the β-lactam system was important for the success of this transformation.[37]



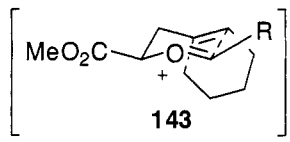
137 **138** **139**

R	Yield %
allyl	83
propargyl	85

Indium catalysts have proven to be very mild catalysts. Reaction of Alder–Ene adduct **140** with aldehydes **141** were proposed to go through an oxonium intermediate **143** to provide the major isomeric product shown **142**.[38]



140 **141** **142**



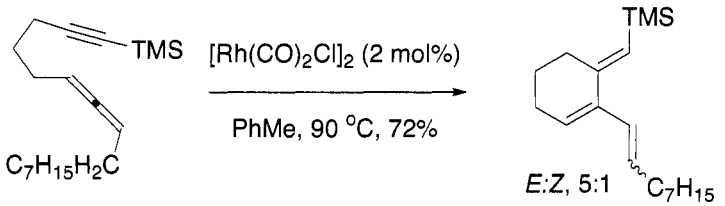
143

R	Yield %, ratio
Ph	97, 99:1
$PhCH_2CH_2$	90, 92:8
PhCH=CH	61, 99:1

Metal-Catalyzed Alder–Ene Reactions

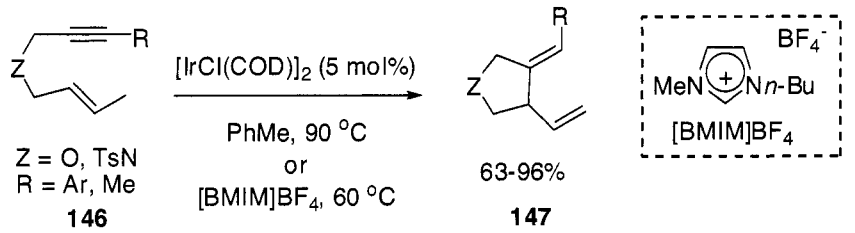
Brummond and co-workers have reported the intramolecular reaction of allenic alkynes catalyzed by Rh or Ir complexes.[39] The formal Alder–Ene product, cross-conjugated trienes, were isolated in good yield under relatively mild conditions. Mechanistically, Brummond suggested a metallocycle similar to what had been proposed by Trost. While conversion

of **144** into **145** using Rh catalyst gave a 5:1 ratio of *E*:*Z* alkenes, use of Ir catalyst provided a 20:1 ratio. In addition, terminal alkynes using Rh catalyst were successfully converted to products while Ir catalysis failed for these substrates.

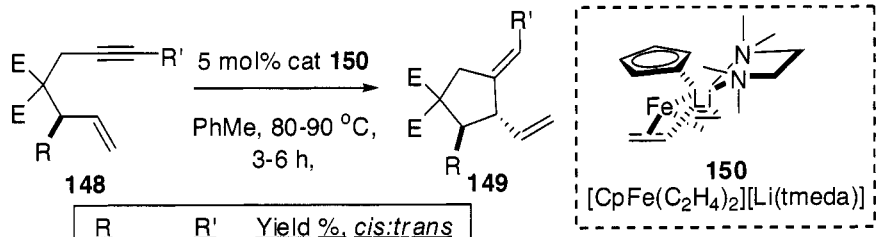


144 **145**

There has been a report of the use of ionic liquids to expedite the metal catalyzed intramolecular Alder–Ene reaction. In this work, an Ir catalyst was used, the yields for the conversion of **146** into **147** were high and the use of the ionic liquid served to reduce the temperature required by about 30 °C.[40]



146 **147**



148 **149** **150**

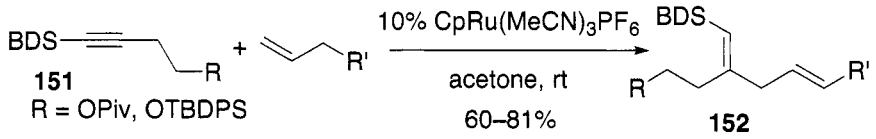
[CpFe(C2H4)2][Li(tmeda)]

R	R'	Yield %, *cis*:*trans*
H	H	0
Me	H	93, 5.8:1
Me	*p*-MeOPh	91, 4.1:1
Me	cyclopropyl	97, 6.7:1

Fürstner and co-workers have published on the Fe-catalyzed formal Alder–Ene cyclization of alkynyl alkenes.[41] Terminal acetylenes did not

pose a problem but substitution of the carbon next to the reacting alkene was required (R ≠ H). *trans*-Products were formed preferentially. The ferrate complex **150** proved to perform quite well for cyclizations such as the conversion of **148** into **149**.

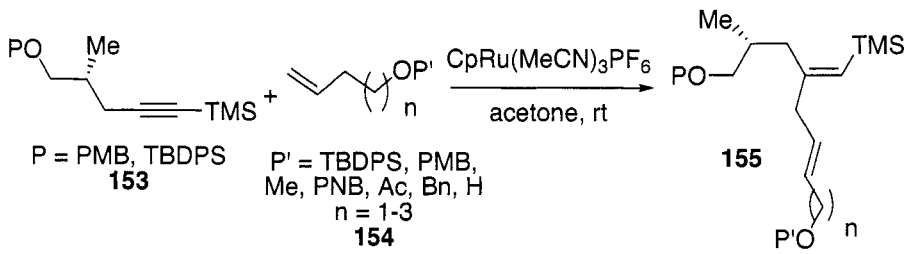
Ruthenium-catalyzed intermolecular reactions have been reported to occur at rt. From this work, Trost reported[42] that a benzyldimethylsilyl (BDS) group was surprisingly stable to acidic and buffered fluoride conditions, making it an excellent protecting group and, subsequently, a good coupling partner in cross-coupling reactions. For the conversion of **151** into **152**, the tolerated alkene functionality reported was alkyl, acetonide, ester or a carbonate.



151
R = OPiv, OTBDPS

152

A dramatic effect of protecting groups was noted in the Ru catalyzed Alder–Ene reaction.[43] In general, it was observed that best results were obtained when P′ was an EWG like an acetate or PNB. In instances for the ene component, wherein n = 1 and P′ was H or Me, the reaction did not proceed due to coordination of this group to the metal; such a coordination would force the dihedral angel between C–Ru and C–H to be > 90°. Such conditions would not permit *syn*-β-hydrogen elimination. In addition, if the PMB group as P′ was used, the authors suggested the formation of a PMB–Ru–Cp sandwich, thus precluding the metal from reacting.

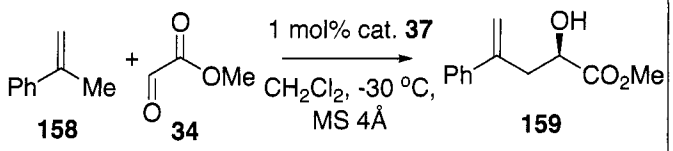


P = PMB, TBDPS
153

P' = TBDPS, PMB, Me, PNB, Ac, Bn, H
n = 1-3
154

155

Ruthenium and iridium catalysts have also been shown to promote the reaction of nitroso compounds with simple ene substrates. In this example, hydrogen peroxide acted as the oxidant to convert the hydroxylamine into the nitroso compound *in situ*. Ru- or Ir-catalyzed reaction with 2-Me-2-butene (**85**) then provides a mixture of regioisomers. The metal utilized greatly influences the ratio of products; Ru was proven to be more twix selective giving an 8:1 ratio of **156** and **157**.[44]

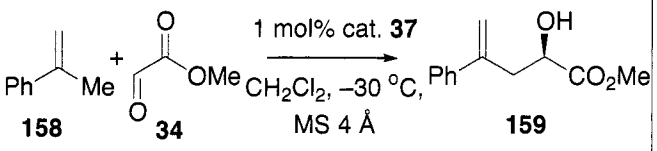


Binol % ee	Yield % % ee **159**
33	92, 91.4
66.8	96, 94.4
100	98, 94.6

Asymmetric Alder–Ene Reactions

Asymmetric Alder–Ene reactions have been accomplished using optically-enriched starting materials, chiral auxiliaries, and chiral catalysts. The use of chiral catalysts has been applied to both chiral Lewis acid catalysis and asymmetric catalysis with chiral ligands. Some of these examples have already been cited: for example, the use of a chiral auxiliary or optically-enriched substrates to generate optically-enriched products (LA catalysis with chiral auxiliary; **30** + **31** → **32** or with optically-enriched starting materials; **75** or **77** →**76** or **78,** respectively; or chiral LA applied to desymmetrization **33** + **34** → **35**). More recent examples are displayed here, in particular, the use of chiral catalysts.

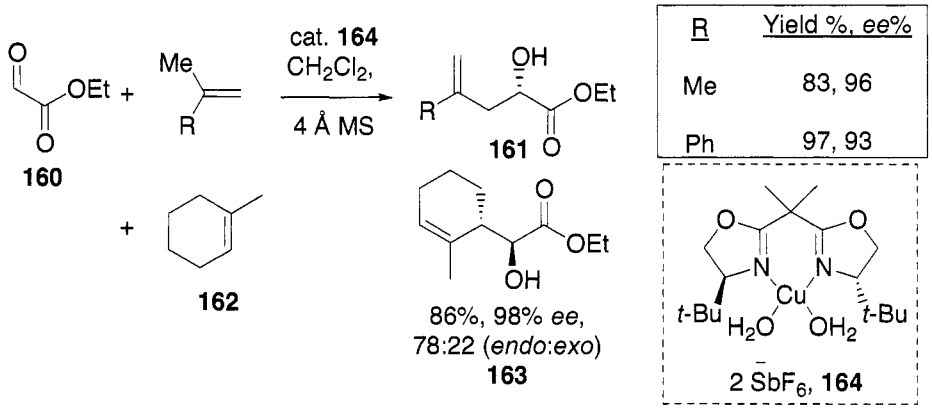
One very interesting characteristic demonstrated for the Alder–Ene reaction using Ti–Binol catalyst **37** is the positive non-linear effect. The authors observed that the %ee of the products generated was greater than the %*ee* of the binol used.[45] As noted by Mikami and co-workers, non-linear effects are indicative of agglomeration of the catalyst.



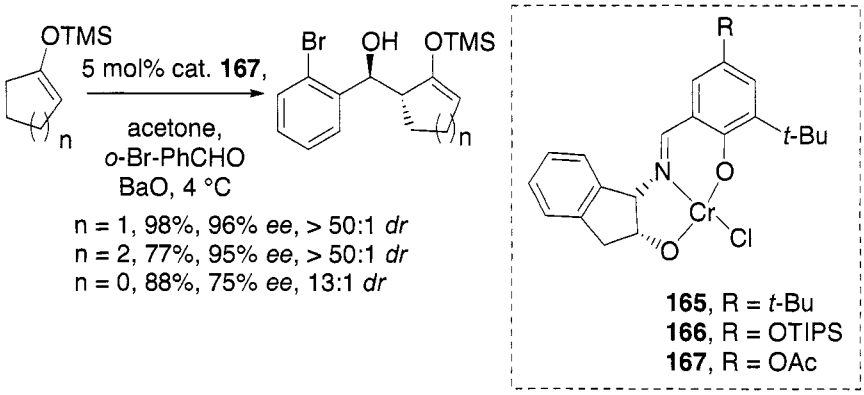
Binol % ee	Yield % % *ee* **159**
33	92, 91.4
66.8	96, 94.4
100	98, 94.6

Evans has reported the use of Cu(II) bis-oxazolinyl (box) complexes for the asymmetric ene reaction of glyoxolate and pyruvate esters.[46] For catalyst **164** 1 mol% was used, the reactions were run at 0 °C or rt, the yield was very good and the %*ee* in most cases excellent. The *endo* product was preferred for Cu promoted reactions (major *endo*-product **163**). In contrast, Evans subsequently reported reactions with *N*-phenylglyoxamide with 1,1-disubstituted alkenes using $Sc(OTf)_3$ with py-box catalysts to provide

preferentially *exo*-type adducts, but again in good yield with exceptional %*ee*.[47] Excess of the glyoxolate ester or amide was typically used.

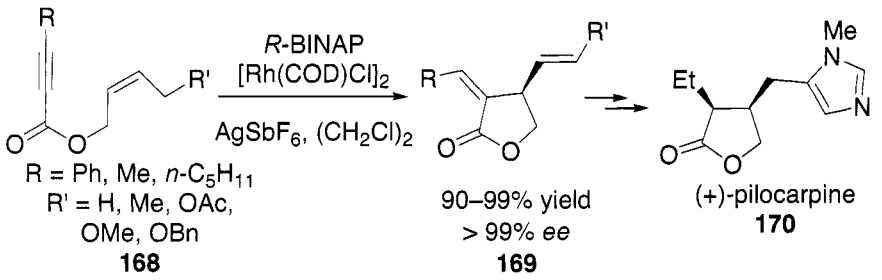


Jacobsen and co-workers have reported a Cr(III)-complex as a catalyst for the Alder–Ene reaction of aldehydes with methyl or silyl propenyl ethers.[48] The optical purities, yields and diastereoselectivity for these catalysts were good. While excess of the ene component was used, the mild conditions and ability to easily unmask the optically-enriched, β-hydroxy ketone suggested this to be a promising new methodology.

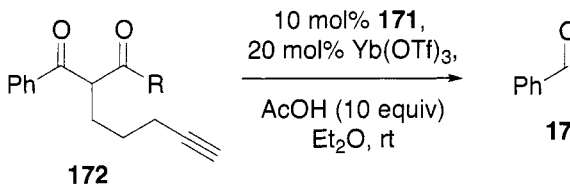


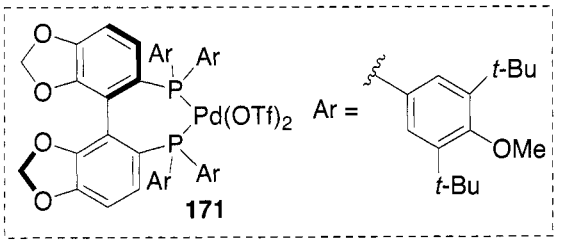
Asymmetric Rh-catalyzed Alder–Ene reactions have been demonstrated by Zhang and co-workers using BINAP as the chiral catalyst.[49] Much like the use of Ti–Binol, Zhang has applied Rh-BINAP to the reactive resolution of two isomeric allyl alkynyl esters. These reaction conditions have been used to prepare optically enriched hydrofurans. Zhang applied this methodology to the formal total synthesis of (+)-pilocarpine. Key to the success of the reaction was the finding that $AgSbF_6$ as an additive allows the

reaction to occur at rt. Many substituents were tolerated and substrates in which R′ = OH, provided the aldehyde. So, in two steps from readily available starting materials, optically-enriched enol (aldehyde) **169** was prepared and in two more steps (+)-pilocarpine **170** can be realized.



An asymmetric and catalytic Conia-type Alder–Ene reaction has been reported using a combination of asymmetric Pd ligand [(DTBM-SEGPHOS)Pd(OTf)$_2$, **171**] and Yb(OTf)$_3$ with AcOH. The reactions are quite dilute, yet both conversion and optical purity were good for the β-keto ester or differentiated β-diketone substrates **172**.[50]



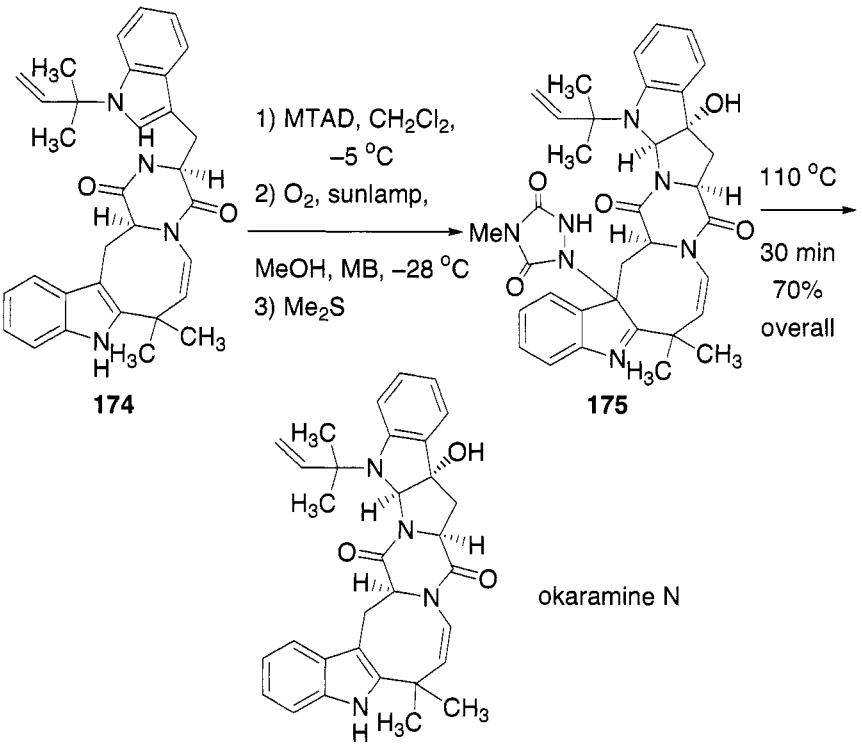


R	Yield %, % *ee*
OEt	86, 89
Oallyl	80, 90
Ot-Bu	94, 80
Me*	90, 70
CH_2*i*-Pr	79, 74

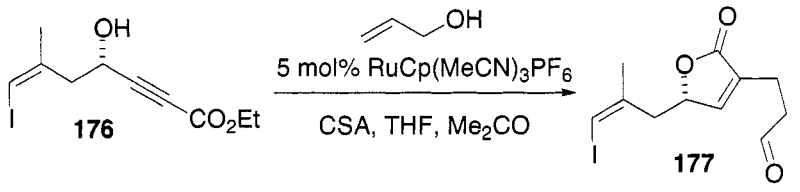
*Reaction run in CH_2Cl_2

1.1.1.6 Synthetic Utility

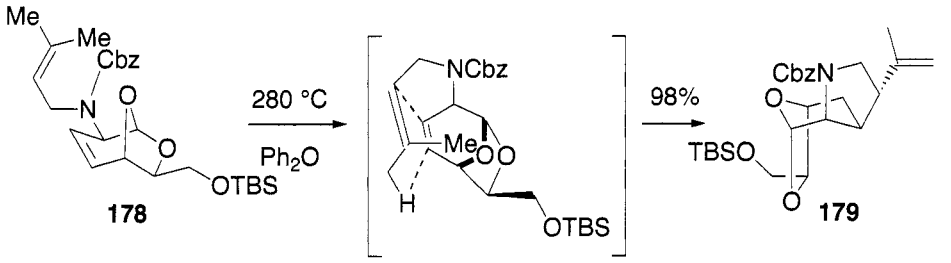
Corey, Baran, and Guerrero used the available MTAD reagent (Alder–Ene reaction) as an elegant method to protect the indole, and a $^1O_2$ reaction to oxidatively couple and oxygenate the other indole ring in the final sequence of steps in their synthesis of okaramine N. The reaction of **174** with MTAD in CH_2Cl_2 followed by $^1O_2$ reaction and reduction of the formed peroxide provided **175**. The retro-Alder–Ene reaction then provided okaramine N in 70% overall yield.[51]



Trauner and Roethle used a Ru-catalyzed allylation to form the branched enol product which readily converts to the aldehyde and *in situ* lactonizes to form **177** in 52% yield. This was used in the total synthesis of bipinnatin J, a natural product isolated from Grogonian coral.[52]

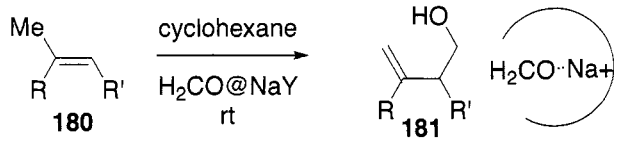


The thermal cyclization of bicyclic amine **178** showed selective *endo*-cyclization to **179,** which was an intermediate in the formal total synthesis of (–)-kainic acid.[53] This thermal cyclization goes through an *endo*-transition state and provides a single product in 98% yield.



Catalysis on Solid Support

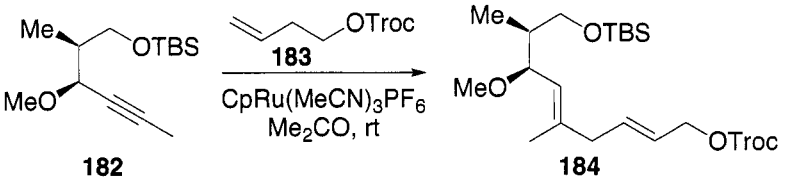
Zeolites have been reported to alter selectivity of $^1O_2$ reactions and oftentimes alter the selectivity of the Alder–Ene reaction. The use of a zeolite to catalyze the Alder–Ene reaction with formaldehyde was recently reported. The formaldehyde was activated by the zeolite and the products **181** formed proved to be very selective for the least hindered site of the alkene.[54]



R	R'	Yield %
Ph	H	94
3,4-diCl-Ph	H	99
Me	*n*-Bu	90

1.1.1.8 Experimental

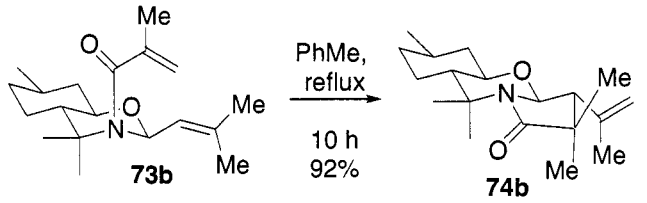
Ru-Catalyzed Alder–Ene (Trost Conditions)



(2*E*,5*E*,7*S*,8*S*)-9-(*t*-Butyldimeithylsilyloxy)-7-methoxy-5,8-dimethylnona-2,5-dienoxycarbonyloxy-2,2,2-trichloroethyl (184)[55]

Alkyne **182** (900 mg, 3.5 mmol) and 3-butenyloxycarbonyloxy-2,2,2-trichloroethane **183** (2.6 g, 10.5 mmol) were dissolved in Me_2CO (7 mL, 0.5 M) and treated with $CpRu(MeCN)_3PF_6$ (76 mg, 0.18 mmol) then stirred for 20 min at rt. The reaction mixture was concentrated and purified by flash column chromatography (SiO_2, 1/9 to 1/3, Et_2O:pet ether) to afford **184** (1.49 g, 85%):

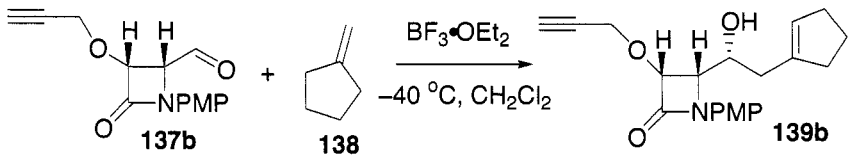
Thermally-Promoted Alder–Ene



(3*R*,3a*S*,4a*R*,6*R*,8a*S*)-3-Isopropenyl-2,2,6,9,9-pentamethyloctahydro-4aH-pyrrolo[2,1-*b*]benzoxazin-1(2*H*)-one (74b)[23]

General Procedure: A mixture of amide **73b** (15 mmol), K_2CO_3 (1 g) and PhMe (50 mL) was refluxed until the reaction was complete. The solvent was eliminated under reduced pressure and the residue was chromatographed on SiO_2 eluting with hexane/EtOAc to give **74b** as a colorless solid.

Lewis Acid-Catalyzed Intermolecular Alder–Ene with Aldehyde



(3*R*,4*S*)-3-Propargyloxy-4-[(*R*)-1-hydroxy-2(1-cyclopentenyl)-ethyl]-1-(*p*-methoxyphenyl)-2-azetidinone (139b)[37]

To a stirred solution of aldehyde **137b** (111 mg, 0.43 mmol) and methylenecyclopentane (2 mmol) in CH_2Cl_2 (10 mL) at –40 °C was added $BF_3 \bullet OEt_2$ (1.2 mmol) dropwise and the mixture was stirred at this temperature for 2 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (3 mL) and the mixture allowed to warm to rt before being partitioned between CH_2Cl_2 and water. The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure followed by flash chromatography (SiO_2; hexanes/EtOAc mixtures) yielded the ene adduct, 123 mg of **139b**, as a yellow solid.

1.1.1.9 References

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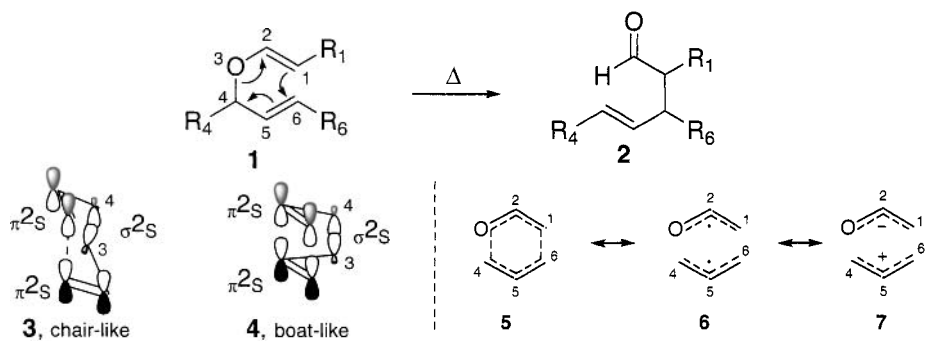
1.1.2 Claisen and Related Rearrangements

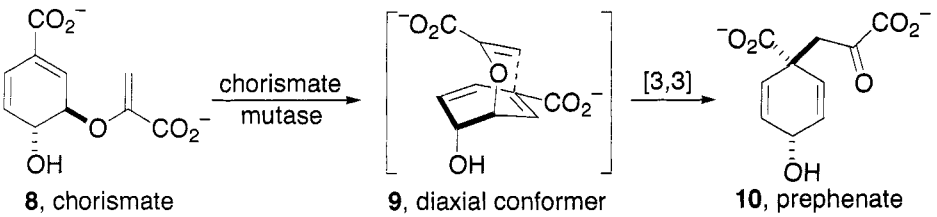
David R. Williams and Partha P. Nag

1.1.2.1 Introduction

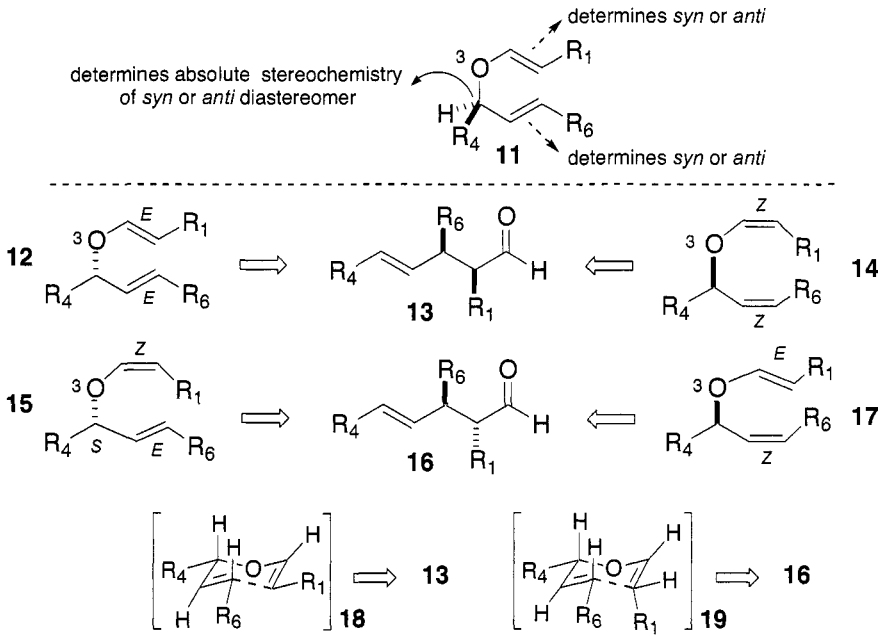
The Claisen rearrangement and its varients represent one of the most powerful C–C bond-forming transformations in organic synthesis.[1] The allyl vinyl ether structural motif **1** smoothly undergoes reorganization to the γ,δ-unsaturated carbonyl compound **2** under thermal or acid-catalyzed conditions. The [3,3]-sigmatropic reaction is a symmetry-allowed pericyclic process which proceeds via the six-membered closed transition state. Both chair and boat-like transition states (**3** and **4**) are suprafacial in nature [$\pi 2_S+\sigma 2_S+\pi 2_S$].[2] Research has been devoted to determine the rate accelerating effect of solvents and substituents at C_1, C_4 and C_6 which suggest the existence of a radical (**6**) or dipolar nature (**7**) of the transition state.[3] Gajewski has described labelling studies that suggests the bond breaking event may proceed prior to the bond making event thereby reinforcing the concept of radical character in an asynchronous reaction profile.[4]



The mechanism was studied extensively in the chorismate mutase-catalyzed conversion of chorismate **8** to prephanate **9**, an important intermediate for amino acid biosynthesis.[5]



One possible role for the enzyme may be to populate and provide electrostatic stabilization of the reactive chair conformer **19**. The outcome of the Claisen rearrangement can be predicted by evaluating three structural features. The alkene geometry of the allyl and the vinyl moieties will determine the outcome of *syn-* or *anti*-diastereoselection, and the stereogenicity at the allylic carbon determines an outcome featuring 1,3-chirality transfer.



One conclusion drawn from the analyses shows that simultaneous changes of the olefin geometries and the inversion of chirality of the carbon center will serve to generate the same product (as exemplified in **12** and **14**). Many variants of the Claisen rearrangement have emerged with broad synthetic applicability and operational advantages. These examples can be categorized based on structural features of the starting substrate as follows:

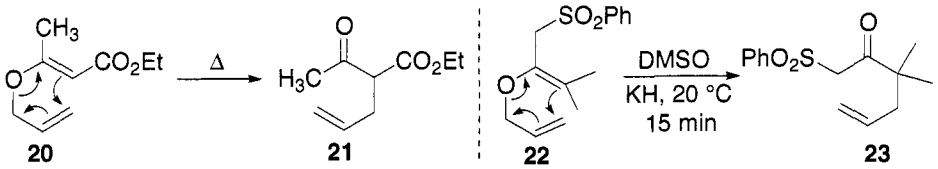
1) Aliphatic Claisen, aromatic Claisen and Saucy–Claisen;
2) Ester enolate Claisen, Ireland–Claisen, Reformatsky–Claisen, Corey–Claisen and Kazmaier–Claisen varients;
3) Carroll rearrangement;
4) Belluš–Claisen rearrangement;
5) Meerwein–Eschenmoser–Claisen rearrangement;
6) Orthoester Johnson-Claisen rearrangement; and
7) Thio-Claisen and aza-Claisen examples. Aza-Claisen process can be subdivided into zwitterionic aza-Claisen, amide enolate Claisen,

iminoketene Claisen example. This chapter will not undertake a comprehensive review, but serves to organize a conceptual summary of the many expressions of the Claisen process and its utility in synthesis.

1.1.2.2 *Aliphatic and Aromatic Claisen Rearrangement*[6]

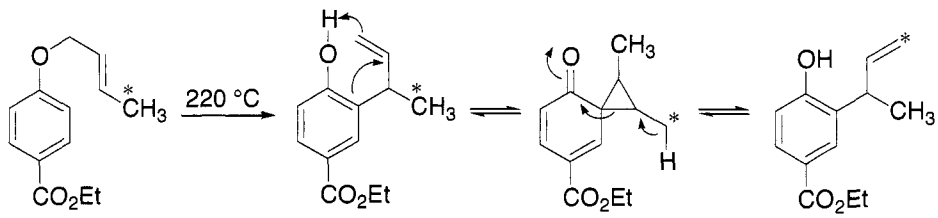
Description and Historical Perspective

In 1912, Claisen first observed the thermal rearrangement of *O*-allyl acetoacetate **20** to yield the γ,δ-unsaturated ketone **21**.[7] The reaction later proved to be general for a broad series of compounds which presented the allyl vinyl ether motif. Carpenter demonstrated that substituents have an important role in the reaction[8] and the presence of anionic π-donor as illustrated in (**22**) greatly accelerate the reaction as documented by Denmark.[9]



20 **21** **22** **23**

Allyl aryl ethers participate in this transformation and result in formation of *O*-allylphenol derivatives. The use of *ortho*-disubstituted allyl aryl ethers often leads to para-allyl arenes as the result of a subsequent Cope rearrangement to re-establish aromaticity. Lauer and Filbert recorded the "abnormal Claisen rearrangement"[10] as a key side reaction for the aryl variant.[11] As proposed by Marvell,[12] the initially formed phenol **25** undergoes a hydrogen transfer involving the formation of the spiro intermediate **26**. The reverse process gives rise to the cleavage of the cyclopropane and production of the isomeric product **27**. Proof of the hypothesis came from the elegant labelling experiment which shows equal isotopic distribution in the case of **25** and **27**.[13]

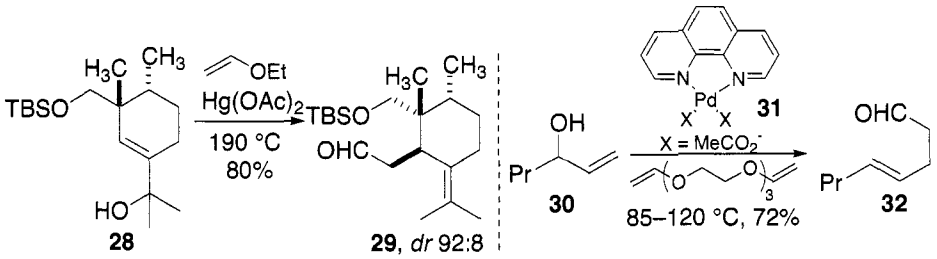


24 **25** **26** **27**

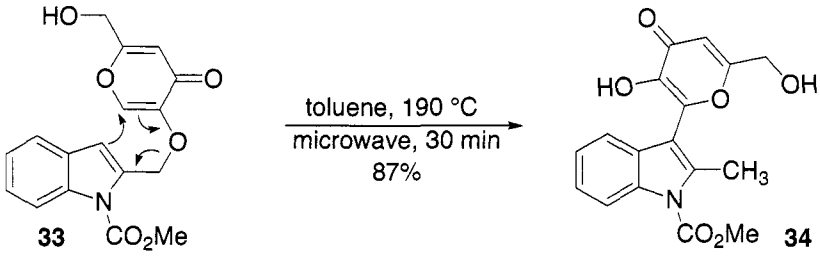
Synthetic Utility

General Utility

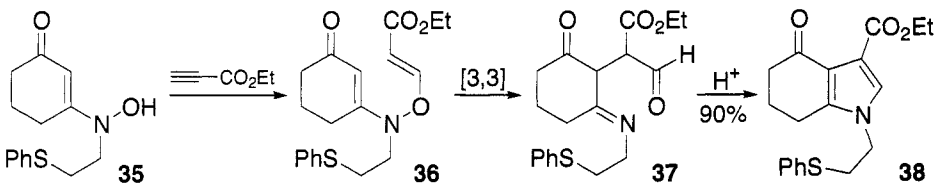
One of the traditional methods for applications of the aliphatic Claisen rearrangement has used Mercuric salts to prepare vinyl ether as illustrated in the use of the allylic alcohol (**28**) en route to aldehyde **29**.[14] The chemical development group at Boehringer–Ingelheim has developd a mild palladium acetate–phenanthroline catalyst **31** for the sequential allyl vinyl ether–Claisen process utilizing commercially available triethyleneglycol divinyl ether which avoids the use of mercuric acetate.[15]



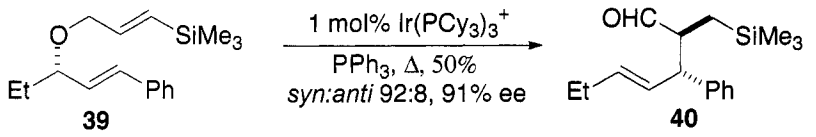
The aromatic Claisen rearrangement has been utilized to synthesise many novel heterocycles[6] as exemplified by the conversion of **33** to biaryl **34**, the core of demethylasterriquinone, which is important in the treatment of diabetes.[16]



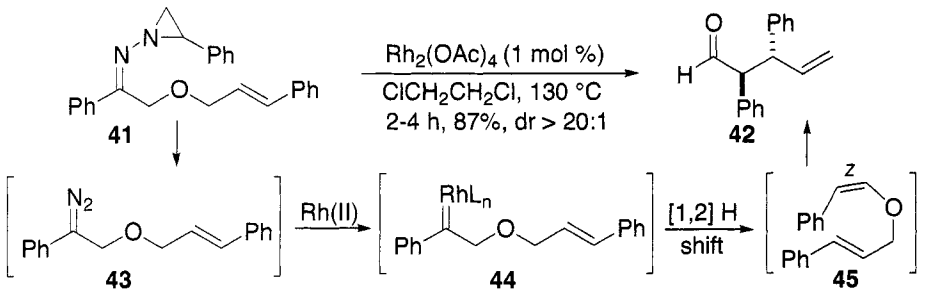
Vedejs has reported an oxaza-Claisen rearrangement to construct the pyrrole derivative **38**. In presence of ethyl propiolate, the vinylogous hydroximic acid **35** undergoes a conjugate addition followed by sigmatropic rearrangement to produce the aldehyde **37**. Cyclization and dehydration resulted **38**.[17]



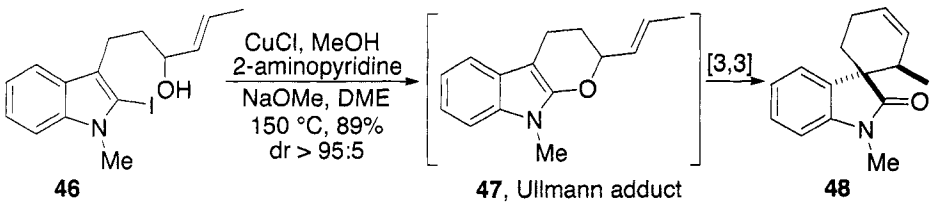
Nelson has recently introduced an example of the Ir(I)-catalyzed olefin isomerisation followed by the Claisen rearrangement for the conversion of bis-allylic alcohol **39** to aldehyde **40**.[18]



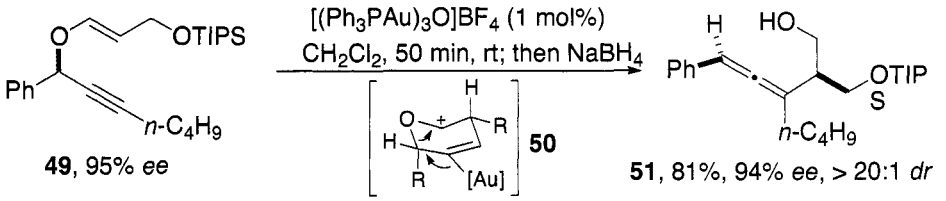
Stoltz and May have described a tandem process involving the rhodium-catalyzed Bamford Stevens reaction and the Claisen rearrangement. Rhodium carbenoid **44** undergoes a facile stereoselective 1,2-hydride migration to generate the allyl vinyl ether **45** which rearranges to aldehyde **42** with high diastereoselectivity.[19]



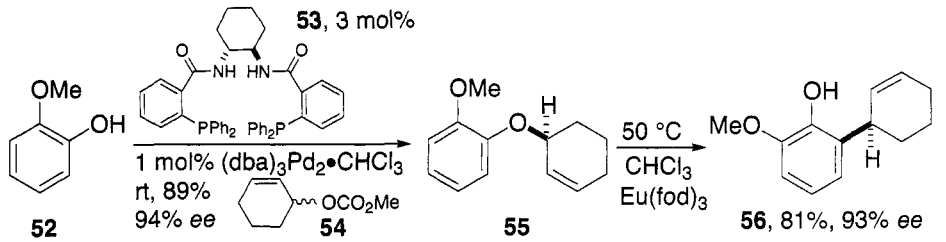
The construction of allyl vinyl ether **47** via an Ullmann coupling was followed by the Claisen rearrangement to deliver oxindole derivative **48** as reported by Kobayashi and co-workers.[20]



The gold-catalyzed rearrangement of vinyl propargyl ethers such as **49** was reported by Toste and Sherry. The intermediate oxonium **50** was initially formed via a 6-*endo-dig* cyclization with the propargylic substituent occuping a pseudoaxial orientation to avoid $A^{1,2}$-strain with the alkenyl gold moiety. Allenic aldehyde **51** was then formed as **50** collapsed via a fragmentation pathway.[21]



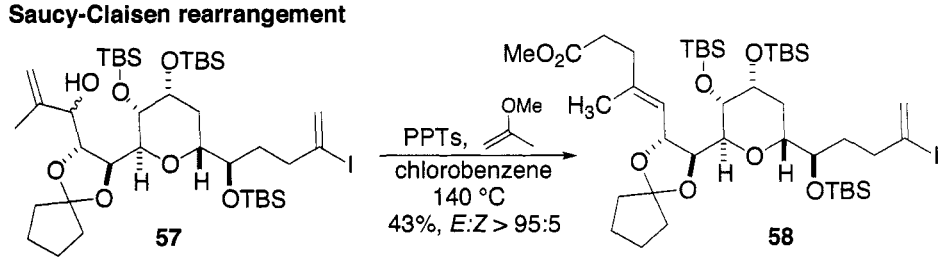
Trost and Toste have utilized asymmetric alkylation method to generate the nonracemic allyl aryl ether **55** which undergoes a facile Claisen rearrangement in presence of $Eu(fod)_3$ to produce **56** with complete chirality transfer.[22]



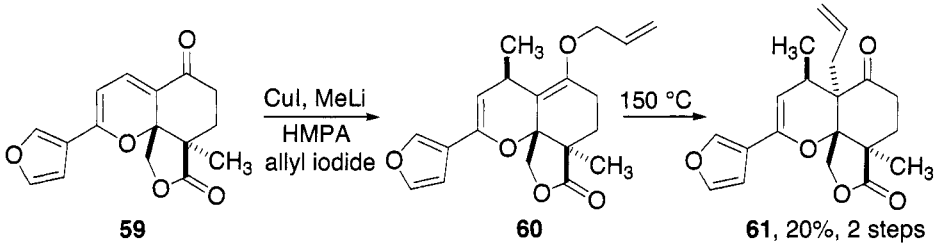
Applications in the total synthesis of natural products

The Claisen rearrangement has routinely been applied in natural product synthesis for the construction of *E*-trisubstituted olefins.[6] For example, at high temperature, the allyl vinyl ether, generated by Saucy exchange conditions from alcohol **57**, resulted in *E*-alkene **58** with excellent diastereoselectivity.[23]

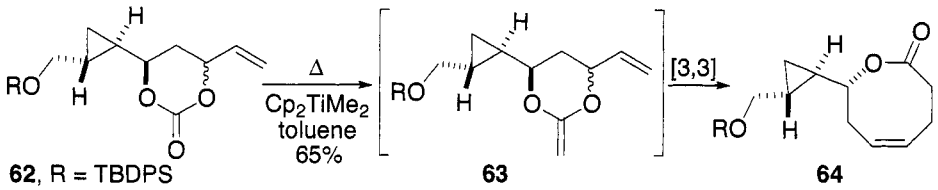
Saucy-Claisen rearrangement

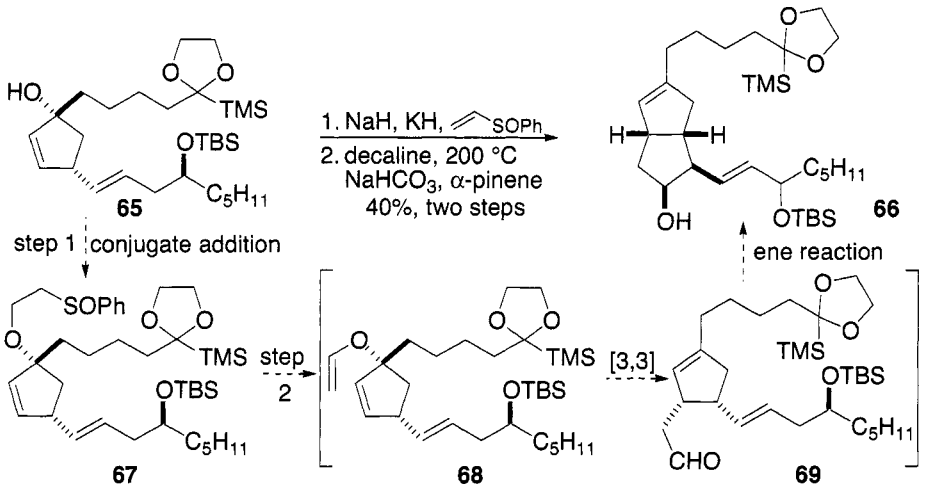


The Claisen rearrangement has also been routinely exercised for the stereocontrolled construction of quaternary carbon centers.[6] For example, the conjugate addition of methyl cuprate to vinylogous ester **59** followed by *in situ* trapping of the enolate with allyl iodide gave the allyl vinyl ether **60**, which was utilized for Claisen rearrangement to furnish **61** as a single diastereomer.[24]



White has reported the use of the Claisen rearrangement to implement a ring expansion strategy from the ketene acetal **63** which was generated from cyclic carbonate **62** via Petasis conditions yielding the lactone **64**.[25]

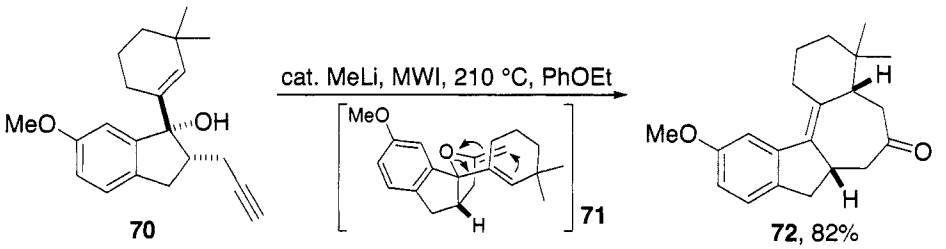




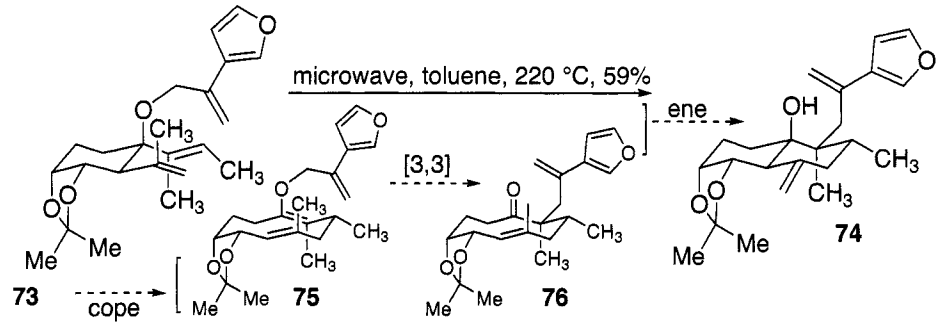
Another useful construction of the allyl vinyl ether motif is illustrated by the reaction of alcohol like **65** with vinyl sulfoxide followed by thermal *syn*-elimination. The subsequent Claisen rearrangement of **68** yielded

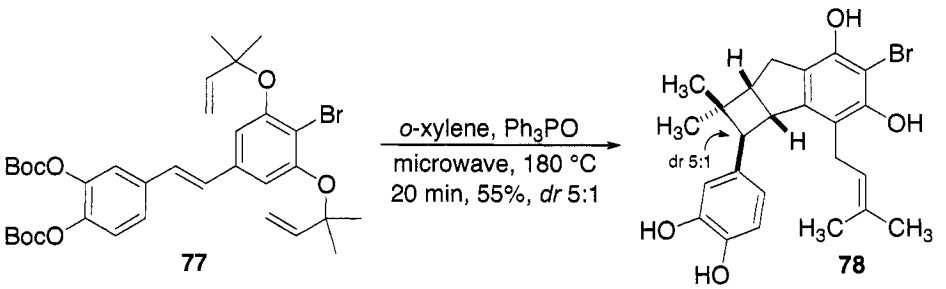
aldehyde **69** which participated in an ene reaction to deliver bicyclic alcohol **66**.[26]

The emergence of microwave techniques has led to applications of Claisen transformations which were otherwise difficult to accomplish. A base-catalyzed 5-*exo*-dig cyclization followed the Claisen rearrangement has been reported by Ovaska for construction of ketone **72** from alcohol **70** under microwave conditions.[27]



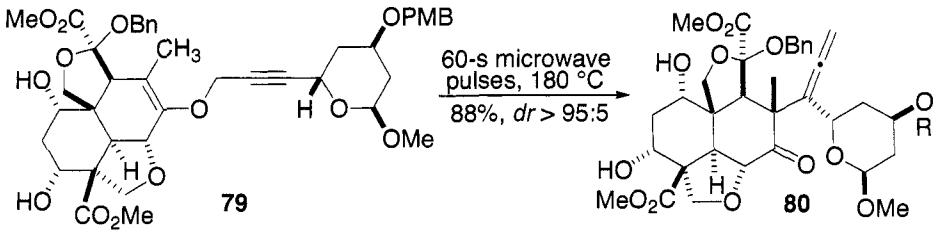
Similarly the substituted decalin **74** was obtained in good yield by the microwave irradiation of **73**. The reaction proceeds via an initial Cope rearrangement to generate the allyl vinyl ether **75** for subsequent [3,3]-sigmatropic transformation to ketone **76**. Transannular ene cyclization yielded the product **74**.[28]



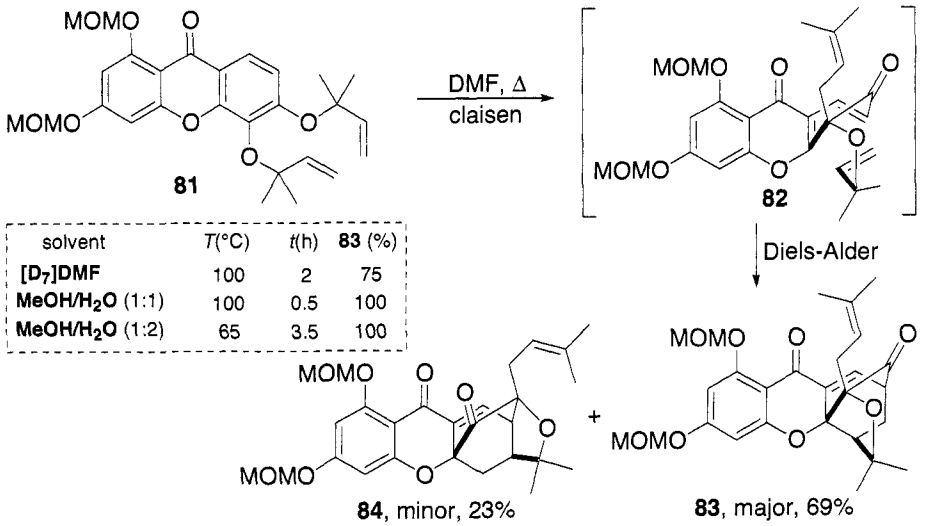


Nicolaou has recently reported the use of microwave irradiation for the Claisen rearrangement of **77**. The rearrangement product then underwent a [2 + 2] cycloaddition and loss of Boc protecting groups to produce the bicyclo[3.2.0]heptane derivative **78**.[29]

When repeated attempts failed to accomplish the Claisen rearrangement of **79** to allenyl ketone **80**, Ley and co-workers relied on microwave irradiation to address this challenging bond construction. When **79** was irradiated with fifteen consecutive sixty second microwave pulses, a reaction proceeded to give a single diastereomer of the allene with excellent yield.[30]



Nicolaou observed a strong solvent dependent rate enhancement in the case of the Claisen rearrangement followed by a Diels–Alder reaction cascade in the conversion of xanthone derivative **81** to **83**.[31] Isomers **83** and **84** were formed and the rate of the formation of **83** was examined. Reactions were completed at lower temperature and in shorter time using aqueous methanol solvent as compared to DMF. The ratio of **83** to **84** (3 : 1) remained constant throughout the course of the rate study. This observation supports previous literature findings which describe the role of hydrogen bonding in the rate acceleration for the Claisen rearrangement.[32]

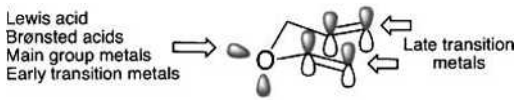


solvent	*T*(°C)	*t*(h)	**83** (%)
[D_7]DMF	100	2	75
MeOH/H_2O (1:1)	100	0.5	100
MeOH/H_2O (1:2)	65	3.5	100

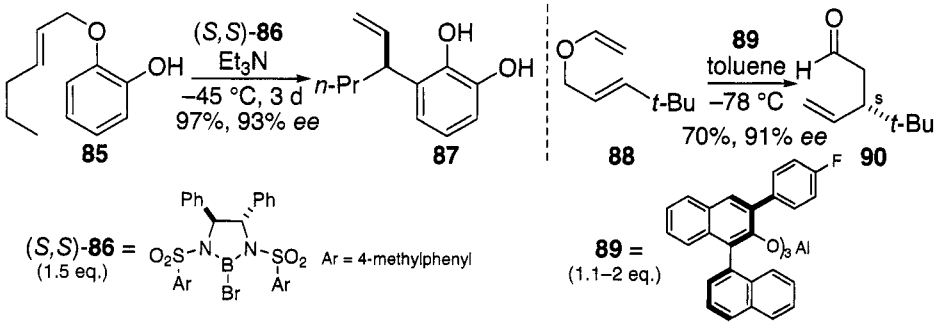
Enantioselective Claisen Rearrangement

The development of a catalytic enantioselective variant of the Claisen rearrangement is an important topic for organic synthesis. Investigations of the use of nonracemic Lewis acids have been undertaken to achieve this goal. The mode of actions for these catalysts can be classified into two categories based upon their reactivity with the allyl vinyl ether moiety. Lewis acids, Brønsted acids, main group metals and early transition metals target the Lewis basic oxygen center to invoke electron-deficiency whereas late transition metals interact with the alkene components.[33]

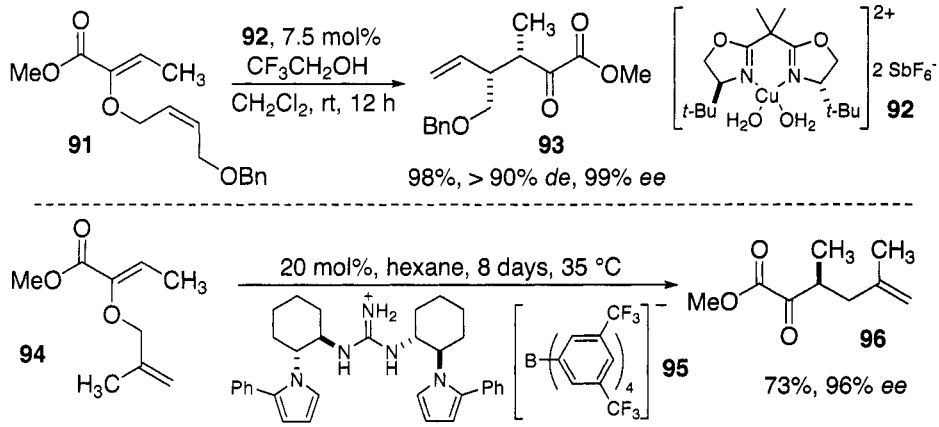
Concept: point of attachment for catalysts



Taguchi has utilised **86** for the enantioselective aromatic Claisen rearrangement[34] whereas Yammoto has reported the successful use of **89** in the aliphatic Claisen process.[35] These early results are encouraging but both examples required more than a stoichiometric amount of the chiral promoters. Successful realization of a catalytic asymmetric Claisen rearrangement has been reported by Hiersemann.[36] In presence of 7.5 mol% of the catalyst [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$ (**92**), allyl vinyl ether **91** undergoes the Claisen rearrangement to produce ketoester **93** with impressive enantio- and diastereochemical selectivity.[37] Computational studies by Balta and Aviyente have proposed that the reaction proceeds through a chair-like arrangement and describe the steric interactions between catalyst and substrate which contribute to the facial selectivity.[38]



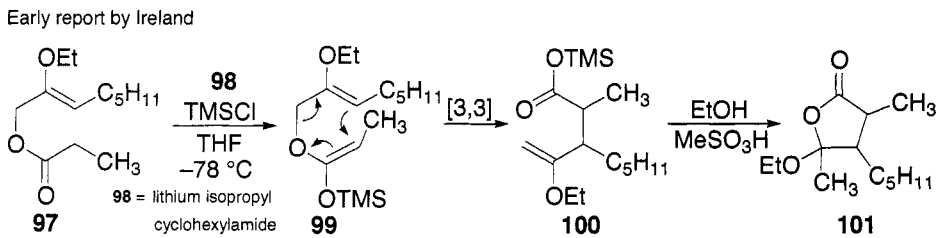
Recently, Jacobson reported an organocatalytic version[39] of the Claisen process where guadinium derivative **95** efficiently promoted the reaction of **94** to generate ketoester **96** with high enantioselectivity.[40]



1.1.2.3 Ester Enolate and Ireland-Claisen Rearrangement

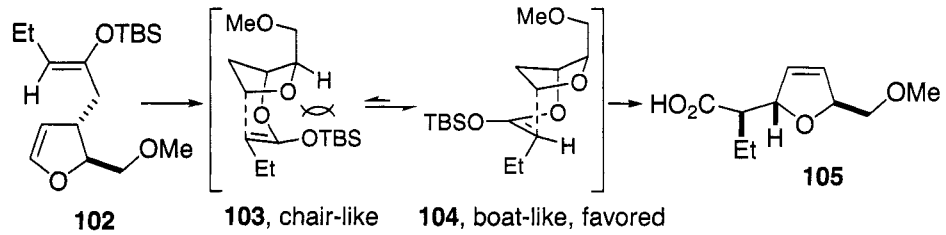
Description and Historical Perspective

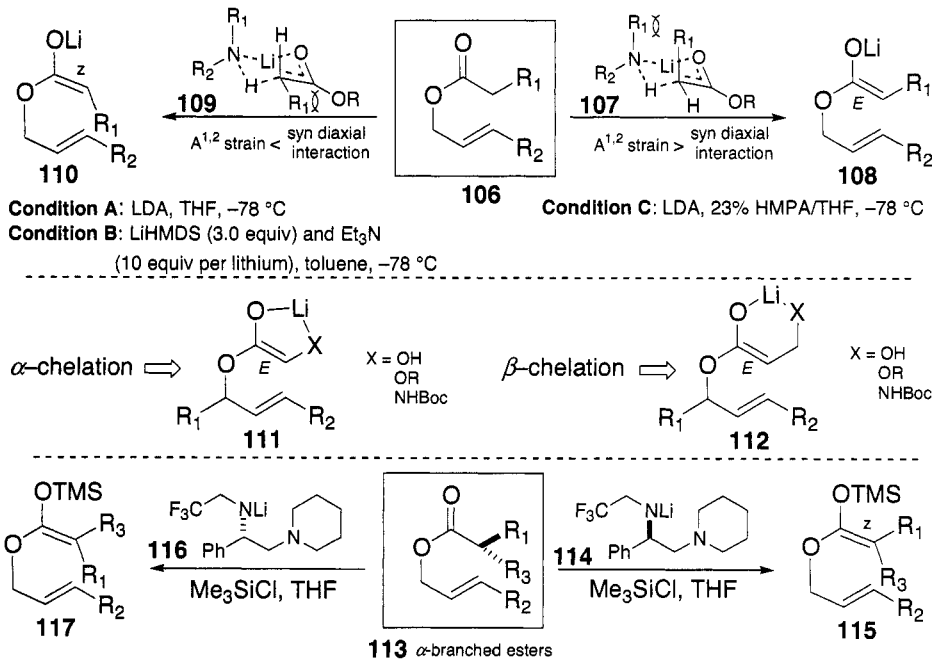
In the seminal paper of 1972, Ireland first described the low temperature enolization of ester **97** with lithium isopropylcyclohexylamide followed by trapping with trimethylsilylchloride to efficiently generate silyl ketene acetal **99**.[41] Unlike the behavior of the initial lithium ester enolate, **99** did not participate in side reactions upon warming to ambient temperature, and smoothly rearranged to **100** which yielded **101** upon treatment with mild acid.



This modification of the Claisen rearrangement has been widely utilized because of its operational efficiency and mild condition.[42] An estimated of 10^6 rate acceleration compared to the parent allyl vinyl ether was observed. Gajewski and Emrani have described elegant deuterium labelling studies that suggest bond breaking event may precede the bond

making event in the transition state.[4] For acyclic cases, reactions occur via chair-like transition states resulting in 1,3-chirality transfer. For cyclic cases conformational constraints may produce boat transition states. For example, ketene acetal **102** undergoes the Ireland–Claisen rearrangement to yield carboxylic acid **105** via boat like arrangement **104**.[43]





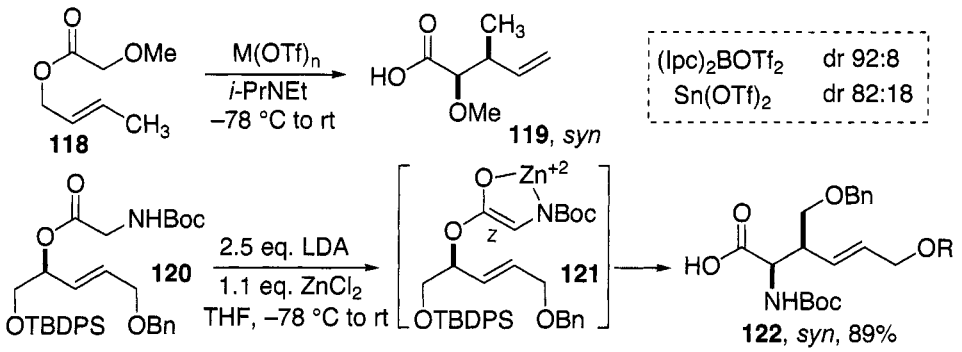
Control of the *E/Z*-geometry of the ester enolate is an essential factor for the overall diastereoselection of the process. Generally the *Z*(O)-lithium enolate **110** is observed with LDA in THF at low temperature.[44] Similar results are obtained with LHMDS–Et_3N in toluene at –78 °C as recently described by Collum.[45] The alternative *E*(O)-enolate **108** was preferentially formed with LDA in a solvent mixture of 23% HMPA/THF.[44] The presence of chelating ligands like HMPA coordinate with lithium cation resulting in a lengthening O–Li distance. As a result, the *syn*-diaxial interaction of R_1 and

the *N*-substituent of the amide is less severe as compared to the $A^{1,2}$-strain of **109**. For compounds presenting α or β-coordinating substituents, preferential formation of the *E*(O)-enoalate is observed with cation chelation (**111** and **112**).[46] Recently, Zakarian disclosed a protocol for stereoselective enolate formation of α-branched esters **113** using the nonracemic base **114**.[47]

Synthetic Utility

General Utility

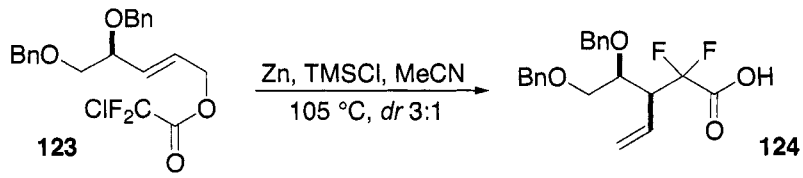
Claisen rearrangement of lithium ester enolates which display characteristics of intramolecular chelation often proceed with reduced yields and the production of side products. Investigators have examined alternative metal cations or Lewis acids which offer increased stability, such as **121**, and improvements of efficiency and yield.[48]



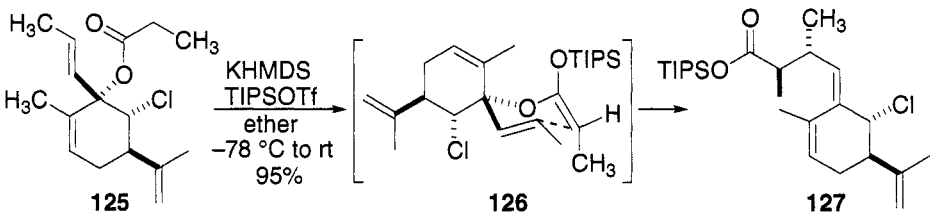
The α-chelation of a metal cation results in the formation of the *Z*(O)-enolate and the participation of *E*-alkene in the [3,3]-process leads to the *syn*-stereoselectivity in the major product. In examples of α-alkoxy substitution, enolate coordination with boron triflates appears to provide the best results.[49] Fused $ZnCl_2$ is the reagent of choice in cases of α-amido substrates.[50]

Ester enolate have been generated under dissolving metal conditions with the reduction of α-halo carbonyl compounds. For example, the use of freshly activated Zn dust following Reformatsky protocol[51] leads to the Claisen rearrangement of zinc enolate derived from **123** to yield acid **124**.[52]

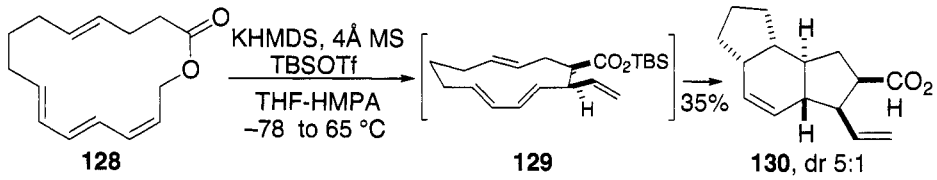
Reformatsky-Claisen rearrangement



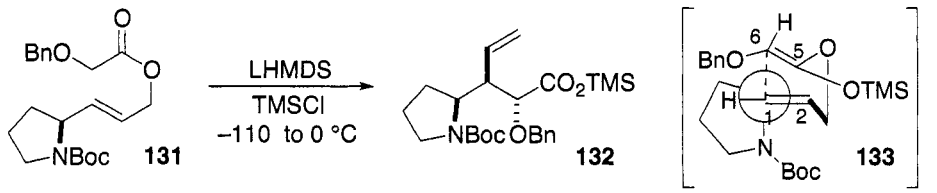
McIntosh has recently reported the Ireland–Claisen rearrangement of the substituted bis-allylic ester **125**. The reaction proceeds via the chair-like arrangement **126**, which avoids steric repulsion between *O*-silyl moiety and neighboring choro substituent. The facile reaction generates trisubstituted *exo*-alkene **127** in high yield excellent diastereoselection.[53]



Roush has executed the Ireland–Claisen ring contraction of the tetraene macrolactone **128** to generate an intermediate diene **129** which subsequently participates in a transannular cycloaddition reaction to afford the tricyclic acid **130**.[54]

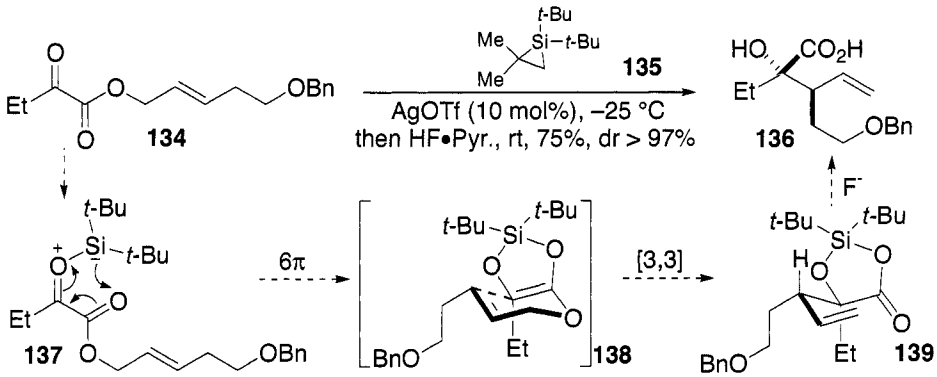


Mulzer has observed a stereoelectronic preference in the Ireland-Claisen rearrangement of **131** which led to a single diastereomer of product **132**.[55] Frontier molecular orbital analysis validates the proposed transition state **133**, where the predisposed arrangement of the enamine secures a favorable interaction between C–N σ* and π* of alkene effectively lowering the LUMO energy of this conformation.[56]

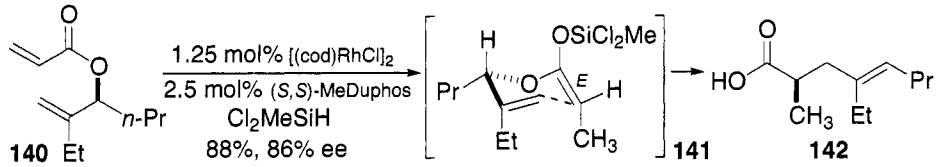


The α-ketoester **134** participates in a novel metal-catalyzed silylene transfer in the presence of silacyclopropane to generate silacarbonyl ylide **137** which undergoes 6π-electrocyclization to provide the silylketene acetal **138**. Subsequent [3,3]-sigmatropic rearrangement proceeds via the chair-like

transition state **138** to yield silalactone **139**. Hydrolysis produces the α-hydroxyacid **136** with excellent diastereoselection.[57]

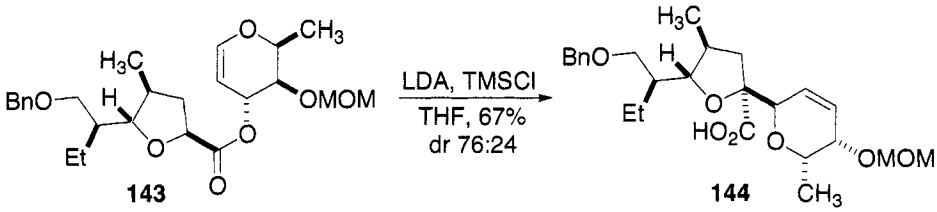


Morken has recently disclosed a Rh-catalyzed stereoselective enolization technique for the transformation of the conjugated ester **140** into the *E*-silylketene acetal utilizing dichloromethylsilane as a reducing agent. Intermediate **141** undergoes the Ireland–Claisen rearrangement to yield **142**.[58]

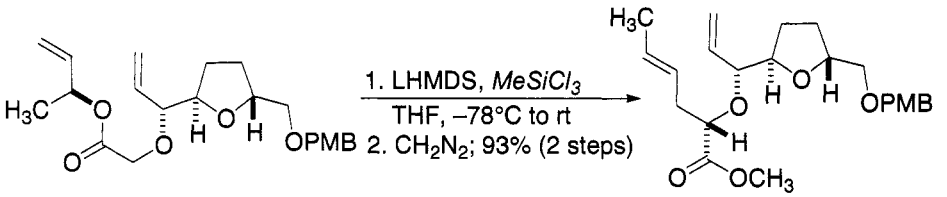


Applications in the total synthesis of natural products

The initial synthetic applications of the ester enolate Claisen rearrangement were reported from the Ireland group.[59] Silyl ketene acetal generated from **143** readily rearranged to the carboxylic acid **144** in moderate yield and diastereoselectivity. The product **144** was subsequently elaborated for the completion of the total synthesis of lasalocid A.[60]

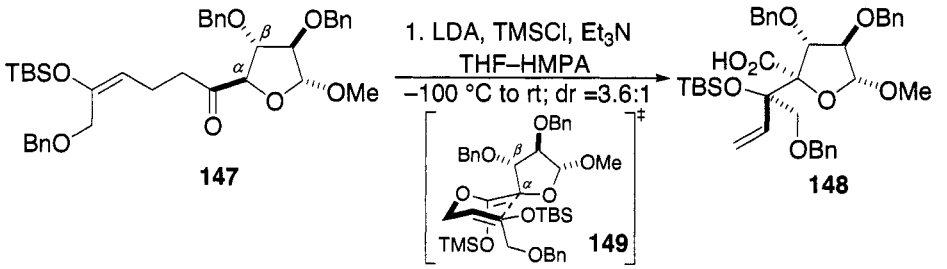


A chemoselective Ireland–Claisen rearrangement has been reported by Fujiwara and co-workers. Methyl trichlorosilane was essential for the success of this transformation by suppressing the [2.3]-Wittig rearrangement pathway. The reaction yields **146** as a single diastereomer after esterification.[61]



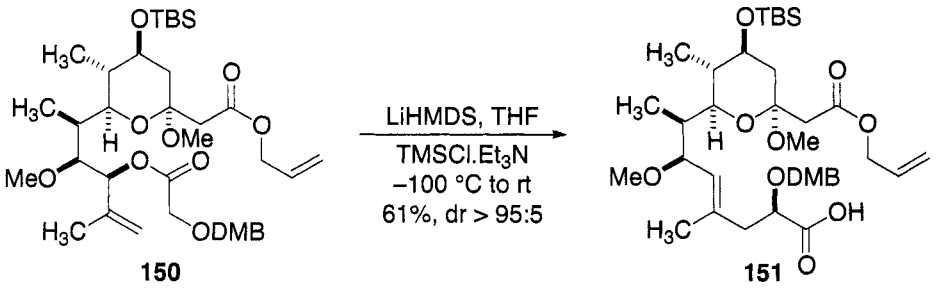
145 **146**

In course of studies toward the synthesis of (+)-zaragozic acid C, Rizzacasa has described the Ireland–Claisen rearrangement of **147** which incorporates a benzyloxy substituent at the β-position. To avoid elimination, enolization is conducted at –100 °C and (*Z*)-enolate was preferentially formed due to chelation. The reaction proceeds via a chair-like arrangement to yield **148** with moderate diastereoselectivity.[62]



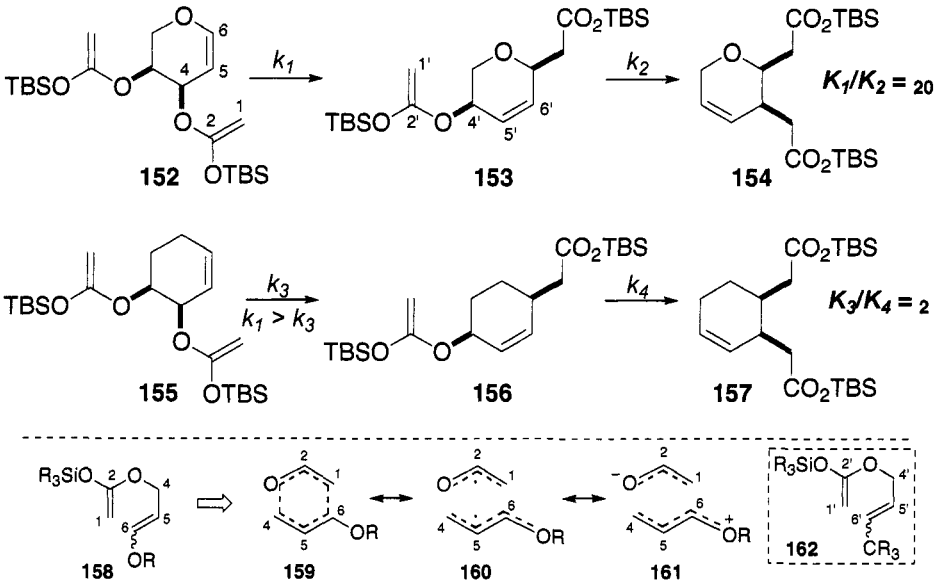
147 **149** **148**

Evans relied on the Ireland–Claisen rearrangement for the construction of the trisubstituted *E*-alkene in **151** during studies toward the synthesis of callipeltoside A. Under standard conditions, **150** smoothly rearranged to yield **151** as a single diastereomer.[63]

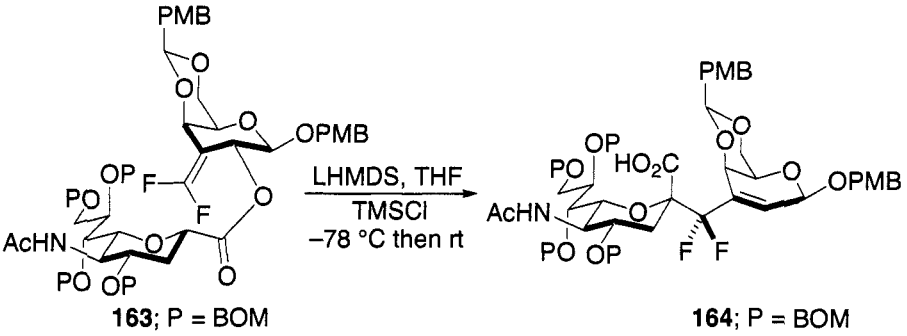


150 **151**

Curran proposed a "vinylogous anomeric effect" concept[64] to explain the observed rate difference of the Ireland–Claisen rearrangements of dihydropyran **152** and cyclohexene system **155**. Oxygen attached to C_6 is proposed to stabilise the polar Ireland–Claisen intermediates **160–161** which contribute to a faster rate of reaction.[65]

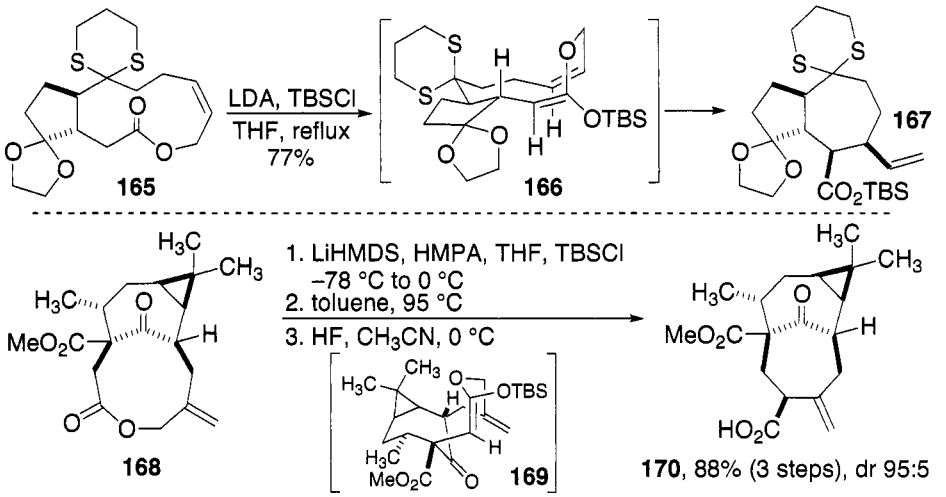


Sodeoka has utilized a stereoselective Ireland–Claisen rearrangement to prepare the CF_2-linked ganglioside GM4. When ester **163** was subjected to the Ireland conditions, one diastereomer **164** was obtained with installation of the difluromethylene bridge.[66]

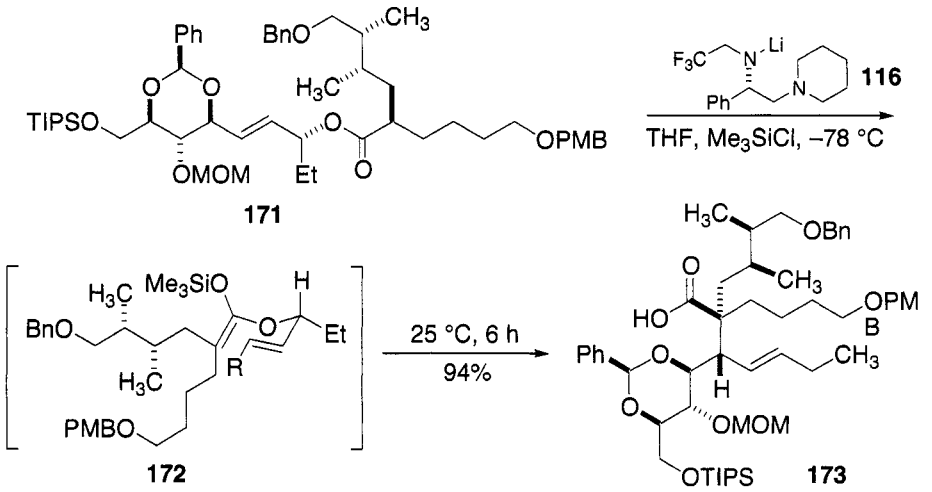


The Ireland–Claisen rearrangement has been used as a ring contraction event. Knight and coworkers[67] reported the construction of the seven-membered ring in **167** from eleven-membered lactone **165** whereas

Funk[68] successfully constructed the core of ingenol **170** beginning with the nine-membered lactone **168**. These elegant applications of the reaction are characterized by good yields and in high diastereoselectivity.

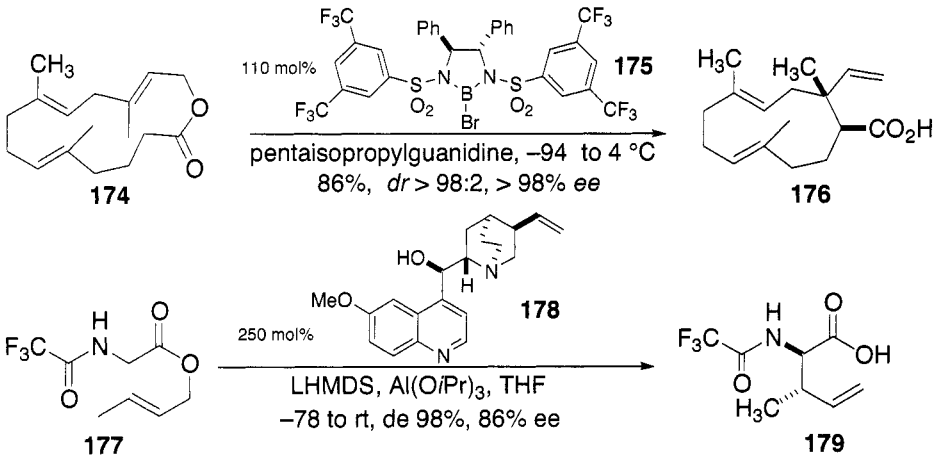


Zakarian has applied his protocol with the stereoselective generation of the silyl ketene acetal **172** beginning with the branched ester **171**. The carboxylic acid **173** was isolated as a single diastereomer in excellent yield en route to the total synthesis of to (+)-pinnatoxin A.[69]



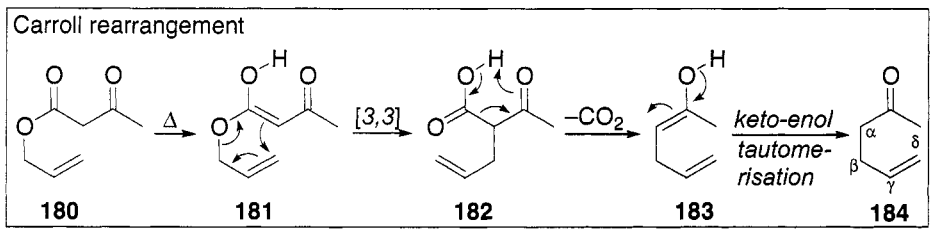
Enantioselective ester enolate-Claisen Rearrangement

Some advancement has been described for the development of a catalytic enantioselective ester enolate Claisen rearrangement. The strong Lewis basic carboxylate functionality present in the Claisen product effectively coordinates with Lewis or Brønsted acids prohibiting the catalytic turnover. Corey has reported the use of stoichiometric bromoborane **175** to generate chiral boron enolate which undergoes [3,3]-sigmatropic rearrangement to yield **176**.[70] Kazmaier relied on excess quinidine **178** to provide for asymmetric induction in the conversion of **177** to amino acid **179**.[71]



1.1.2.4 Carroll Rearrangement

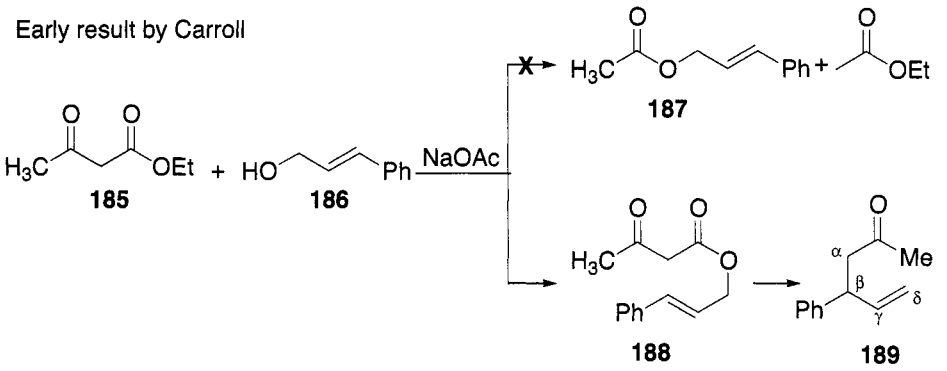
Description



The Carroll rearrangement[72] involves thermal- or base-mediated [3,3]-sigmatropic rearrangement of a β-keto allyl ester (**180**) to a γ,δ-unsaturated ketone (**184**). The reaction passes through the isolable β-keto carboxylic acid (**182**) that readily decarboxylates to give rise to the enol **183** which tautomerises to the more stable ketone.

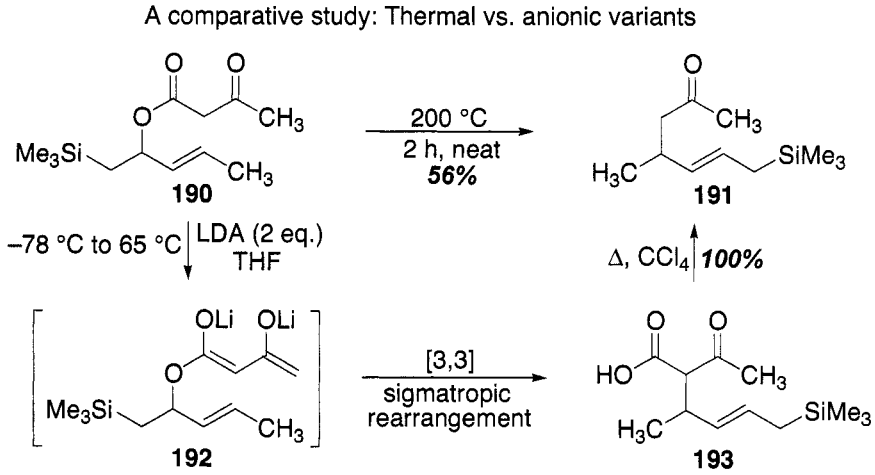
Historical Perspective

In 1940, the reaction was unexpectedly discovered by M. F. Carroll[73] while attempting the acetylation of various allylic alcohols. When cinnamyl alcohol (**186**) was treated with ethyl acetoacetate (**185**) in the presence of catalytic sodium acetate, the anticipated acetate **187** was not formed via a retro-Claisen condensation. However, the methyl ketone **189** was isolated.



Although Carroll identified the production of cinnamyl acetoacetate (**188**), the detailed mechanistic rationale was later provided by W. Kimel and Arthur C. Cope in 1943.[74] The proposal invoked a pathway similar to the Claisen rearrangement. In 1968, Hill and Synerholm proved this hypothesis to be correct and studied the stereospecificity of the reaction.[75]

Variations and Improvements

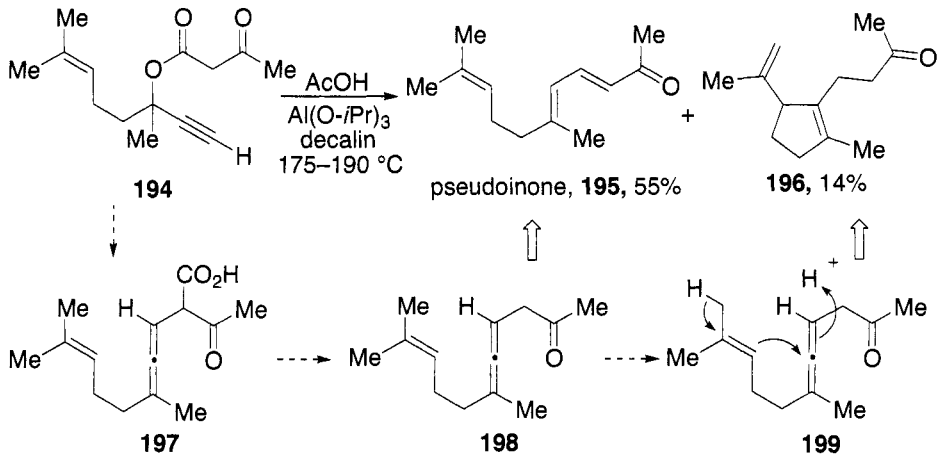


Wilson and Price reported that dianions of allylic acetoacetates, which are generated using 2 equivalents base, rearranged at room temperature or in refluxing THF in high yield.[76] This mild method allowed for the isolation of the intermediate β-keto acid and proved to be superior to the harsh pyrolysis conditions used in the early studies. The observation of poor yields of the ketone **191** at high temperature can be overcome by treating acetoacetate **190** with LDA (2.0 equiv) at –78 °C. The resulting dienolate smoothly rearranged in refluxing THF to keto-acid **193** which readily underwent decaboxylation to the ketone **191** in quantitative yield.

Synthetic Utility

General Utility

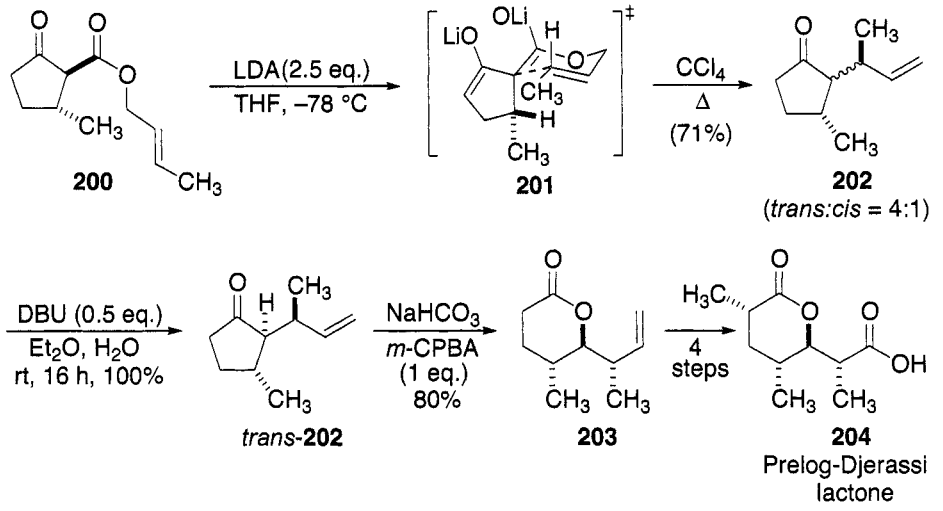
The accessibility of nonracemic allyl acetoacetates makes the Carroll rearrangement an attractive strategy to assemble molecular complexity with adjacent tertiary and quaternary stereocenters.[77] In the late 1950s, researchers at Hoffmann–La Roche utilised propargylic acetoacetate **194** to synthesise pseudoinone **195**.[78] Pyrolysis in the presence of Brønsted acid initiated the Carroll rearrangement to yield allenyl ketone **198** which tautomerised to pseudoinone **195**. The minor product **196** resulted from Brønsted acid-mediated π-cation cyclisation of **199**.



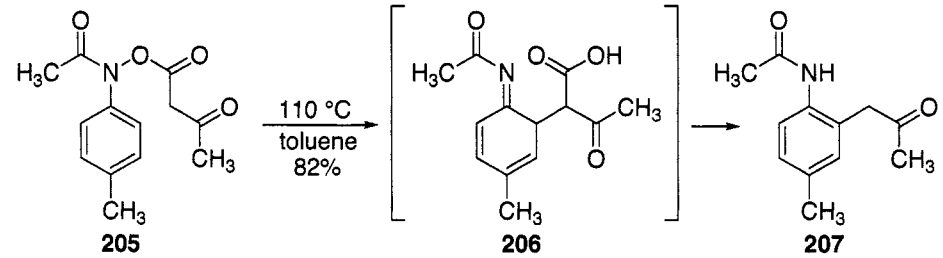
Rodriguez and co-workers envisioned the Carroll rearrangement as the key step in the preparation of the Prelog–Djerassi lactone **204**. The dienolate of **200** conveniently rearranged via a chair-like transition state **201** to the β-keto acid which underwent decarboxylation to give a 4:1 mixture of cyclopentanone epimers.[79] Epimerization under thermodynamic conditions

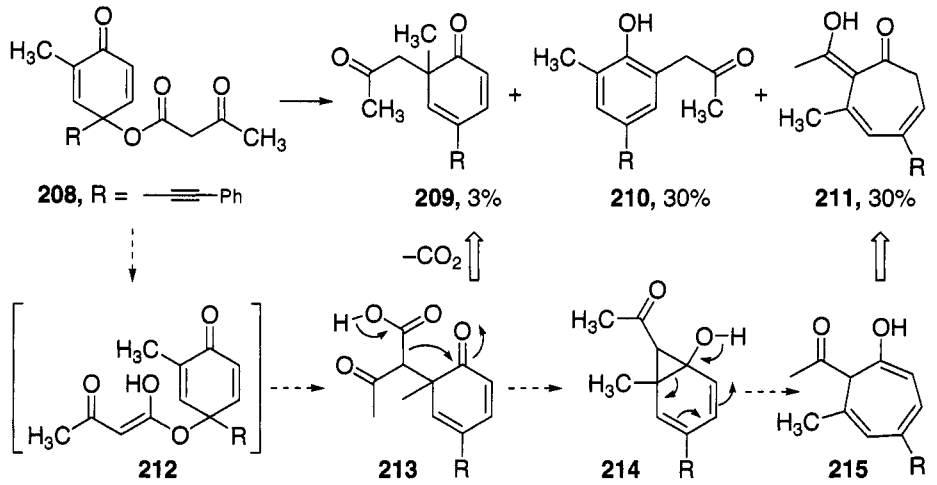
resulted in the *trans* adduct **202** and Baeyer–Villiger oxidation revealed the lactone **203** which was subsequently transformed to the target compound.

The Carroll rearrangement is also an effective procedure for the synthesis of functionalised aromatic compounds. The efficient Carroll rearrangement of *N,O*-diacylarylhydroxylamine **205** in refluxing toluene is an example generating the aryl ketone **207**.[80] In this study, Coates and Said exploited the lower N–O bond energy to facilitate the bond breaking event during the course of the reaction.



Hetero-Carroll rearrangement

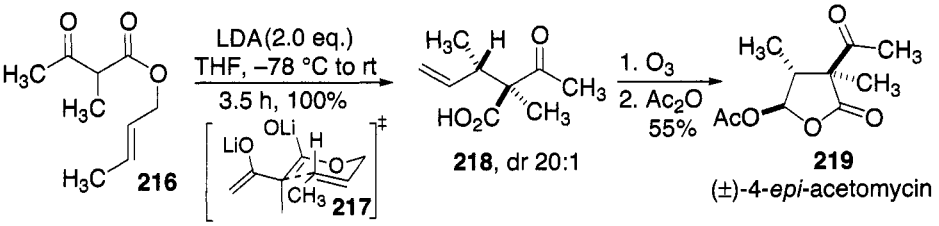


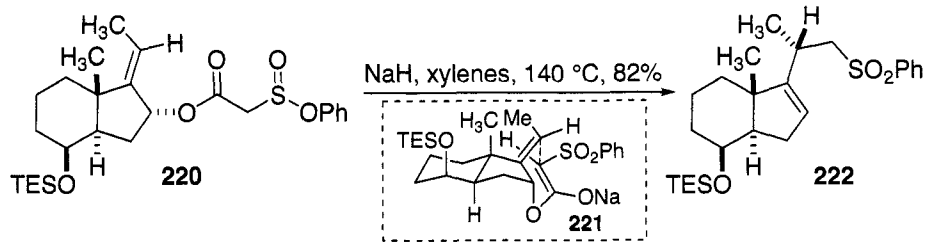


Sorgi and co-workers have shown that *p*-quinol acetoacetate (*in situ* generated from *p*-quinol, diketene and cat. DMAP) undergoes the Carroll rearrangement to provide aryl acetone derivatives.[81] Compound **208** was examined to study the regiochemical preference of the rearrangement. The reaction proved to be non-selective yielding a 10:1 mixture of aryl ketone **210** (non-substituted) and 1,4-diketone **209** (substituted). Ketone **211** arose from the initial Carroll rearrangement via **212** and decarboxylation led to enol formation which participated in an intramolecular aldol condensation followed by ring expansion to furnish **211**.

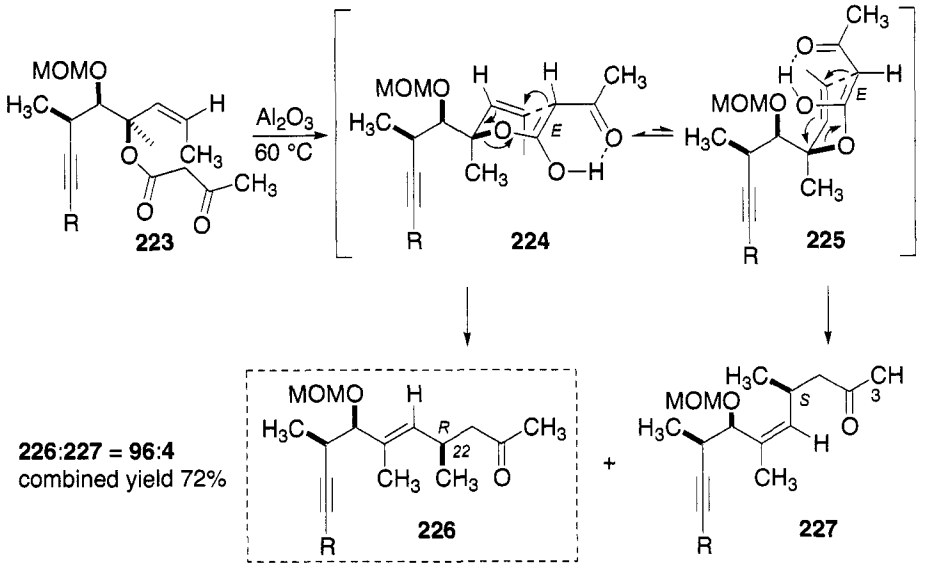
Applications in the total synthesis of natural products

Eschavarren and co-workers used the Carroll rearrangement as the key step for the total synthesis of (±)-4-*epi*-acetomycin. The dianaion of acetoacetate **216** underwent rearrangement to give the keto acid in quantitative yield. The excellent stereoselectivty of the process can be explained by the chair transition state **217**. Ozonolysis of the olefin followed by acetylation gave the target molecule **219** with high diastereoselection.[82]





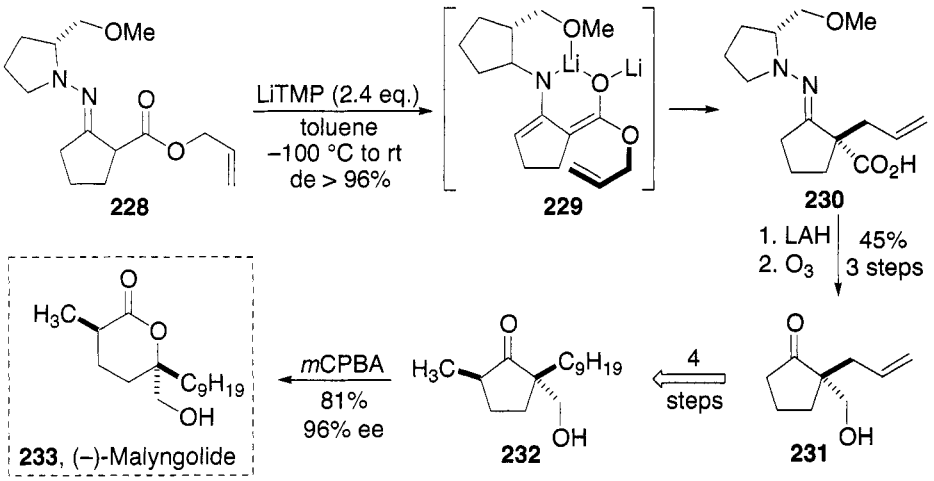
In the course of the synthesis of vitamin D analogues, it has been shown that allylic α-sulfonyl acetates are effective structural motifs (like allylic acetate) to facilitate the Carroll rearrangement. When sulfonyl ester **220** was treated with NaH in refluxing xylene, sulfone **222** was obtained in excellent yield and diastereoselectivity.[83] The reaction presumably passes through the chair transition state **221** in which the sulfone and methyl groups occupy a pseudoequatorial positions.



In studies of the total synthesis of zincophorin, Cossy and coworkers devised an impressive Carroll rearrangement strategy to construct the trisubstituted *E*-olefin and install the C_{22}-methyl stereocenter in one step.[84] Thermal and anionic conditions resulted in elimination reactions (conjugated diene) due to the tertiary nature of the allylic alcohol in the starting acetoacetate **223**. Adsorption of **223** on neutral alumina followed by heating the dry powder at 60 °C gave the desired diastereomer **226** in good yield with excellent diastereoselection. The Carroll rearrangement presumably proceeds

through the favored transition state **224** where the functionalized alkyl chain occupies the equatorial position.

Asymmetric Carroll Rearrangement

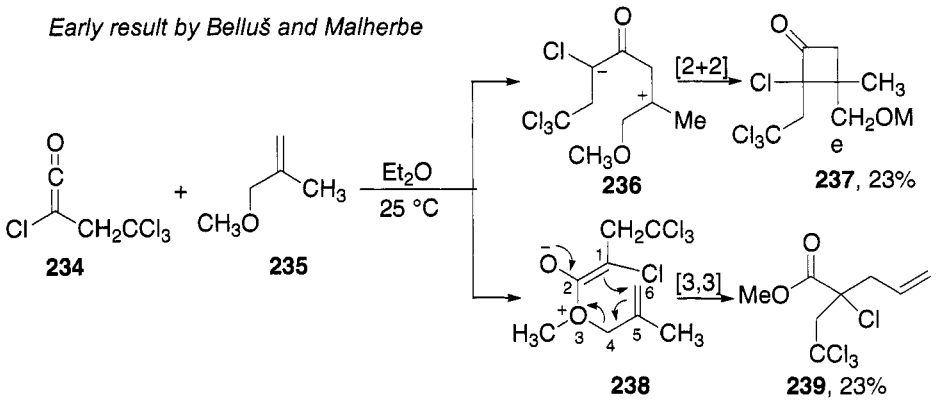


An asymmetric variant of the Carroll rearrangement has been developed in the Enders laboratory based on the RAMP/SAMP hydrazone chiral auxiliary. Successful realisation of this technique was implemented later in the total synthesis of (–)-malyngolide.[85] RAMP derived β-hydrazono ester derivative **228** was treated with LiTMP to generate the highly organised dianion **229** which smoothly rearranged to the acid **230** in high yield with excellent diastereocontrol. Reduction of the acid followed by removal of the auxiliary generated the β-hydroxy cyclopentanone **231** which was transformed into cyclopentanone **232** in four steps. Baeyer–Villiger oxidation provided the lactone **233** with complete retention of stereochemistry.

1.1.2.5 Belluš–Claisen Rearrangement

Description and Historical perspective

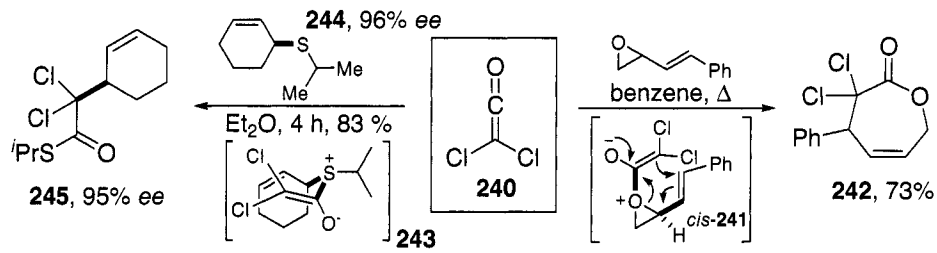
In 1978, Belluš and Malherbe described this variant of the Claisen rearrangement in the course of studies toward the [2 + 2] cycloaddition of ketene **234** and allylic ether **235**.[86] The presence of the γ,δ-unsaturated ester **239** in the product mixture along with the expected product **237** led to the rationale which roposed formation of zwitterionic intermediate **238** resulting from the trapping of ketene by the ether oxygen.



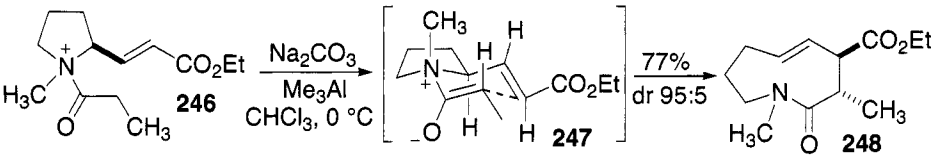
Intermediate **238** undergoes facile [3,3]-sigmatropic reorganization since rate accelerating components for the Claisen rearrangement are incorporated with the positive charge at C_3 as well as the negatively charged substituent at C_2 in the hexadiene framework. The rearrangement exhibits all of the characteristics of the classical Claisen rearrangement and proceeds through a chair-like transition state. Further studies have revealed that tertiary allylamines and allylic thioethers are also suitable substrates for the rearrangement.[87] Lewis acid activation induces a pronounced rate enhancement and permits the participation of the less electrophilic ketene in the process.

Synthetic Utility

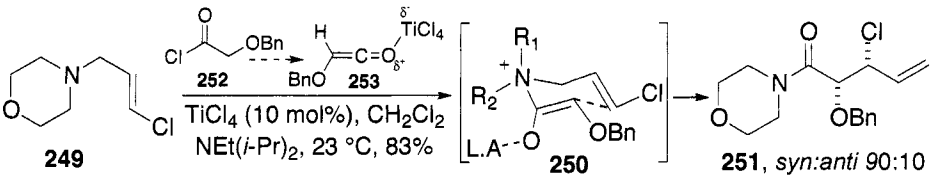
When the heteroatom of the allyl component is incorporated within a carbocycle, the following Belluš–Claisen rearrangement produces a four carbon ring expansion often utilized in the formation of medium-sized lactams, lactones and thiolactones. For example, the oxirane reacts with ketene **240** to generate zwitterion **241** which undergoes rearrangement to lactone **242**.[88] Mild reductive processes (Zn/H^+, Bu_3SnH, H_2/cat. *etc.*) are available to remove α-chloro substitients from **242**. The Belluš–Claisen rearrangement is an efficient process for 1,3-chirality transfer as exemplified by the conversion of thioether **244** to thioester **245** with excellent stereocontrol.[89]



The stereoselective of the ring expansion reaction for the nonracemic 2-pyrrolidine acrylic ester **246** and related systems has been thoroughly investigated by Nubbemeyer.[87] The reaction proceeds via the chair-like transition state **247** and yields 2-azonine **248** with excellent *trans*-diastereoselection.[90] Products characteristically display *E*-olefin embedded within a medium-sized ring. Nubbemeyer has studied the relative stability of these slowly interconverting conformers of medium-ring lactams which exhibit planar chirality and effectively demonstrated this chemistry in natural product synthesis.[87]

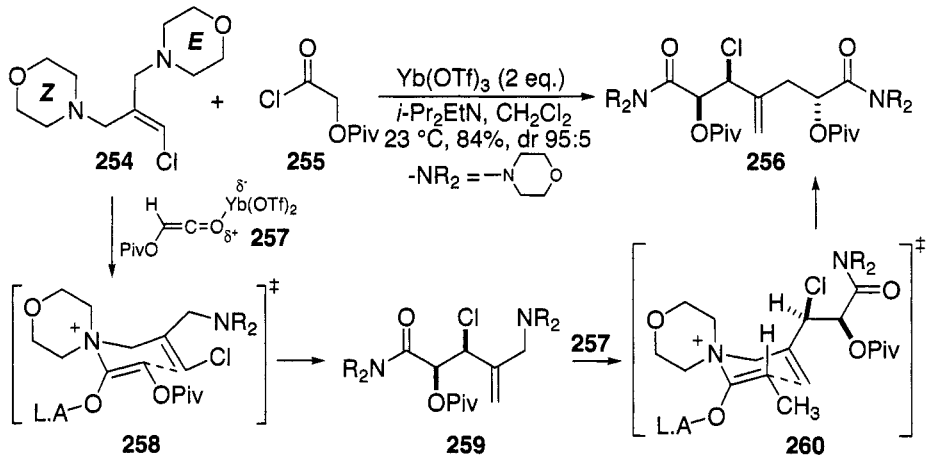


MacMillan has developed a Lewis acid-catalyzed Belluš–Claisen rearrangement in which a range of allylamines can add to ketenes via Lewis acids activation (**253**).[91] This activation–addition pathway generates the zwitterionic allyl alkenyl ammonium complex as shown for **250** which effectively rearranges to amide **251** with excellent *syn* selectivity.



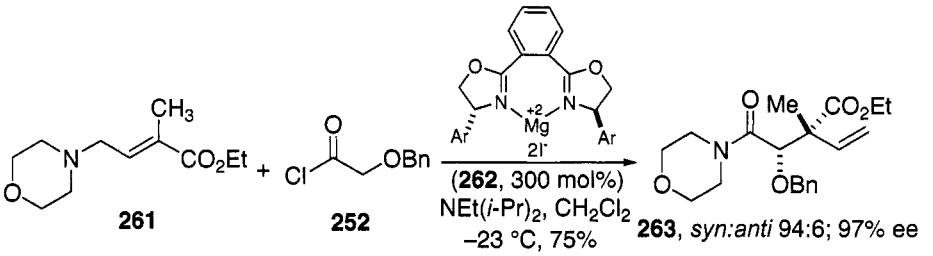
Application of this process in a tandem sequence was also reported by the MacMillan group.[92] The *E*-amine of diamine **254** preferentially reacted with the ketene to generate **258** which rearranged to allyl amine **259** with high *syn* selectivity. An additional equivalent of ketene triggered the second Belluš–Claisen rearrangement. This reaction proceeded via chair-like

transition state **260** where the sterically-crowded amide moiety was positioned away from the axial methylene group.



Enantioselective Belluš–Claisen Rearrangement

Although examples of auxiliary-controlled stereoselective Belluš–Claisen rearrangements have appeared in the literature, the Lewis acid-mediated enantioselective version is a more attractive alternative for practitioners. MacMillan and Yoon have reported that the nonracemic Lewis acid complex **262** efficiently promotes an enantioselective Belluš–Claisen rearrangement with formation of amide **263** in good yield and with excellent selectivity.[93]

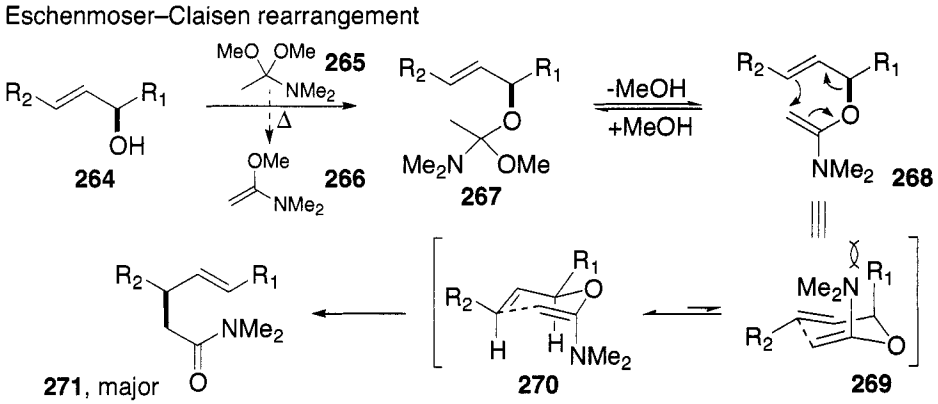


1.1.2.6 Meerwein–Eschenmoser Claisen Rearrangement

Description

The Meerwein–Eschenmoser Claisen rearrangement is a variant of the Claisen process which is described by the thermal rearrangement of ketene

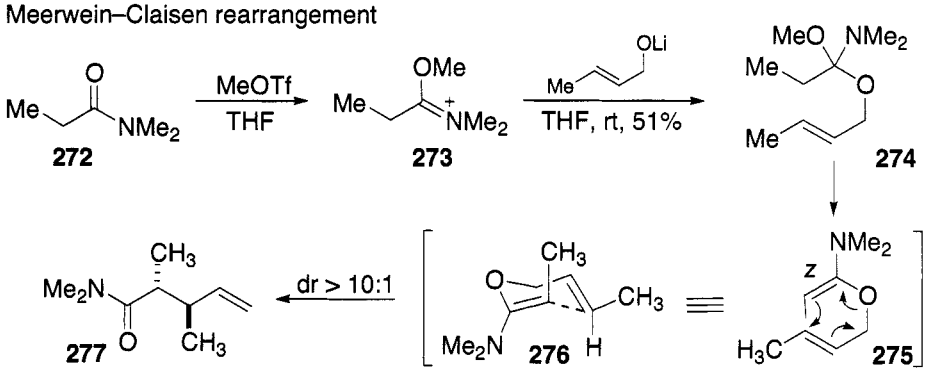
N,O-acetal **268** as derived from allylic alcohol **264** to yield the *γ,δ*-unsaturated amide (**271**).[94] The reaction proceeds through chair-like transition state **270** where the minimization of 1,3-*syn*-diaxial interactions between the alkylamine moiety and R_1 substitution (*c.f.*, **269**) lead to the formation of di- or tri-substituted *E*-olefin **271** in a highly diastereocontrolled fashion.



Historical Perspective

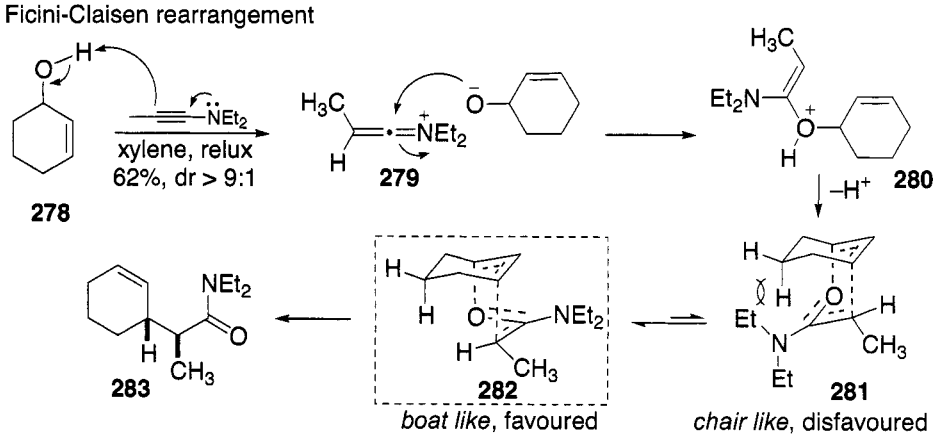
In 1961, Meerwein observed that allylic ketene *N,O*-acetals readily rearranged at elevated temperatures.[95] Typical Meerwein conditions produced the *N,O*-acetal **275** by trapping amidinium ion **273** with an allylic alkoxide. The orginal report relied on "Meerwein's salt" for the *O*-alkylation of amides for the generation of amidinium ions. Welch later reported a mild protocol to generate amidinium ion by utilizing methyl triflate at ambient temperature.[96] Subsequent elimination of methanol from *N,O*-acetal **274** revealed the thermodynamically more stable *Z*-ketene *N,O*-acetal **275** which smoothly rearranged to the amide **277** with high diastereoselectivity. In 1964, Eschenmoser introduced a procedure where allylic alcohol **264** was refluxed in the presence of *N,N*-dimethylacetamide dimethyl acetal **265** to generate ketene *N,O*-acetal **268**.[97] This practical approach greatly expanded the utility of this transformation and has become the recipe of choice for most practitioners.

Meerwein–Claisen rearrangement



Variations and Improvements

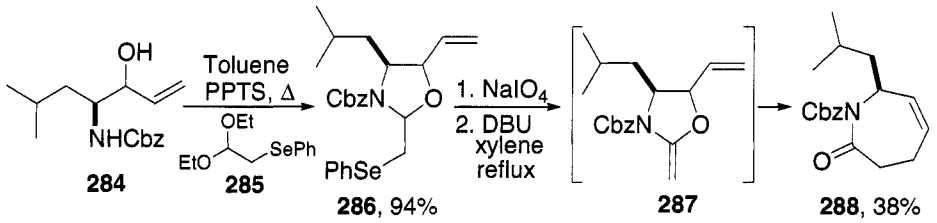
Ficini-Claisen rearrangement



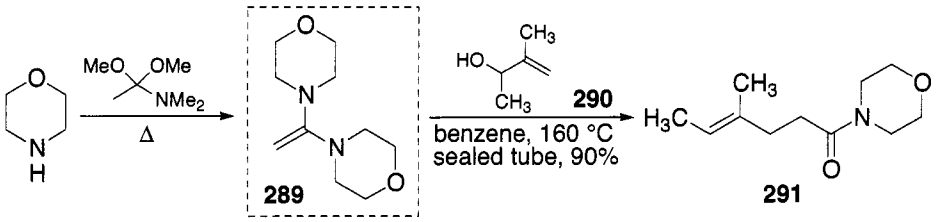
Soon after the literature accounts of Meewein and Eschenmoser in literature, Ficini developed (1966) an elegent method to derive *N,O*-acetals by reacting allylic alcohols with yanamines in the presence of Lewis acid or at high temperature.[98] Bartlett subsequently examined the process in the case of various clyclohexenol derivatives.[99] The rationale assumes an intermediate keteniminium ion **279** which is trapped by 2-cyclohexenol to furnish the *E*-ketene *N,O*-acetal **280.** Rearrangement to afford amide **283** occurs at elevated temperatures. Analysis of the stereochemical outcome of the reaction has stongly suggested a favoured boat-like transition state **282** since the competing chair-like transition state **281** suffers from destabilizing nonbonded steric interactions.

Holmes has also reported an interesting route to synthesise ketene *N,O*-acetals starting with phenylselenyl acetal **286**. In the example, transacetalization of **285** with aminoalcohol derivative **284** results phenylselenyl *N,O*-acetal **286**. Selenoxide formation and *syn*-elimination

provides ketene *N,O*-acetal **287** which undergoes rearrangement to lactam **288** in refluxing xylene.[100]



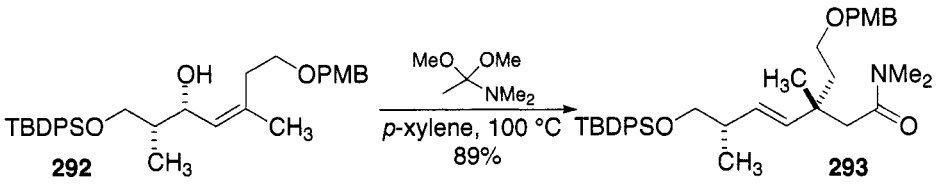
In the light of the emergence of morpholine amides as substitutes of Weinreb amides, a direct incorporation of the former in the Eschenmoser–Claisen product is strategically attractive for synthesis. Trauner and co-worker have treated allylic alcohol **290** with *N,N*-morpholine acetal **289** at high temperature, generating *in situ* the ketene *N,O*-acetal which smoothly rearranged to morpholine amide **291**.[101]



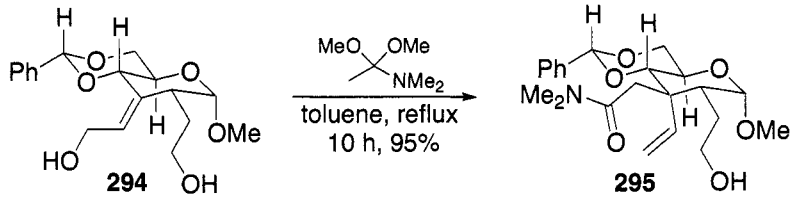
Synthetic Utility

General Utility

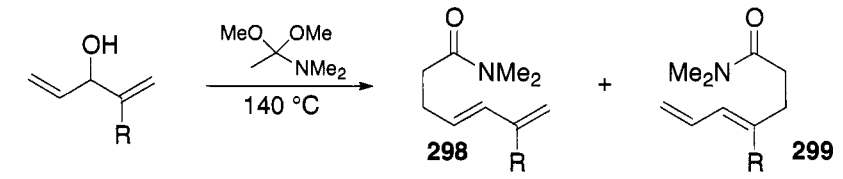
The Meerwein–Eschenmoser Claisen rearrangement consistently delivers improved yields and often superior selectivity when compared to other variants of the Claisen rearrangement. The protocol tolerates a wide range of functional groups due to effectively neutral reaction conditions. High stereoselectivity for reliable 1,3-chirality transfer in the construction of quaternary stereogenecity was evident from the studies of Williams and co-workers as the reaction proceeds via a six-membered chair-like transition state. The allylic alcohol **292** was subjected to Eschenmoser–Claisen conditions yielding a single diastereomer amide **293**.[102]



The substrate-controlled Eschenmoser–Claisen rearrangement beginning with pyranoside **294** gives amide **295** as a single diastereomer.[103]

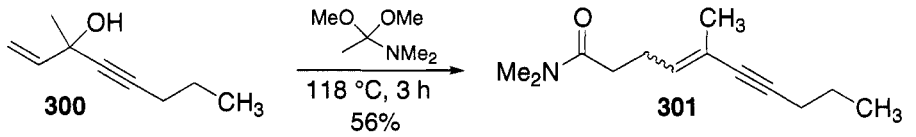


Parker has studied the regiochemical outcome of the Meerwein–Eschenmoser Claisen rearrangement in dialkenyl carbinols (**296** and **297**) and the realated propargyl-alkenyl carbinol (**300**) system. The less substituted alkene participated in the rearrangement (e.g., **298**), and the process differentiated between an alkene and an alkyne resulting in the formation of enyne amide **301**.[104]



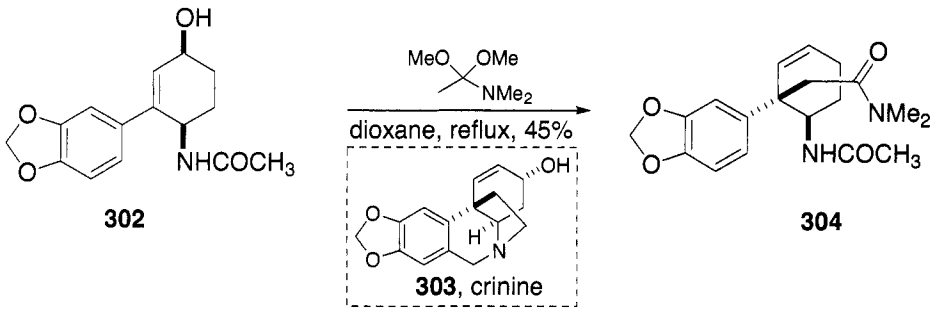
296, R = Me (91%)
297, R = OMe (93%)

R = Me, **298**:**299** 97:3
R = OMe, **298**:**299** 74:26

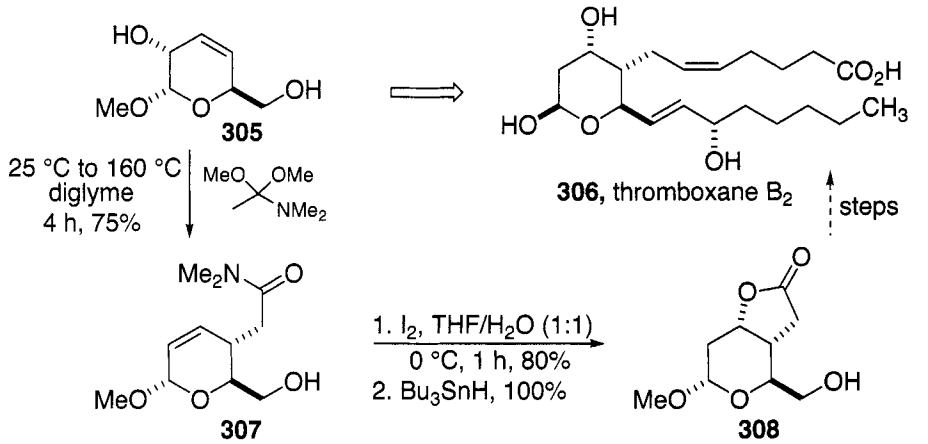


Applications in the total synthesis of natural products

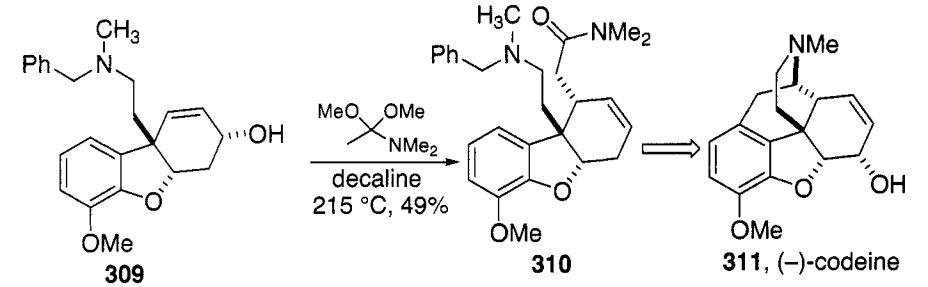
The potential of the the Meerwein–Eschenmoser Claisen rearrangement was exploited by Muxfeldt and co-workers in the course of their studies of crimine alkaloid total synthesis. Allylic alcohol **302** was treated with **265** in refluxing dioxane resulting in a single diastereomer of β-aryl amide **304**.[105]



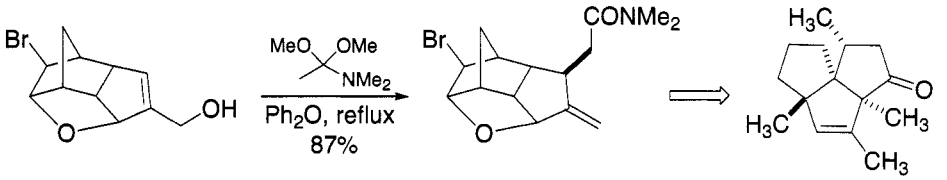
Corey has reported the diastereocontrolled formation of the tetrahydropyran core of thromboxane B_2 utilizing the Eschenmoser–Claisen rearrangement from allylic alcohol **305** to produce amide **307**.[106] Iodolactonization followed tin hydride reduction afforded the lactone **308** which was subsequently transformed to the target molecule.



When other Claisen variants failed, Iorga and Guillou relied on Eschenmoser–Claisen conditions to convert the allylic alcohol **309** to the amide **310**. The key intermediate **310** was subsequently converted into codeine **311**.[107]

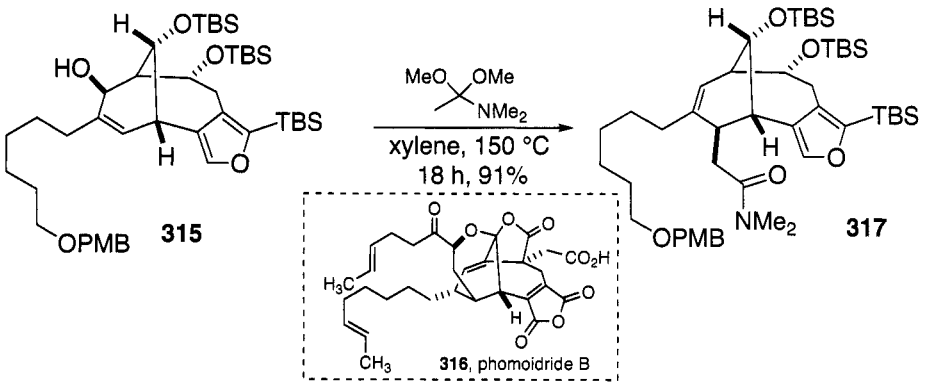


Ogasawara has described the treatment of allylic alcohol **312** with **265** to produce an Eschenmoser–Claisen rearrangement yielding *exo*-acetamide **313** as a single diastereomer in studies leading to (+)-amicenone.[108]

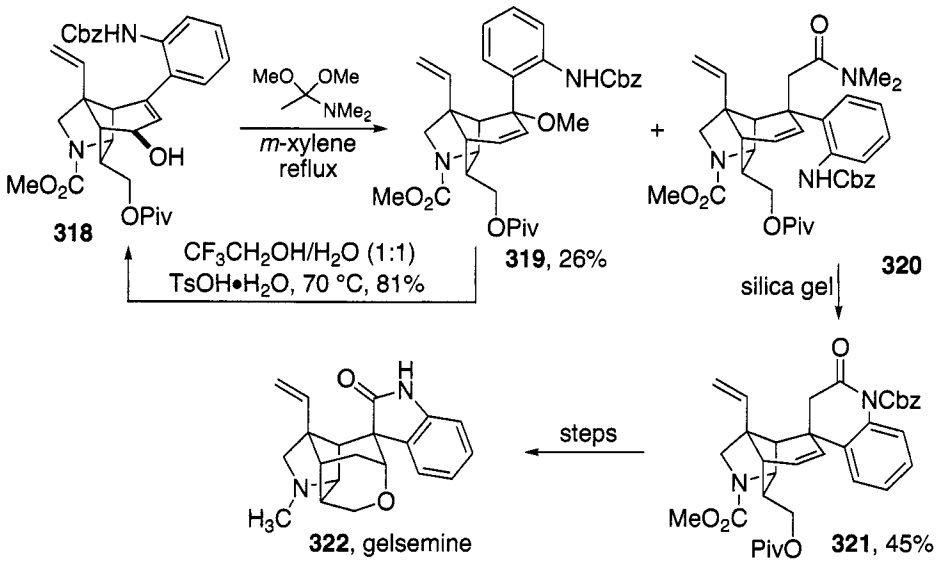


312 **313** **314**, (+)-arnicenone

Another impressive illustration of the Eschenmoser–Claisen rearrangement is displayed in the pathway leading to the Danishefsky's total synthesis of phomoidride B.[109]

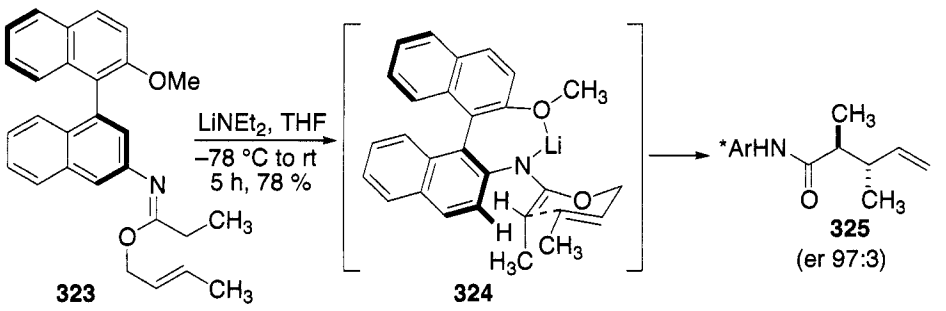


The allylic alcohol (**315**), embedded in complex bicyclo[4.3.1] system, was smoothly converted to amide **317**. Danishefsky also relied on the Eschenmoser–Claisen rearrangement for construction of the spirocyclic quaternary stereocenter which poses a formidable challenge for efforts toward the synthesis of gelsemine.[110] Allylic alcohol **318** was subjected to the Eschenmoser–Claisen conditions to generate amide **320** which was converted to the lactam **321** in presence of mild acid (silica). Other Claisen variants proved to be unsuccessful in these efforts.



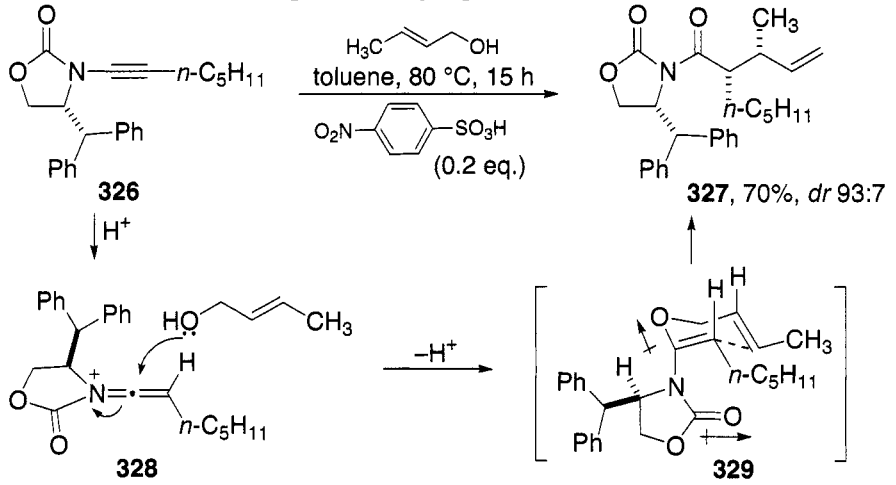
Asymmetric Meerwein–Eschenmoser Claisen Rearrangement

Metz and Hungerhoff used imidate **323** as a substrate for the Meerwein–Eschenmoser Claisen rearrangement, where the *N*-aryl component is a nonracemic binapthylamine which is suitably positioned to serve as a chiral auxiliary.[111] Treatment of **323** with lithium diethylamide generates the highly organised azaenolate **324** which efficiently undergoes rearrangement to the amide **325** at 0 °C. High enantiocontrol in the process can be attributed to the preferential shielding of one face of the azaenolate by the binapthyl moiety.

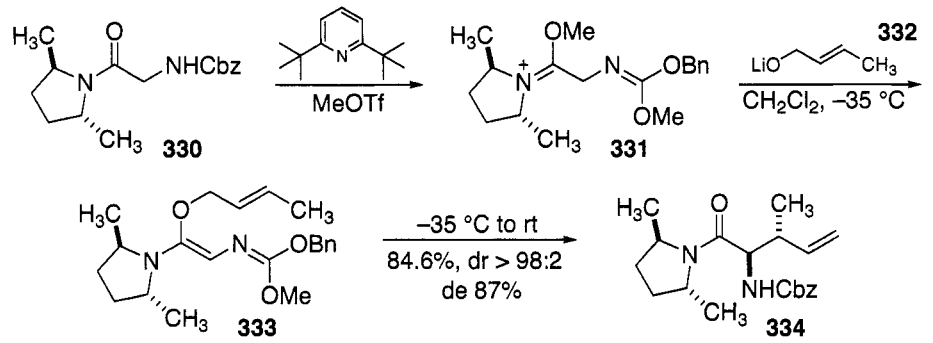


Hsung and co-workers have developed an asymmetric Ficini–Claisen rearrangement which is based on the chiral yanamide **326**. In presence of Brønsted acid, yanamide is generated putative ketene iminium species **328** which trapped allylic alcohol to result in formation of *E*-ketene aminal. The

Ficini–Claisen rearrangement proceeded via the dipole minimized chair-like transition state **329** leading to the major product **327**.[112]



Hruby and co-workers utilized the C_2-symmetric pyrrolidine derivative as an auxiliary for asymmetric induction in studies of the Meerwein–Claisen rearrangement to yield *trans* β-alkyl γ,δ-unsaturated amino acids (**334**).[113] Treatment of amide **330** with a reactive alkylating agent yielded the amidinium ion **331** which was trapped with alkoxide **332**. Upon warming to the ambient temperature, the ketene *N,O*-acetal underwent diastereoselective Meerwein–Claisen rearrangement to **334** in excellent yield with high stereocontrol.

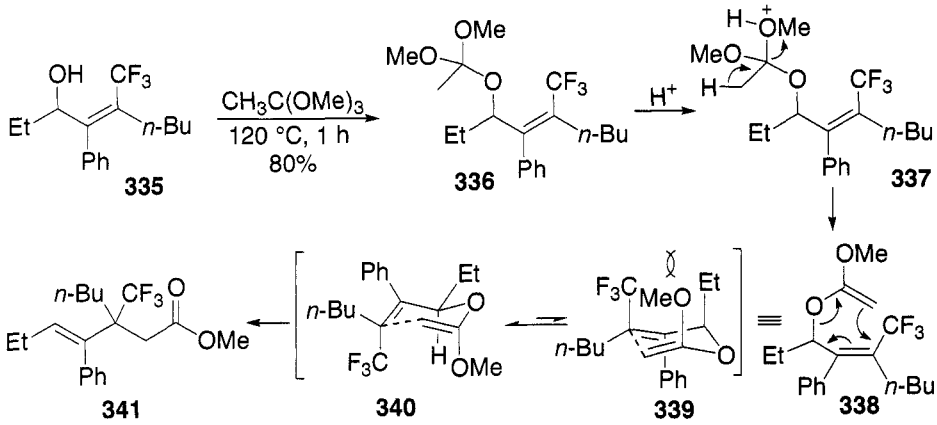


1.1.2.7 Johnson–Claisen rearrangement

Description

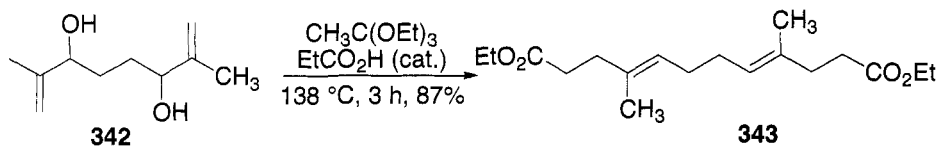
The orthoester Johnson–Claisen rearrangement[114] describes the thermal rearrangement of the ketene acetal **338**, which is derived by refluxing allylic

alcohol **335** in the presence of trimethyl orthoacetate under mildly acidic condition, to yield the γ,δ-unsaturated ester (**341**).[115] Initially the mixed orthoester **336** extrudes one molecule of methanol to produce the ketene acetal **337**. At elevated temperature, the rearrangement of **338** proceeds via the chair-like transition state **340** which presents the minimization of 1,3-*syn* diaxial interactions leading to the substituted *E*-olefin **341** in a highly diastereocontrolled fashion.



Historical Perspective

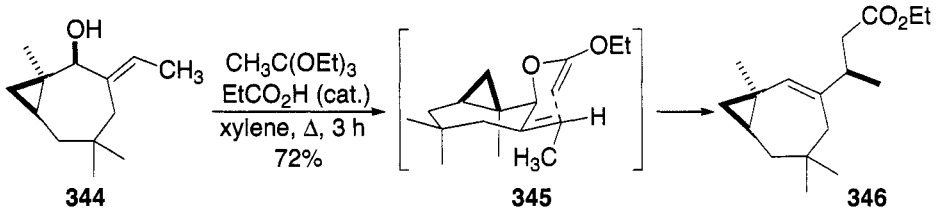
W. S. Johnson and coworkers developed this protocol in the course of endeavours towards the synthesis of all *trans*-squalene.[116] Upon heating with ethyl orthoacetate, the bis-allylic alcohol **342** yielded di-ester **343** to accomplish a double homologation strategy. Johnson recognized the potential of this [3,3]-sigmatropic rearrangement since the operation simultaneously produced two *E*-trisubstituted alkenes as a single diastereomer. Further elaboration of intermediate **343** resulted all (*E*)-squalene.



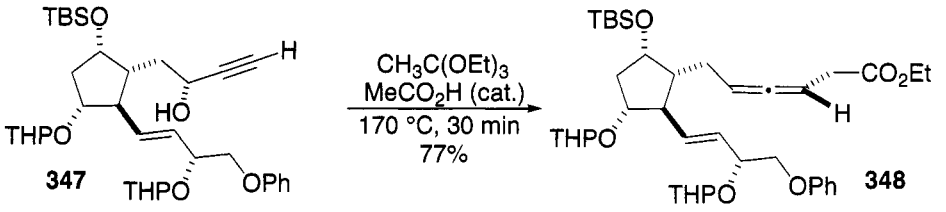
Synthetic Utility

The orthoester Johnson–Claisen rearrangement has been extended with great success for many applications in natural product synthesis. Paquette utilized the efficient 1,3-chirality transfer of the rearrangement in studies of africanol.

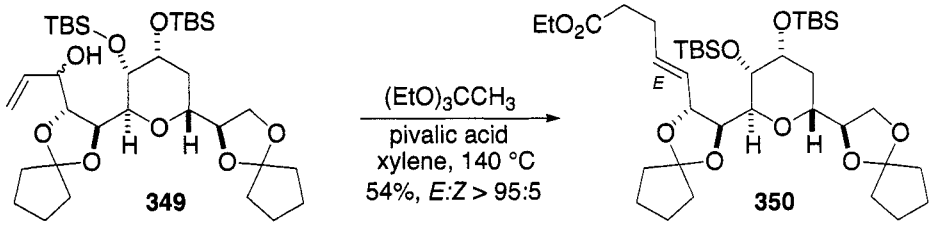
Alcohol **344** was smoothly converted to ester **346** with excellent stereocontrol.[117]



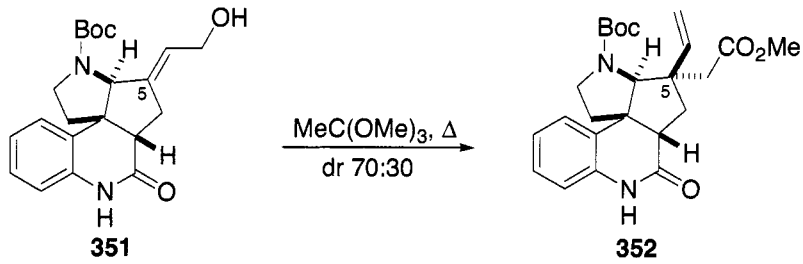
Similarly, Cooper used the orthoester Johnson–Claisen rearrangement for the stereospecific construction of nonracemic allene **348** from the chiral alcohol **347** with efficient rearrangement of the propargylic system.[118]



Roush has reported on the *E*-selective nature of the orthoester Johnson–Claisen rearrangement with the conversion of the alcohol **349** to the *E*-ethylester **350**.[23]

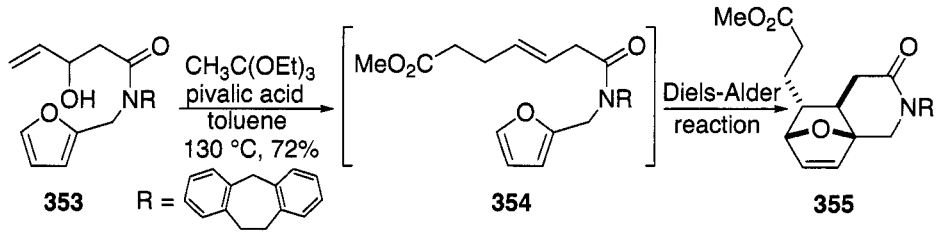


As in the case of all variations of the Clasien rearrangement, the [3,3]-sigmatropic process is routinely applied for the construction of stereogenicity at quaternary carbon centers. During studies toward the total synthesis of meloscine, orthoester Johnson–Claisen rearrangement was utilized as the key bond formation event when many other attempts to construct the C_5 quaternary stereocenter in this sterically-demanding environment failed. Treatment of **351** with trimethyl orthoacetate at elevated temperature readily afforded the ester **352** with moderate diastereoselection.[119]



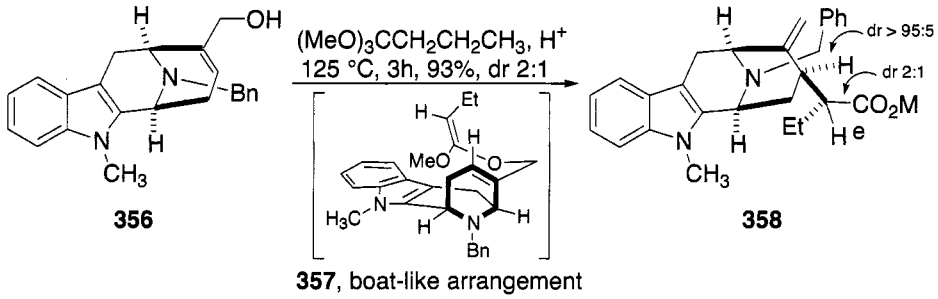
351 **352**

Jacobi has described an elegant tandem application of the Johnson–Claisen reaction and the Diels–Alder cycloaddition to generate **355**. The nature of the nitrogen substituent (R) directly influences the efficiency of the subsequent thermal cyclization of the initial rearrangement product **354**.[120]



353 **354** **355**

Cook has relied on the Johnson–Claisen rearrangement for the conversion of allylic alcohol **356** to ester **358**. The reaction proceeds via a boat-like transition state **357** to yield 2:1 diastereoselection of the exocyclic stereogenic center of **358**.[121]

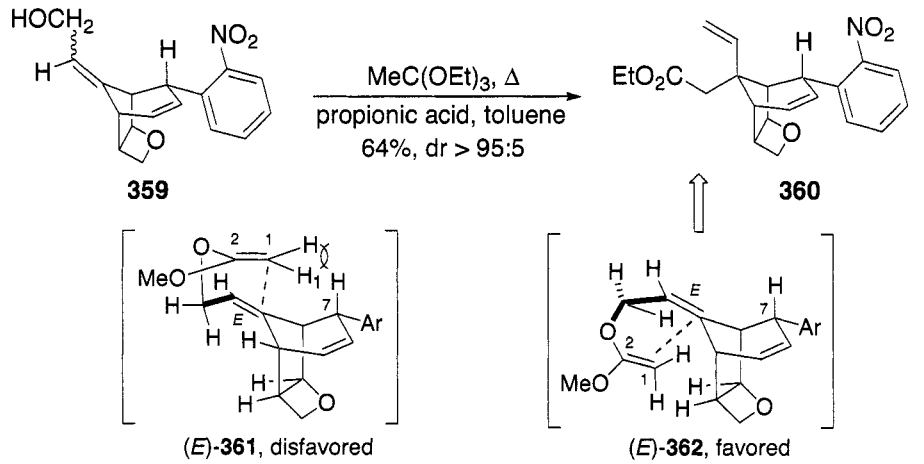


356 **358**

357, boat-like arrangement

Danishefsky has described a substrate-controlled Johnson–Claisen rearrangement outcome when a single diastereomer, identified as ester **360**, was independently produced from (*E*)- and (*Z*)-isomers of alcohol **359**.[110] Subsequently this process was studied by Aviyente, Ozturk, and Houk.[122] The Computational studies of the (*E*)- and (*Z*)-ketene acetals originating from **359** revealed that facial selectivity was controlled due to steric interactions of

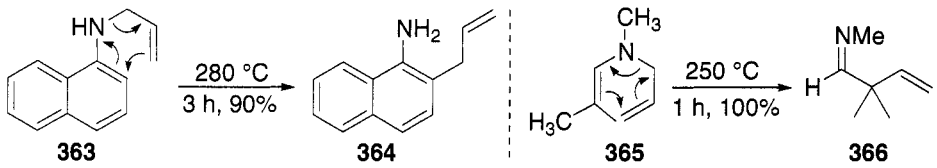
H_1 as exemplified be (*E*)-**361** with axial C_7–H which destabilize transition state leading to the diastereomer of ester **360**. Calculations also indicate attractive interactions of C_1 of the ketene acetals with the hydrogens of the ring fused oxetane as depicted in arrangement (*E*)-**362**.



1.1.2.8 aza-Claisen rearrangement

Description and Historical perspective

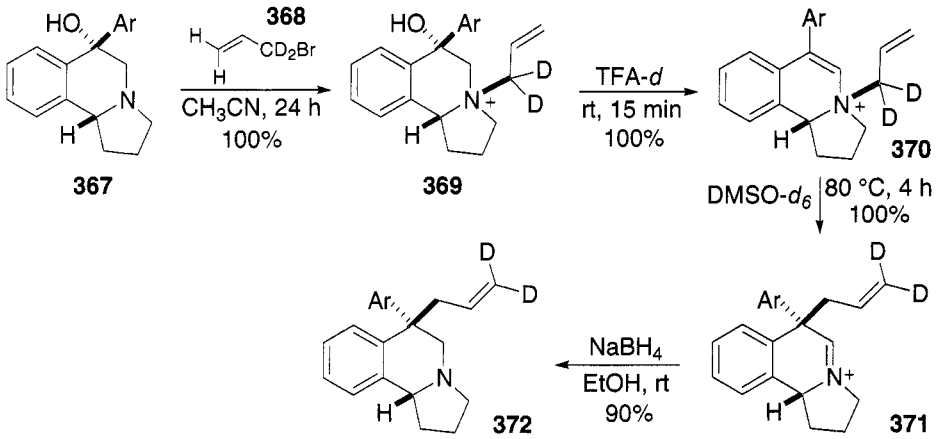
The aza variant of the Claisen rearrangement is described as the replacement of the oxygen atom at C_3 with a nitrogen atom within the basic 1,5-diene framework.[123] Depending on the nature of the substrate, rearrangement products may contain imine/enamine, arylamine, amide/lactam or nitrile functionality. The synthetic utility of the aza-Claisen rearrangement has been widely displayed in areas of alkaloid and heterocycle synthesis. Renewed attention has been given to the aza-Claisen process with the development of methods for asymmetric induction where the nitrogen atom can serve as point of attachment for a chiral auxiliary or coordination of nonracemeic catalyst. The use of quaternary ammonium salts or coordination of Brønsted or Lewis acids cause significant rate acceleration in aza-Claisen. Marcinkiewicz[124] first reported the rearrangement of *N*-allyl napthylamine **363**, and a few years later, Hill disclosed the aliphatic variant of this reaction as allyl vinylamine **365** was converted to imine **366** at elevated temperature.[125]



363 **364** **365** **366**

Synthetic Utility

Maryanoff and McComsey have studied the concerted suprafacial nature of the aza-Claisen rearrangement in the pyrrolo-[2,1-*a*]isoquinoline system **367** by deuterium labeling studies.[126] Quaternary *cis*-fused salt **370** underwent aza-Claisen rearrangement with allyl inversion to yield iminium species **371** which was reduced *in situ* to amine **372**.

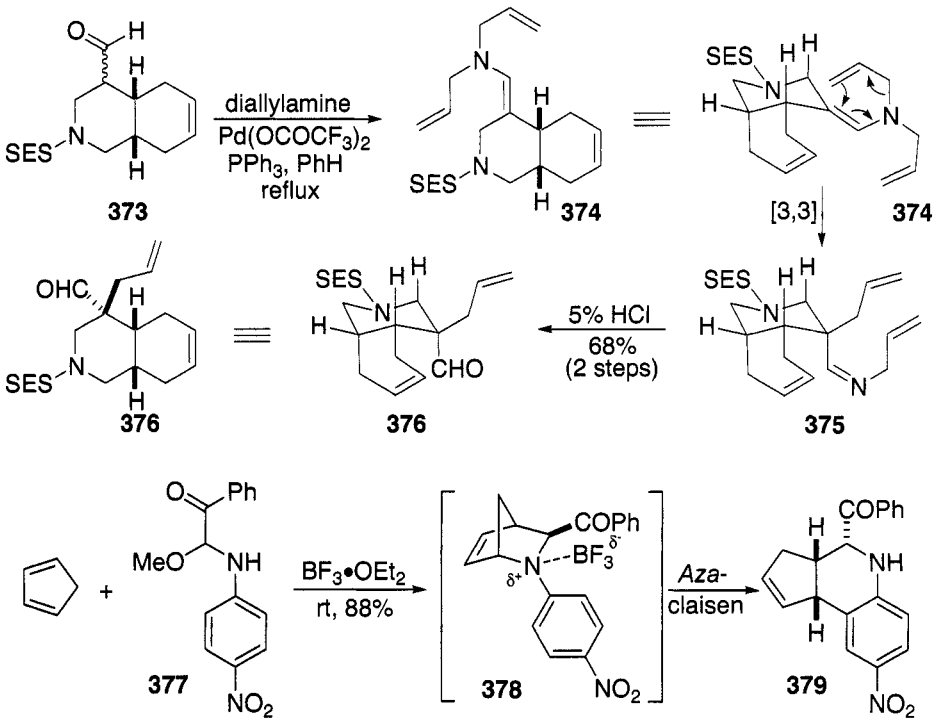


367 **369** **370** **371** **372**

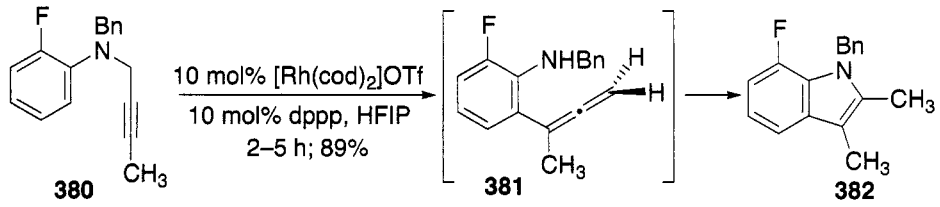
One of the most useful ways to construct the aza-Claisen structural motif condenses carbonyl compounds with allylamine. Weinreb utilized Murahashi's protocol[127] of the palladium-mediated aza-Claisen rearrangement in the course of the synthesis of madangamine A.[128]

Treatment of a mixture of epimers of aldehyde **373** with diallylamine in the presence of $Pd(O_2CCF_3)_2/PPh_3$ initially generated the enamine **374** which underwent substrate controlled aza-Claisen rearrangement from the convex face of the bicyclic framework to yield imine **375**. Hudrolysis via an acidic workup yielded aldehyde **376** as a single diastereomer.

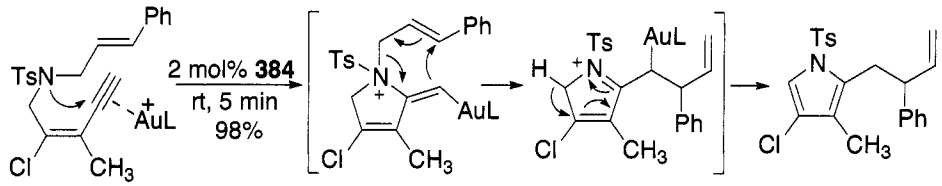
Prato developed a Lewis acid-mediated tandem Diels–Alder/aza-Claisen rearrangement sequence where the *in situ* generated cycloadduct **378** from aminal **377** and cyclopentadiene underwent aza-Claisen rearrangement at ambient temperature in presence of $BF_3 \cdot OEt_2$ in high yield.[129]



Saito and Hanzawa have reported a cationic rhodium(I)-catalyzed aza-Claisen rearrangement of *N*-propargyl aniline **380**. The un-catalyzed thermal variant required extremely high reaction temperatures and produced poor conversions. The mild protocol is an efficient entry for the synthesis of various indole derivatives. The reaction proceeds through the *o*-allenylaniline intermediate **381** and a subsequent cyclization results in **382**.[130]

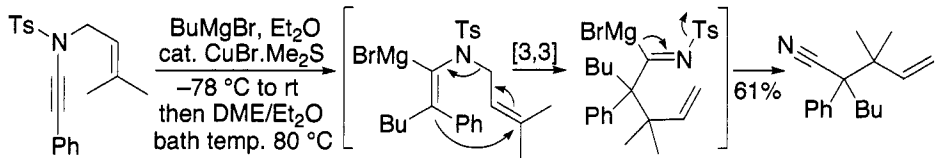


Gagosz has studied a gold(I)-catalyzed process to convert various allyl pentynyl tosylamides to functionalized pyrroles under mild conditions. Alkyne activation by Au(I) triggers a nuclephilic cyclization of tosylamide to generate the presumed alkenyl gold intermediate **385** which undergoes aza-Claisen rearrangement. Aromatization followed by protodemetalation leads to the pyrrole **387**.[131]



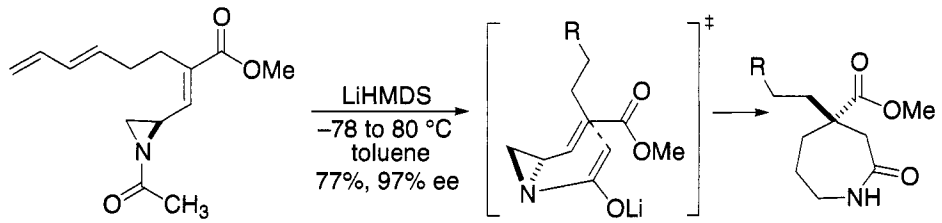
383 **384** = $(p\text{CF}_3\text{Ph})_3\text{PAuNTf}_2$ **385** **386** **387**

A carbomagnesiation of ynamides followed by aza-Claisen rearrangement reaction sequence was reported by Yorimitsu and Oshima.[132] Copper catalyzed addition of the alkyl Grignard reagent to ynamide **388** gave rise to alkenyl Grignard species **389** which underwent aza-Claisen rearrangement at elevated temperature. The putative metallo-imine **390** suffers rapid elimination of magnesium sulfinate to furnish nitrile **391**.



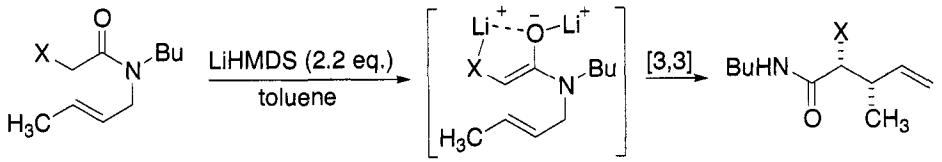
388 **389** **390** **391**

Amide enolates also efficiently participate in the aza-Claisen rearrangement. For example, the nonracemic divinylaziridine **392** has been reported to undergo rearrangement to generate the medium ring-sized lactam **394** in good yield and with excellent enantioselectivity. This 1,3-chirality transfer proceeds via a boat transition state **393** and the relief of ring strain is significant driving force for this ring expansion process.[133]



392 **393** **394**

Tsunoda has rationalized a role for chelation with preferential formation of the *Z*-enolate **397** from *N*-crotyl glycolamide **395** and glycinamide **396**. At elevated temperature, the *(Z)*-ketene *N,O*-acetal **397** exhibits a facile aza-Claisen rearrangement with excellent *syn* selectivity.[134]

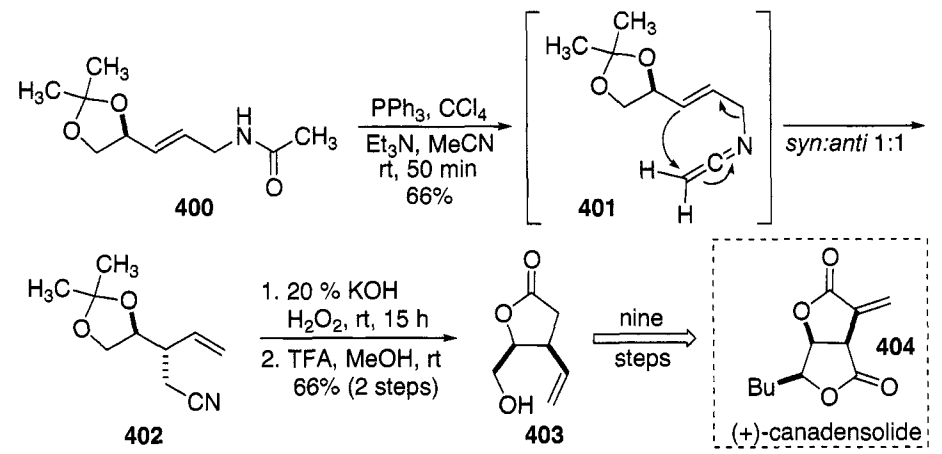


X = OH (**395**)
X = NH_2 (**396**)

397

398, 74%, *syn:anti* 98:2
399, 74%, *syn:anti* 96:4

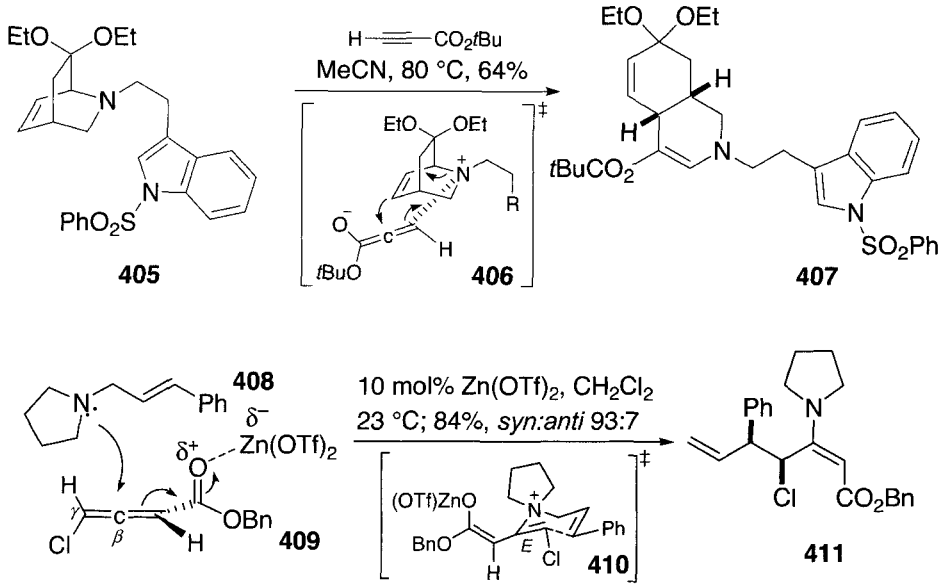
The iminoketene Claisen rearrangement also has broad synthetic applicability as the substrates can be prepared *in situ* by a simple dehydration of easily accessible *N*-allyl acetamide derivatives. Nubbemeyer relied on the substrate-controlled iminoketene Claisen rearrangement of **401** to access the nitrile **402**.[135] The unselective process generated a mixture of diastereomers, and **402** was then converted in two steps to hydroxy lactone **403** which was used as a key intermediate for the synthesis of canadensolide. In a zwitterionic aza-Claisen rearrangement, a charge-separated species is initially formed as tertiary amines condense with neutral electrophiles such as activated alkyne or allenoate esters. Due to this charge separation, the reaction proceeds at lower temperature as compared to the pyrolysis conditions used in early studies. For example, when amine **405** was treated with propiolester, the initial zwitterionic intermediate **406** smoothly rearranged to isoquinoline derivative **407**.[136]



400 **401** **402** **403**

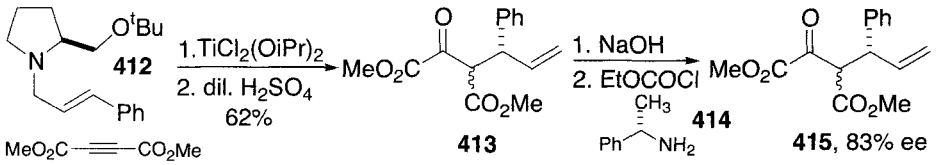
MacMillan has developed a Lewis acid-catalyzed addition–rearrangement sequence which facilitates the conjugate addition of allylamine **408** to allenoate ester **409** to generate the zwitterionic intermediate for the Claisen rearrangement.[137] The minimization of steric interactions between the ammonium species and the γ-allenyl substituent led

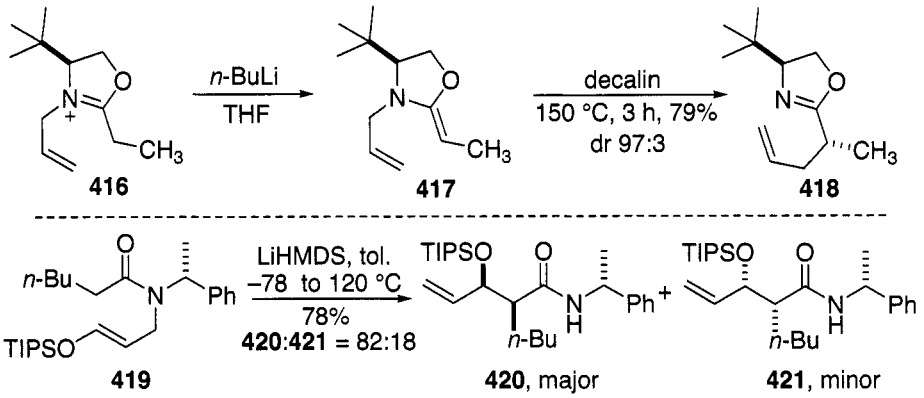
to the preferential formation of the *E*-enamine. The reaction proceeds via a chair-like transition state **410** to yield *β*-enamino ester **411**.



Asymmetric Aza-Claisen Rearrangement

The search for a single structural motif to serve as a chiral auxiliary for the diversity of examples of the aza-Claisen rearrangement continues to produce some advancement. The prolinol derivative[138] **412**, oxazoline derivative[139] **416**, and (*R*)-1-phenylethanamine derivative[140] **419** have been utilized to provide moderate to good asymmetric induction in specific cases as exemplified below.

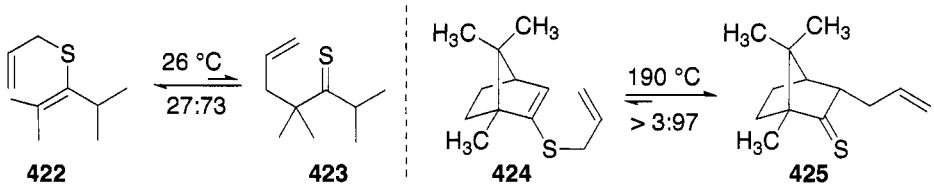




1.1.2.9 Thio-Claisen rearrangement

Description

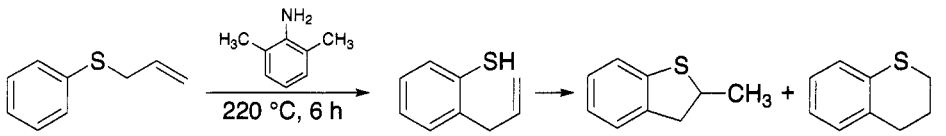
Replacement of the oxygen atom in the allyl vinyl ether structural motif of a Claisen rearrangement with a sulfur atom describes the thio-Claisen rearrangement.[141] The reaction is faster as compared to the parent oxygen-analogue since the weak C–S bond is involved in bond breaking event.[142] Classic studies by Brandsma[143] and Metzner[144] independently showed that the thermodynamics for the reaction are not always favorable due to the formation of the comparatively weak carbon sulfur π-bond in the product. In a simple aliphatic thio-Claisen rearrangement, the starting sulfide **422** is in dynamic equilibrium with the thioketone **423**. One of the many parameters which can drive the reaction is the relief of ring strain, as exemplified in the case of sulfide **424**.[141] Apart from allyl vinyl sulphides, compounds such as dithioesters, thionesters, thioamides, thioketones, sulfoxide and sulfonium ions can participate in the thio-Claisen rearrangement and some of these cases will be discussed in the following sections.[141]



Historical Perspective

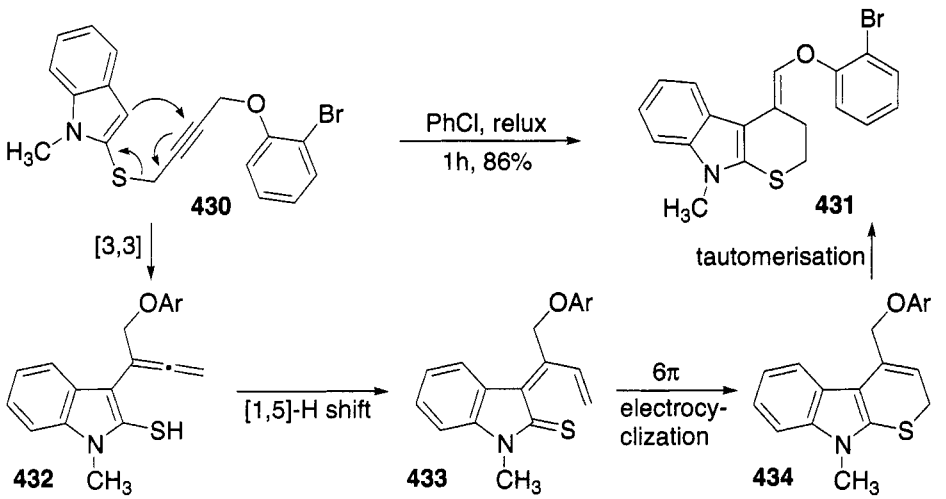
An early report by Hurd and Greengard[145] in 1930 concerning the conversion of allyl aryl sulfide **426** to 2-allylthiophenol was subsequently validated by Kwart.[146] In addition to other details, Kwart showed that the mode of

cyclisation to produce **428** or **429** from thiophenol **427** was dependent on experimental parameters. Soon after Kwart's studies, Brandsma[147] revealed the first report of an aliphatic thio-Claisen rearrangement and subsequent investigations by Lawesson[148] advanced the scope of the aliphatic variant of this process.

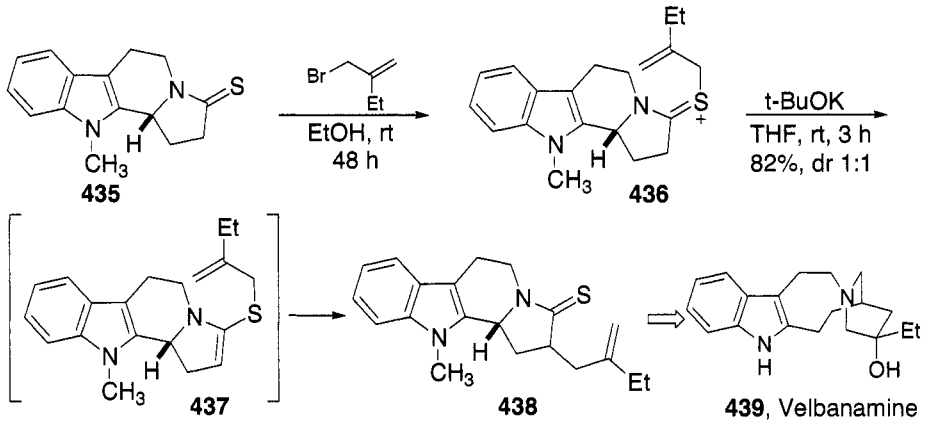


Synthetic Utility

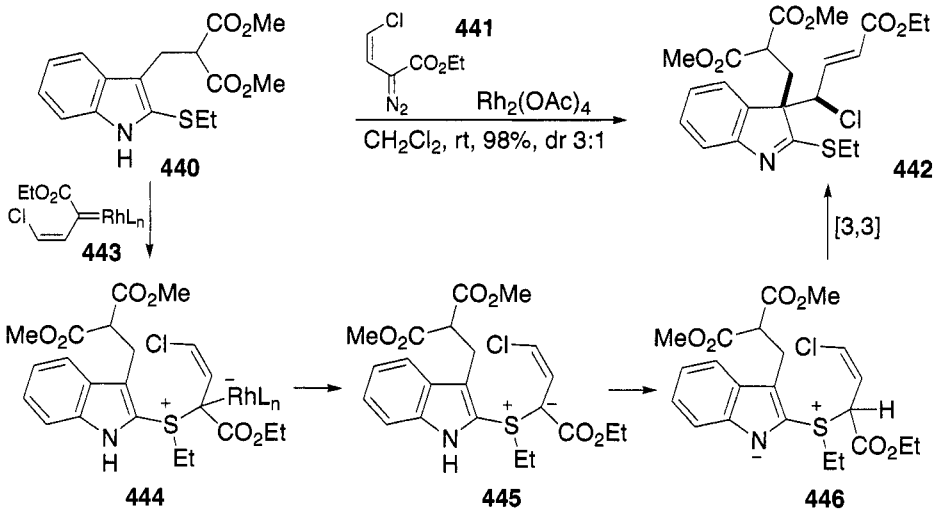
Of the many applications of the thio-Claisen rearrangement, a majority of examples are directed towards the synthesis of novel heterocyclic systems.[141] Majumdar has reported a chemoselective thio-Claisen rearrangement as the allyl propargylic sufide **430** was preferentially transformed to thioindole **431**. The short-lived **432** underwent a sequential [1,5]-H shift and a thermal electrocyclization to give the thiopyranoindole **434** and subsequent tautomerisation provided **431**.[149]



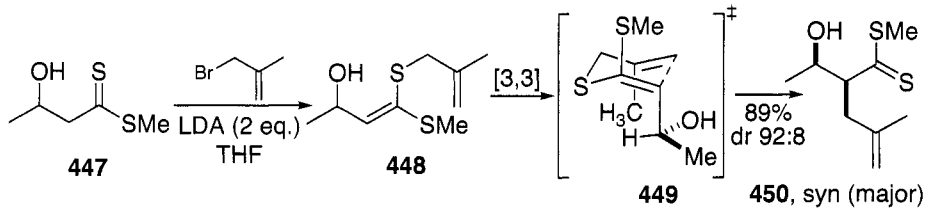
Applications of the thio-Claisen rearrangement towards the synthesis of natural products are also well documented.[141] Takano utilized a thio-Claisen rearrangement during the course of studies toward the synthesis of velbanamine.[150] Alkylation of **435** was followed by treatment with base to generate ketene *N,S*-acetal **437** which smoothly rearranged to thioamide **438**.



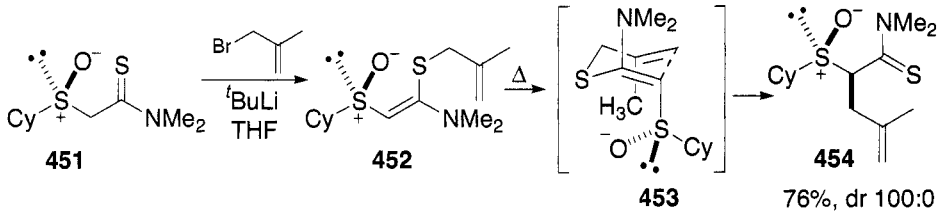
Rainer has studied the sulfonium ylide-mediated thio-Claisen rearrangement.[151] Rhodium carbenoid **443**, generated from rhodium acetate and alkenyl diazoacetate **441**, reacted with the 2-ethylthioindole **440** to reveal the sulphur ylide **445**. Proton shift generated the ketene aminethio acetal **446** which underwent thio-Claisen rearrangement to yield indoline **442** in excellent yield.



The substrate-controlled stereoselective thio-Claisen rearrangement is an active area of investigation.[141] For example the rearrangement of the ketene thioaminal **448** to β-hydroxy thioester **450** efficiently occurs at ambient temperature with excellent *syn*-diastereoselection.[152] Similarly, chiral sulfoxides can efficiently promote high diastereoselection in the thio-Claisen rearrangement as illustrated in the formation of **454**.[153]

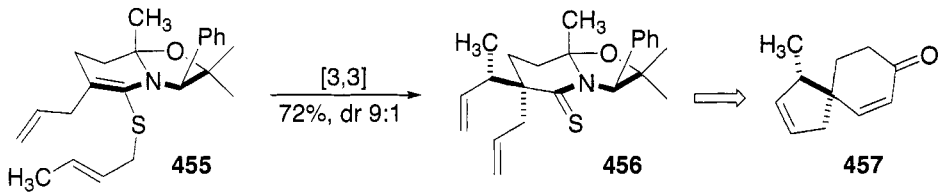


The deprotonation and *S*-alkylation sequence from **451** proceeded without racemisation and resulted in the ketene thioaminal **452**. At elevated temperature, **452** rearranged to provide thioamide **454**. Proposed transition states **449** and **453** indicate that stereoelctronic effects play an important role in the reaction outcome.

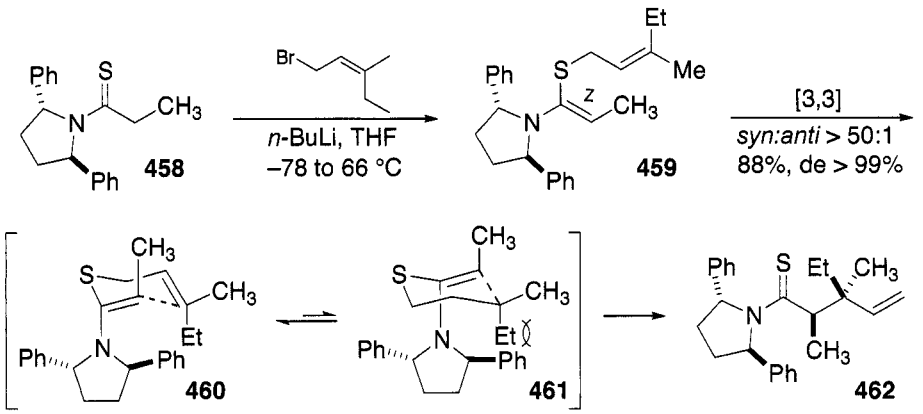


Asymmetric Induction in the Thio–Claisen Rearrangement

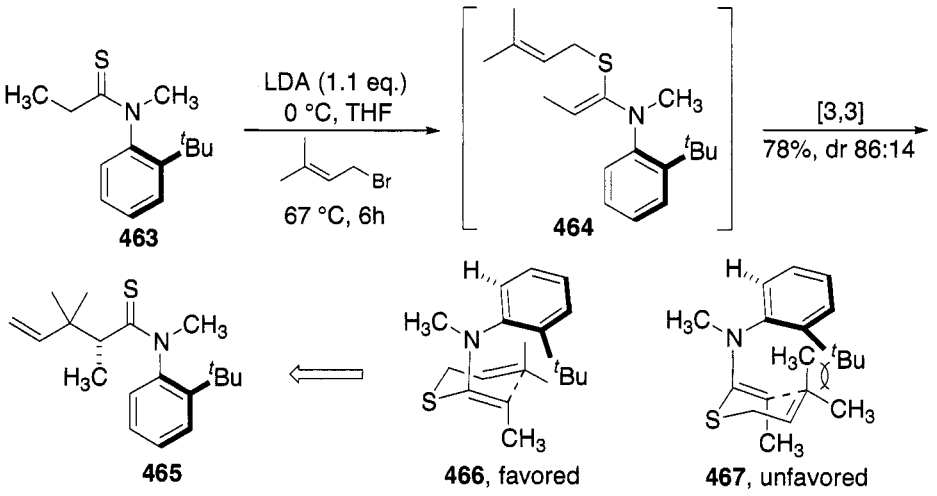
The design of a chiral auxiliary for the thio-Claisen rearrangement of *N,S*-ketene acetals must address the problem of free rotation of the C–N bond as configurational rigidity is essential for high asymmetric induction. Pioneering work of A. I. Meyers developed a rigid bicyclic thiolactam framework for the asymmetric thio-Claisen rearrangement.[154] For example ketene thioaminal **455** smoothly provided the thio-Claisen rearrangement in good diastereoselection to deliver thioamide **456** which was subsequently converted into nonracemic spiro-cyclohexenone **457**.



Rawal efficiently utilized the C_2-symmetric pyrrolidine derivative **458** to induce facial control as **459** rearranged to thioamide **462** in excellent yield and high diastereoselection.[155]



Metzner and co-workers have relied on the inherent axial chirality of atropisomeric thioanilide **463** to promote the stereoselective thio-Claisen rearrangement.[156] The *ortho-t*-Bu substituent forced the arene ring to adopt an orthogonal conformation with respect to the thioamide moiety. *S*-Alkylation of **463** led to the formation of the ketene thioaminal **464** which underwent the thio-Claisen rearrangement in good yield and high facial selectivity. In the transition state **467**, the *ortho-t*-Bu group was competing to occupy same three dimentional space with the alkyl substituents, a scenario which was minimized in the favored TS **466**.



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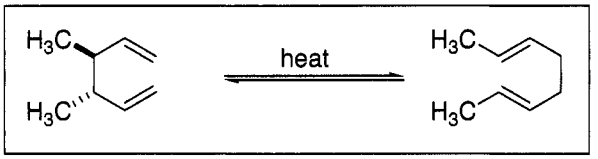
1.1.3 Cope and Related Rearrangements

Richard J. Mullins and Kyle W. McCracken

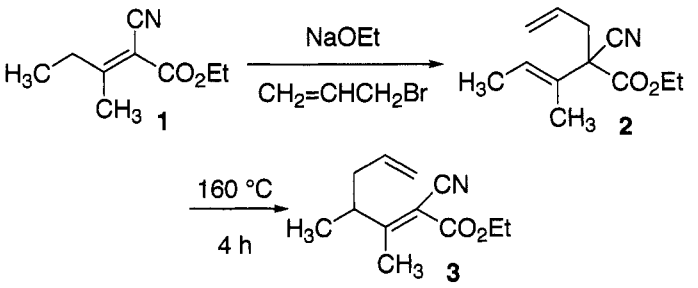
1.1.3.1 Description

The Cope rearrangement is the reversible, thermal [3,3]-sigmatropic rearrangement of 1,5-dienes.[1]



1.1.3.2 Historical Perspective

In the late 1930s, Cope authored a series of papers describing the introduction of substituted vinyl groups via the malonic and cyanoacetic ester syntheses,[2–5] and it was these experiments that led to the serendipitous discovery of the Cope rearrangement. Alkylation of the anion of **1** led to the expected formation of **2**. However, upon heating, **2** underwent reorganization to give **3**, in what has come to be known as the Cope rearrangement.[6] Since this discovery, the Cope rearrangement has been thoroughly studied and characterized by Cope and others.

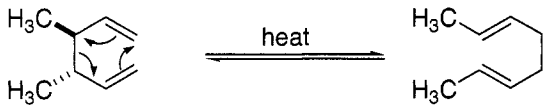


It was initially thought that electron-withdrawing groups, such as the cyanide and ester substituents of compound **1**, were required to weaken the sigma bond allowing rearrangement to occur. While Cope subsequently demonstrated that the reaction can occur in the absence of electron withdrawing groups,[7] their presence in certain positions results in a substantial rate enhancement.[8]

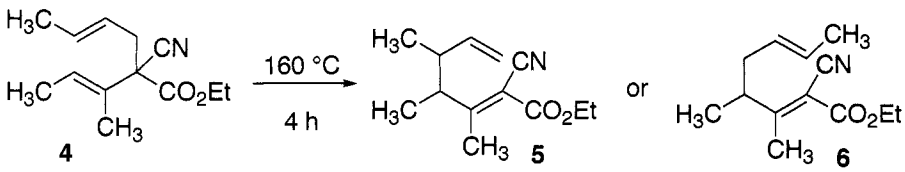
Over the course of the last 68 years since the landmark discovery of this reaction, the Cope rearrangement has captivated the entire organic chemistry community, including the physical and theoretical organic chemists enthralled by the subtle details of its mechanism, and the synthetic chemists, who have used the Cope and its variants, as extremely powerful tools for the stereoselective construction of a diverse array of organic products.

1.1.3.3 Mechanism

When first reported by Cope and Hardy, similarities between this and the Claisen rearrangement were immediately recognized, and it was thus hypothesized that the reaction proceeds through a concerted, intramolecular, cyclic transition state.[6] To confirm this mechanism, a series of experiments were conducted which strongly supported Cope's initial postulate.



Cope first determined that the reaction proceeds with inversion of the migrating allyl group. When compound **4** was rearranged, it yielded exclusively product **5** as opposed to **6**.[1] Further evidence supporting the cyclic mechanism was the confirmation that the transition state was unimolecular which stemmed from experiments in which mixtures of esters containing different allyl groups were subjected to the rearrangement conditions, and it was observed that there was no exchange of allyl groups between the two compounds in the mixtures.[1]



Following acceptance of the concerted, cyclic mechanism, the exact nature of the transition state was discovered by Doering and Roth in 1962. Their studies demonstrated that while the reaction proceeds through either a chair-like or boat-like transition state, if both are possible, the chair-like transition state is kinetically favored.[9]

While the Cope rearrangement is considered to be a concerted [3,3]-sigmatropic rearrangement, it displays a unique response to attached substituents, which suggest the involvement of biradical intermediates.

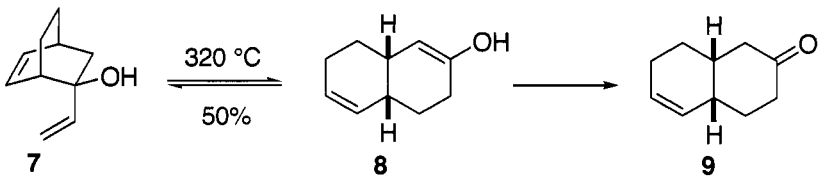
Numerous mechanistic studies have been done with the aim of elucidating the subtler details of the Cope and related mechanisms. However, this review focuses on the synthetic aspects of the Cope and related rearrangements, and thus, readers interested in these mechanistic explorations are directed to other reviews of this topic.[10–15]

1.1.3.4 Variations and Improvements

A number of variants of the Cope rearrangement have been developed as a means of either increasing the rate or shifting the equilibrium of the reaction by means of attached substituents. A number of reviews describing the use of the Cope rearrangement in synthetic endeavors have been written.[16–35]

Oxy-Cope

The development of the oxy-Cope rearrangement by Berson and Jones[36,37] was a seminal event in the history of the Cope rearrangement, as it represented the first simple modification of the 1,5-hexadiene system that dramatically shifted the equilibrium of the reaction. In some ways, this discovery ushered in a new era, in which the Cope rearrangement became more than an interesting template for study by physical organic chemists. Indeed, its value as a synthetic tool increased tremendously over the following years, resulting in the discovery of the anionic oxy-Cope rearrangement a decade later. In its discovered form, the oxy-Cope rearrangement possesses a hydroxyl group at the 3-position of the 1,5-hexadiene system, which results in formation of an enol upon [3,3]-sigmatropic rearrangement.[38–40] The propensity to then tautomerize to the more stable ketone dramatically shifts the equilibrium in the direction of the product **9**. The synthetic utility of the oxy-Cope rearrangement was recognized very early on, as it provided a facile entrée into functionalized decalin systems.

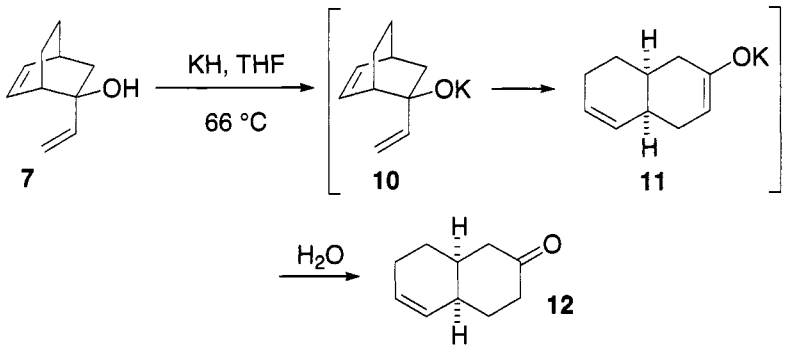


7 **8** **9**

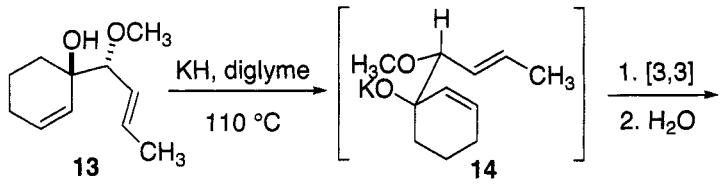
Anionic Oxy-Cope

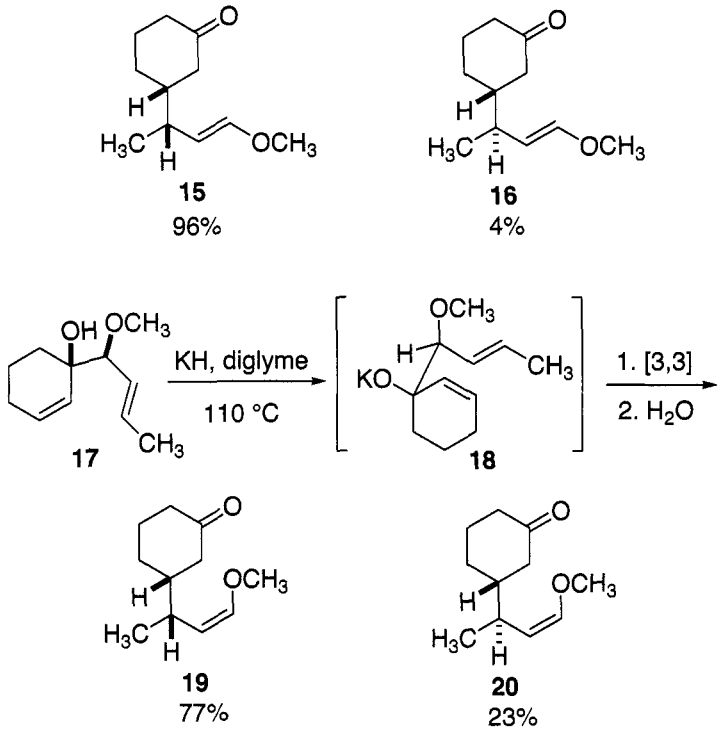
Discovered in 1975 by Evans and coworkers,[41] the anionic oxy-Cope rearrangement has emerged as the most synthetically useful of the variants described here, relegating the oxy-Cope to antiquity as a synthetic method.

Treatment of dienol **7** with KH in THF resulted in a remarkably facile Cope rearrangement of **10** to give **12** following hydrolysis of **11**. The magnitude of the rate acceleration as compared to the dienol itself has been calculated to be 10^{12} and when the additive 18-crown-6 is utilized, 10^{17}. The influence of 18-crown-6 suggests that the rearrangement is accelerated upon ion-pair dissociation. The exo-isomer of **7** under the same conditions (KH, THF, 66 °C) does not undergo the rearrangement, suggesting that this is a concerted [3,3]-sigmatropic process. The reaction was proven to be quite general, as shortly after its initial discovery, it was demonstrated on a variety of substrates.[42]



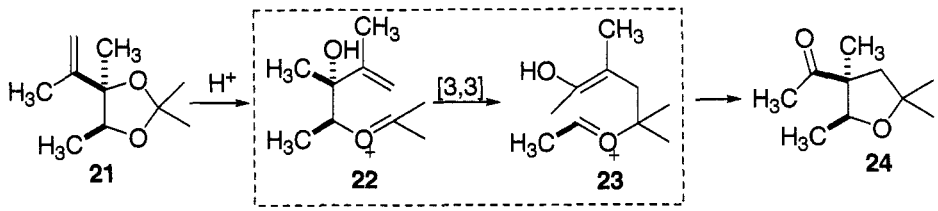
A notable example which provides insight into the transition state of the anionic oxy-Cope is demonstrated in the rearrangement of diastereomers **13** and **17**.[42] A high degree of stereospecificity is realized in the preparation of **15** from **13** as a result of the highly favored chair-like transition state which holds the methoxy substituent in the equatorial position. In comparison, the chair-like transition state **18** arising from **17** places the methoxy substituent in the axial position, destabilizing the transition state, and leads to the formation of a significant amount of **20**, likely via a boat-like transition state. The discovery of the anionic oxy-Cope rearrangement has not only enabled the synthesis of tremendously complex natural products, but it has also inspired a large number of delicate mechanistic studies to determine the exact degree of bond-breaking and formation in the transition state.





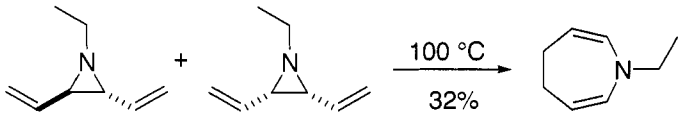
2-Oxonia-Cope

In 1987, when rationalizing the formation of **24** from **21**, one mechanistic pathway suggested by Overman and coworkers involved the formation of intermediate **22** which might undergo a concerted 2-oxonia[3,3]sigmatropic rearrangement followed by an intramolecular aldol reaction.[43] While other evidence in these studies favors an alternate mechanism, the oxonia-Cope mechanism suggested here has in fact been identified as a competitive,[44–48] and sometimes favored pathway[49–51] in a number of transformations.



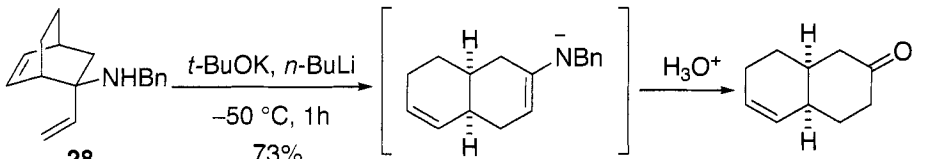
Amino-Cope

Relatively few examples of the Cope rearrangement featuring an amino group in the 3-position of the 1,5-hexadiene system exist.[52–54] The first example of such transformation was reported by Stogryn and Brois[55] when the steam distillation of the isomeric mixture of **25** and **26** resulted in the preparation of **27**, along with unreacted **25**. The lack of reactivity of the *trans*-aziridine **25** in the rearrangement process provided evidence that the reaction to **29** proceeds via a Cope process.



25 **26** **27**

As in the anionic oxy-Cope, it was anticipated by MacDonald and coworkers[56] that a similar rate increase should be observed in the anionic amino-Cope rearrangement. As shown in the transformation of **28** to **12**, the anion-accelerated reaction proved substantially more facile than the amino version. While extremely harsh conditions (230 °C in octane) were required to prepare **12** directly in only 40% yield, deprotonation of the amino group resulted in facile rearrangement at low temperature to give **12** in 73% yield. Notably, the *exo*-isomer of **28** underwent a similar rearrangement to give **29**, implicating a fragmentation followed by a Michael addition reaction rather than the concerted sigmatropic rearrangement.[57] This mechanistic understanding has been confirmed via calculations by Houk and others.[58]

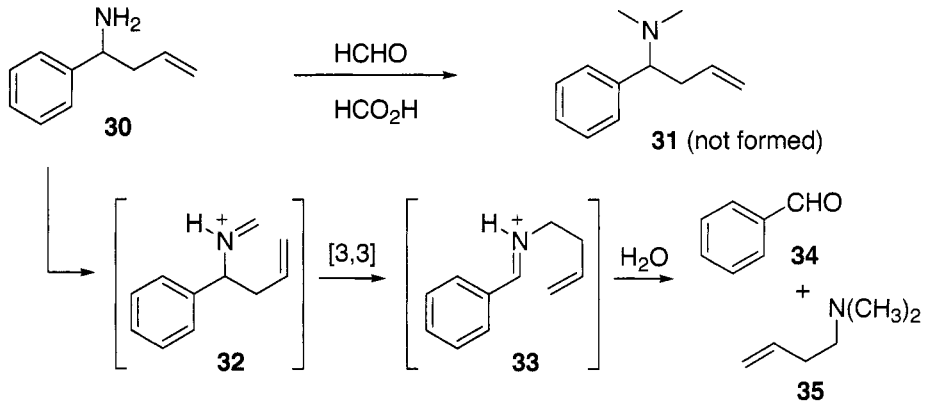


28 **29** **12**

2-Aza-Cope

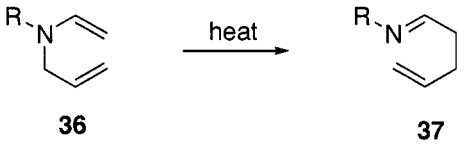
Shortly after the discovery of the Cope rearrangement, Horowitz and Geissman serendipitously discovered the 2-aza-Cope variant.[59] Upon attempting the reductive amination of **30** for the preparation of dimethylamine **31**, they observed the formation of debenzylated amine **35**. Investigation of the mechanism resulted in its elucidation as a Cope

rearrangement of the resulting iminium ion **32** produced on reaction of **30** with formaldehyde.



3-Aza-Cope

Perhaps better classified as an amino-Claisen rearrangement, the 3-aza-Cope rearrangement, first discovered in 1967,[60] is represented by the thermal rearrangement of allyl vinyl amine **36** to give imine **37** as shown in the general example below. While examples of the aliphatic version are rare, a number of studies have made use of the allyl phenyl amine rearrangements, but these are more typically referred to as the amino-Claisen rearrangement and will not receive much attention here.[61,62] When charged quaternary amines are used in **36**, the resulting iminium ion can be easily hydrolyzed to give aldehydes. This so called 3-azonia-Cope has emerged as an ideal candidate for the study of supramolecular catalysis within a self-assembled host.[63–65]

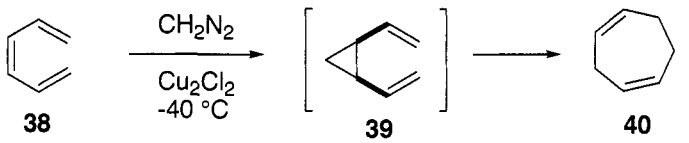


36 **37**

Cyclopropyl-Cope

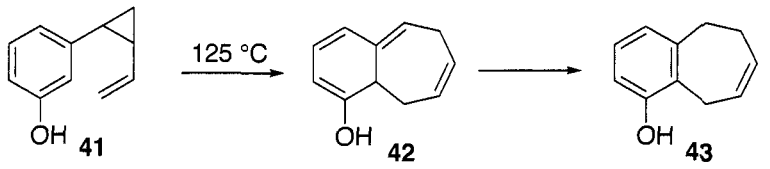
Twenty-one years after the discovery of the Cope rearrangement, the cyclopropanation of 1,3,5-hexatriene (**38**) by diazomethane in the presence of cuprous chloride resulted in the rearranged structure **40**, instead of the expected cyclopropane product.[66–68] In what is referred to as a divinylcyclopropane rearrangement (or cyclopropyl-Cope rearrangement), the *cis*-orientation of the alkenes and the relief of cyclopropane ring strain

results in a facile Cope rearrangement to form the cycloheptadiene **40**. The fact that the reaction occurs even at temperatures as low as –40 °C gives insight into how much the activation barrier has been lowered as a result of the effects mentioned here. Notably, *trans*-divinylcyclopropanes are still able to rearrange, albeit through a different mechanism, and requiring temperatures in excess of 100 °C. The reaction gained instant notoriety in the synthetic arena, as it provided a reliable solution for synthesis of 7-membered rings.[69–74]



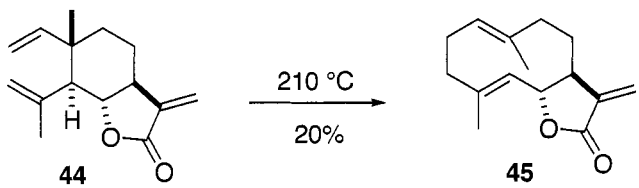
Aromatic-Cope

As seen in the above variations, the simple and reversible Cope rearrangement of 1,5-hexadiene systems can be made more synthetically useful by the addition of substituents which drive the reaction in a single direction. It stands to reason that one of the more difficult Cope rearrangements to perform would involve a substrate in which one of the participating double bonds of the 1,5-diene system is also part of an aromatic structure, providing an activation barrier potentially too high to overcome. For this reason, some 38 years after the discovery of the parent reaction, the first example of the aromatic Cope rearrangement was discovered when **41** was heated to 125 °C, resulting in the formation of **42** and rapid tautomerization to the aromatic compound **43**.[75] Clearly, the high activation barrier imposed by losing aromaticity in the first step is overcome by the relief of ring strain in the cyclopropyl system. Since its initial discovery, the aromatic-Cope rearrangement has been executed employing benzene[76–80] and other heteroaromatic ring systems.[81–86] In most of the synthetically useful examples of the aromatic-Cope rearrangement, an additional variant (oxy-aromatic- or anionic-oxy-aromatic-, for example) is coupled to ensure completion of the reaction.



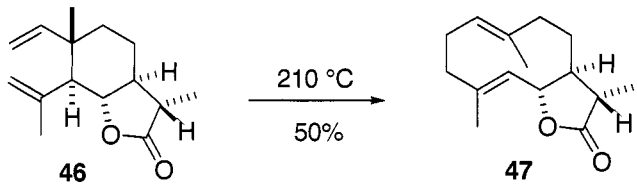
1.1.3.5 Synthetic Utility

Unlike some other variants, the pure Cope rearrangement has not received wide application in complex molecule synthesis. This is primarily due to the reversibility of the rearrangement as well as the elevated temperatures required to overcome the high activation barrier. In the absence of product stabilization or reactant destabilization, often present in the variants, the Cope rearrangement is energetically neutral and will often result in a nearly 1 : 1 mixture of reactant and product. An illustration of this is found in the synthesis of (+)-costunolide (**45**) by Grieco and Nishizawa. In the final step of the total synthesis, compound **44** undergoes Cope rearrangement to produce **45** in 20% yield, along with a 42% yield of recovered starting material.[87]



44 **45**

Slightly more encouraging was the rearrangement of **46** in these same studies to produce dihydrocostunolide (**47**) in 50% yield with approximately 50% recovered starting material.[87]

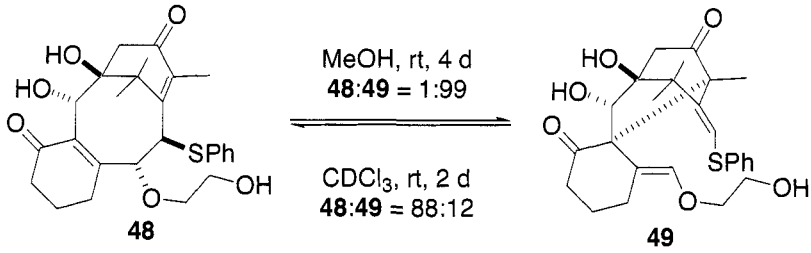


46 **47**

Taking advantage of this, Barrero[88,89] reduced commercially available, natural costunolide to give **47** which was then subjected to Cope rearrangement to give **46** as a means of converting the germacrolide to elemanolide **46** in 88% yield after three recycling events.[90]

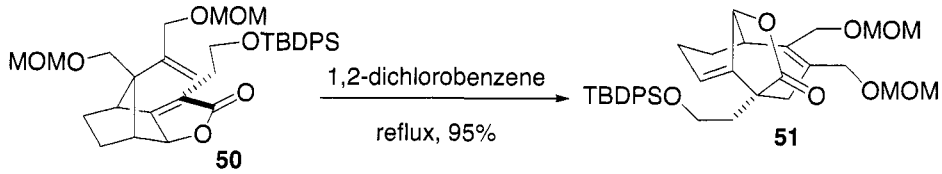
In some cases, product distribution is influenced by the solvent used. As observed in efforts toward the synthesis of taxane diterpenoids, intermediate **48** when left standing in methanol for three days was completely converted to **49**.[91] On the other hand, in the aprotic solvent $CDCl_3$, **48** was present in an 88:12 ratio with **49**. These results are rationalized as follows. The strain of the bridgehead double bond in **48** causes **49** to be favored thermodynamically. In the presence of MeOH, where intermolecular hydrogen bonding is predominant, spirocycle **49** is

favored. On the other hand, in $CDCl_3$, intramolecular hydrogen bonding imposes strain in the spirocycle **49**, shifting the equilibrium to **48**.



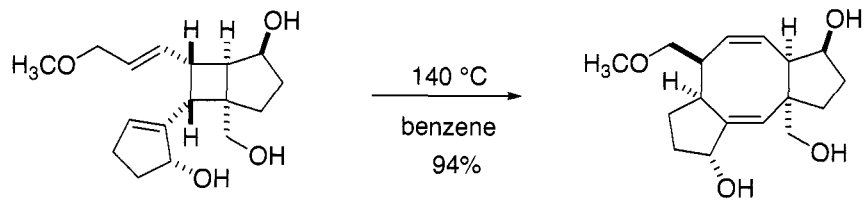
48 **49**

The examples above demonstrate the concept that relief of strain can be a driving force for the Cope rearrangement. The synthesis of the tetracyclic core of CP-225,917 utilized this relief of strain to drive a thermal Cope rearrangement. The intermediate **50**, highly strained as a result of the bridgehead alkene undergoes efficient rearrangement in refluxing dichlorobenzene to give **51** in an impressive 95% yield.[92]



50 **51**

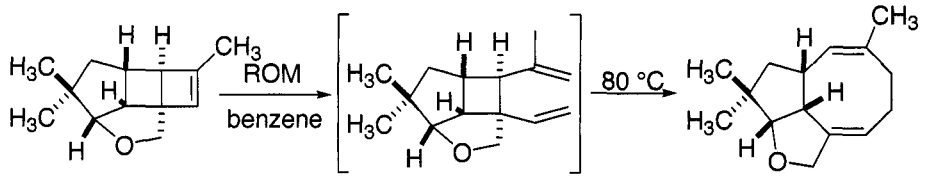
Snapper and coworkers have effectively used this idea of relieving strain in the Cope rearrangement as a means of preparing 5–8–5 ring systems utilizing their intramolecular [2 + 2]-photocyclization methodology. Specifically, in a reaction with substantial precedence,[93] the Cope rearrangement of triol **52** relieves the strain of the cyclobutane in the efficient conversion to **53**, completing the synthesis of the 5-8-5 ring system.[94]



52 **53**

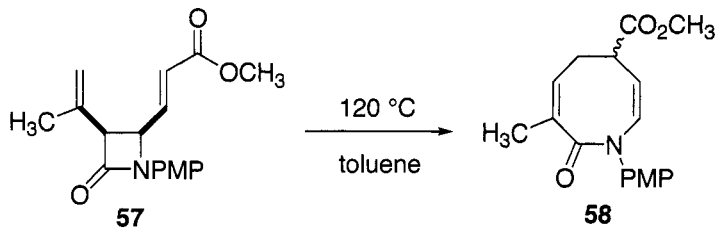
This strategy has been successfully applied to the synthesis of (+)-asteriscanolide. Ring opening metathesis of the highly strained cyclobutene photoadduct **54** results in formation of the *cis*-dialkenyl cyclobutane **55** with

the alkene termini appropriately situated to undergo facile Cope rearrangement. As such, in the same pot, thermal rearrangement occurs to provide **56**,[95] a compound which can be easily elaborated to an intermediate in Wender's synthesis[96] of the natural product.

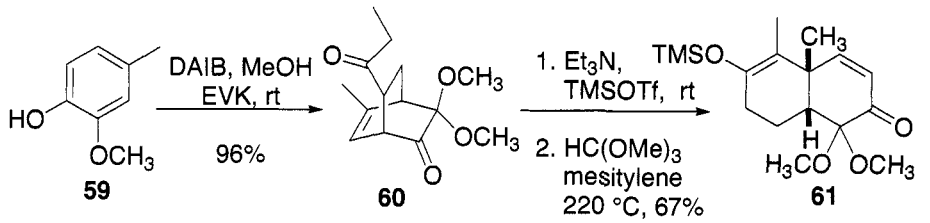


54 **55** **56** 74%

Similar results have been obtained in the [3,3]-sigmatropic rearrangement of *cis*-divinyl-β-lactams as a general method to prepare tetrahydroazocinones.[97,98] In a reaction that has proven to be general for a number of substrates, heating at 120 °C in a sealed tube resulted in rearrangement from **57** to **58**. When a chiral directing group is attached to the lactam nitrogen, rearrangement occurs through a boat-like transition state[99] to give optically pure products.



57 **58**

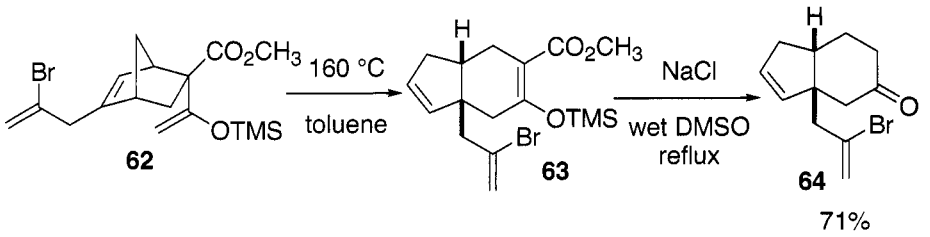


59 **60** **61**

The Cope rearrangement is prominently featured as a key step in the stereocontrolled four-step synthesis of *cis*-decalins advanced by Liao and coworkers.[100–103] As demonstrated in the first total synthesis of (±)-eremopetasidione, beginning with cresol (**59**), oxidation in methanol afforded the *in situ* diene, which subsequently undergoes a Diels–Alder reaction with ethyl vinyl ketone to give **60** as a single isomer.[104] Transformation of **60** to a silyl enol ether sets the stage for the Cope rearrangement, affording **61** in

good yield upon heating. Other groups have utilized similar strategies for the synthesis of *cis*-decalins.[105,106]

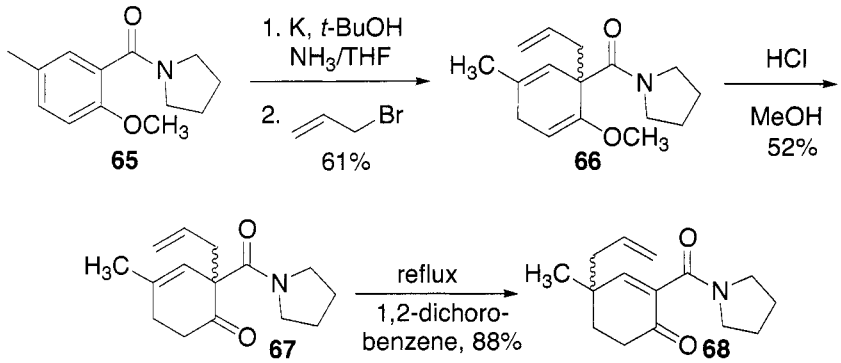
Corey has utilized a similar Cope rearrangement of a silyl enol ether in the synthesis of gibberellic acid[107] and cassiol.[108] Heating of **62** effected Cope rearrangement to provide **63**, which without purification was subjected to decarboxylation under Krapcho conditions to give **64** in good yield. A similar strategy was used in the Wender synthesis of reserpine.[109]



62 **63** **64**

71%

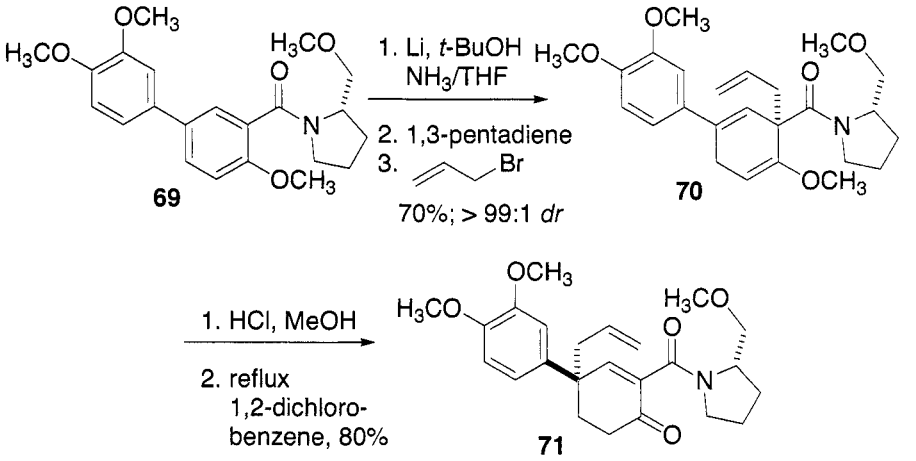
Malachowski and coworkers have developed a creative and efficient method for the stereoselective synthesis of quaternary carbon atoms using a Birch reduction/Cope rearrangement sequence.[110] The entire sequence, illustrated below, begins with the Birch reduction of **65**, followed by enolate trapping with allylbromide to give **66**.[111] Hydrolysis of the enol ether results in **67**, which undergoes an efficient Cope rearrangement to give **68** containing a quaternary carbon. Conjugation with the amide in **68** is presumed to favor rearrangement.



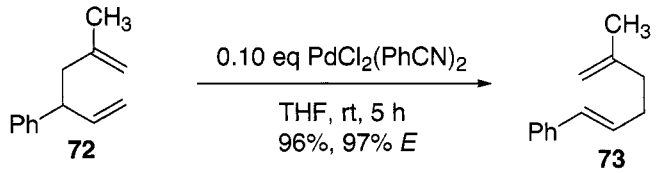
65 **66** **67** **68**

Utilizing a chiral, non-racemic amide, the reaction has been performed with high levels of diastereoselectivity, as demonstrated in the total synthesis of (+)-mesembrine.[112] Birch reduction and alkylation produces **70** in > 99 : 1 *dr*. Hydrolysis and thermolysis results in the rearranged product **71** in good yield. The diminished yield in this example, as compared to above, is likely due to the competitive conjugation with aromatic ring in

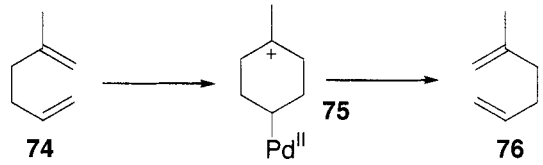
the **70**. This method has also been applied to the synthesis of (–)-lycoramine.[113]



Discovered in 1966,[114] the Pd(II)-promoted[115] and Pd(II)-catalyzed[116,117] Cope rearrangement has become an important tool in synthetic endeavors. Catalysis of the Cope rearrangement by palladium salts such as $PdCl_2$ provides rate enhancements as high as 10^{10} while also offering higher levels of stereoselectivity than their thermal counterparts.[116,118,119] In one of the early examples described by Overman, a predominant contributor in this area, **72** was smoothly converted to **73** in the presence of $PdCl_2(PhCN)_2$ at room temperature.[116]

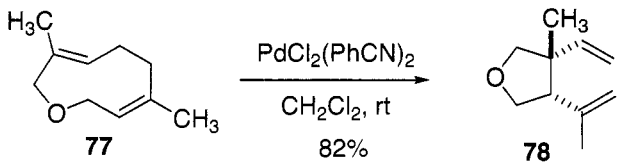


Mechanistic studies have suggested that the reaction proceeds through the palladium-bound six-membered cation **75**.[120–124]



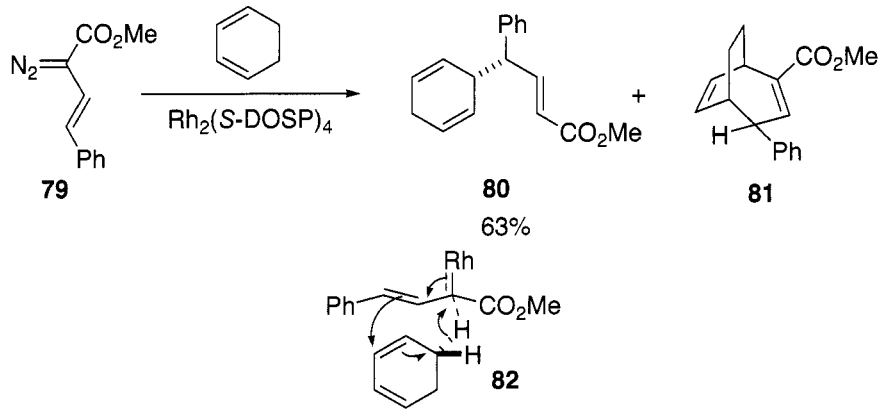
The Pd(II)-catalyzed Cope rearrangement has been applied extensively in synthetic efforts. One example which warrants mention is the

rearrangement to **78** of the chiral, non-racemic, nine-membered cyclic diene **77**, which was prepared via kinetic resolution.[125]



Another recently reported variant of the palladium catalyzed Cope rearrangement utilizes Pd(0) to effect the transformation.[126,127] In this case, the reaction is presumed to proceed through a bis-(η^3-allyl)Pd(II) intermediate via insertion of Pd(0) into a non-strained C–C bond.

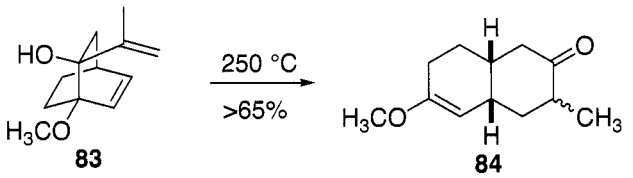
An extremely elegant and useful methodology for natural product synthesis which deserves mention in this context comes from the work of Davies and coworkers.[128–135] Their novel reaction manifold was discovered in 1999 when attempting a standard C–H insertion into 1,3-cyclohexadiene of the rhodium carbenoid derived from **79**. In lieu of the expected product, **80** was prepared by what is considered a combined C–H insertion/Cope rearrangement,[136] proceeding through transition state **82**. The byproduct **81** results from an alkene cyclopropanation reaction, followed by Cope rearrangement. A similar extension of this methodology featured C–H activation, followed by the siloxy-Cope rearrangement.[137]



Oxy-Cope

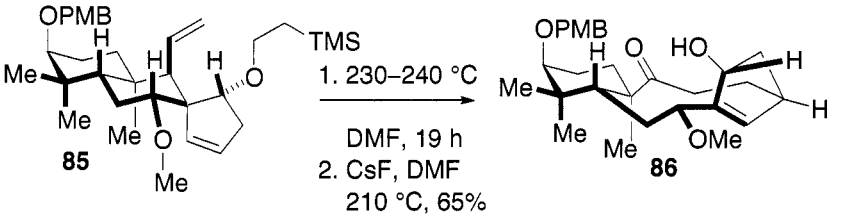
Because of the mild conditions enabled by the discovery of the highly efficient anionic oxy-Cope rearrangement, the oxy-Cope has received significantly less attention as a viable synthetic method. In fact, in modern chemical literature, a search for the term oxy-Cope brings up a number of

articles where, in actuality, the anionic oxy-Cope is being utilized instead. Still, several notable syntheses have been developed making use of the oxy-Cope itself. For example, Evans and coworkers[138] exploited the thermal rearrangement of diene **83** for preparation of the *cis*-decalin system **84**, an intermediate in the synthesis of (±)-luciduline, a *Lycopodium* alkaloid.



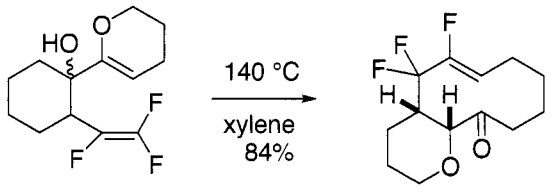
83 **84**

In 1996, Paquette and coworkers utilized the oxy-Cope rearrangement for synthesis of (–)-*O*-methylshikoccin and (–)-*O*-(methylepoxy)shikoccin, highly cytotoxic metabolites from plants of the genus *Rabdosia*.[139] Thermal reaction of spirocycle **85** resulted in **86** following cleavage of the protecting group.



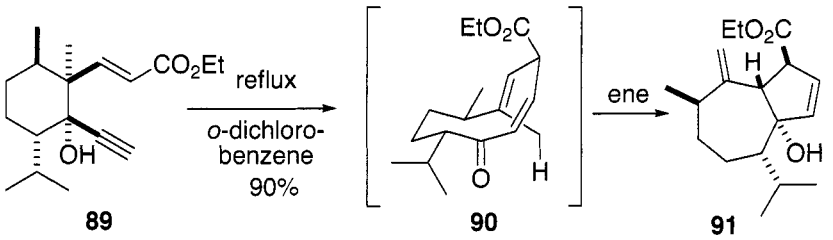
85 **86**

In some cases, the use of the thermal oxy-Cope rearrangement is preferable to the anionic oxy-Cope because of the potential base sensitivity of the molecule undergoing rearrangement. Such was the rationale for use of the oxy-Cope in the rearrangement of fluorinated divinylcyclohexanols.[140] Concerns over the high nucleophilicity of potassium alkoxides along with the highly electrophilic nature of perfluoroalkanes resulted in the use of thermal rearrangement of divinyl cyclohexanol **87** as a general method for the preparation of fluorinated ketone **88**.



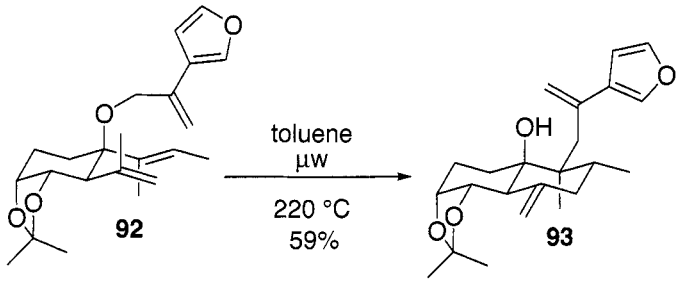
87 **88**

The carbonyl produced in the oxy-Cope rearrangement leads naturally to its coupling with other C–C bond forming processes. A fortuitous discovery of such a process revealed itself in the thermal rearrangement of **89**.[141] Expecting a ring enlargement, the authors were surprised to isolate **91**, the product of a transannular ene reaction of oxy-Cope product **90**.



89 **90** **91**

Similar processes have been designed and utilized extensively by Barriault and coworkers for efforts in natural product synthesis.[142–148] An impressive example of this strategy was utilized for the synthesis of the *neo*-clerodane skeleton of teucrolivin A.[149] Thermal rearrangement of **92** under microwave irradiation results in a tandem sequence featuring an oxy-Cope rearrangement, followed by the Claisen rearrangement and subsequent ene reaction to give **93**.

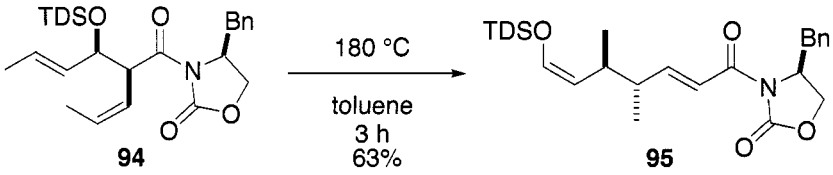


92 **93**

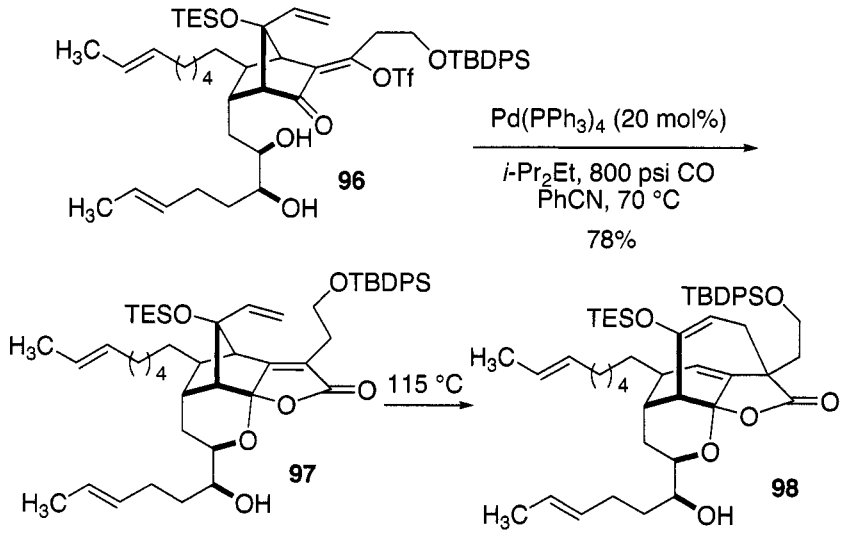
Siloxy-Cope

First demonstrated in the Schneider laboratories, chiral aldol products have been widely utilized as substrates for siloxy-Cope rearrangements,[150] the products of which have been elaborated to enantiopure and highly functionalized tetrahydropyrans,[151,152] piperidines,[153,154] cyclohexanes[155] and substructures of polyol natural products.[156,157] As demonstrated in the synthesis of the insect pheromone lasiol,[158] silyoxy-1,5-diene **94**, prepared via an Evans *syn*-aldol, undergoes facile rearrangement to provide the 1,2-*trans*-dimethyl arrangement of **95** in good yield and with high

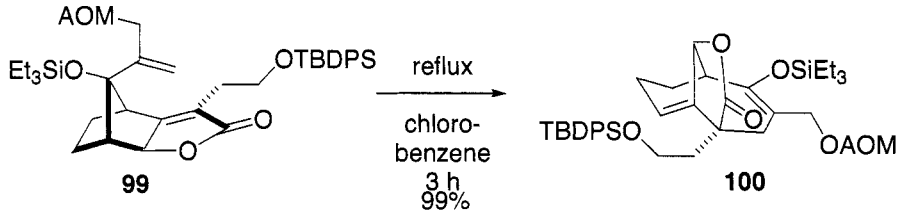
stereoselectivity. The stereoselectivity arises from a chair-like transition state in which the silyl ether preferentially occupies the pseudoaxial position.



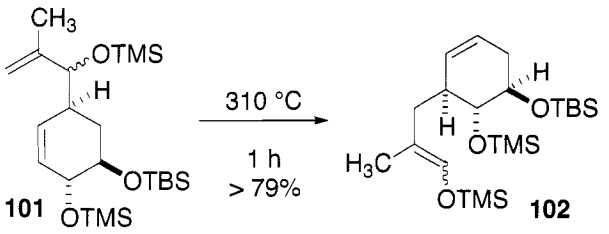
The syntheses of the related molecules CP-225917 and CP-263114 and other members of the phomoidride family have employed the siloxy-Cope rearrangement as key transformations. In one of the more impressive demonstrations of this concept, Leighton and coworkers[159–162] utilized the late-stage, tandem carbonylation/siloxy-Cope rearrangement of **96** to provide **98** in outstanding yield.



Clive and coworkers[163,164] have studied a similar transformation aimed at the same family of molecules. Heating of **99** in chlorobenzene resulted in thermal rearrangement to give **100**.

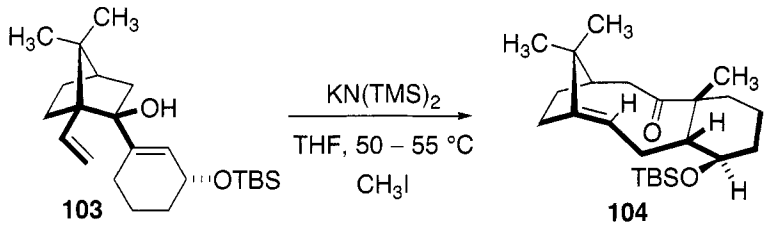


In one of the early applications of the siloxy-Cope rearrangement in synthesis, Danishefsky and coworkers utilized the process for the synthesis of *N*-acetylactinobolamine.[165,166] Rearrangement of **101** resulted in the formation of **102** in good yield.



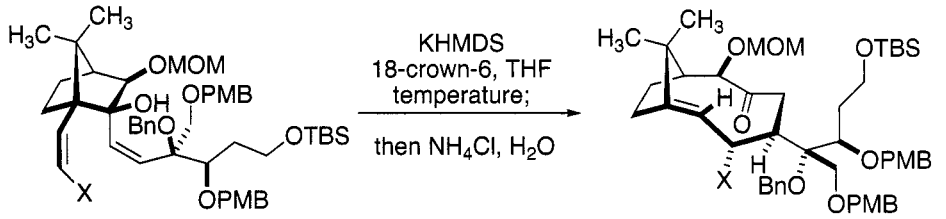
Anionic Oxy-Cope

Amongst those researchers that have studied the anionic oxy-Cope rearrangement, the achievements of Paquette are especially noteworthy. Not only has he been successful at utilizing it for complex natural product synthesis,[167–174] he and his coworkers have also provided novel insights into the subtle details which influence patterns of reactivity in these well-studied systems. Primary amongst these studies were those directed at natural (+)-taxusin[175–179] which featured the anionic oxy-Cope rearrangement/enolate alkylation sequence of **103** to give **104**.



While the above reaction enabled the synthesis of (+)-taxusin, it barely scratches the surface of Paquette's contribution to the development and understanding of the anionic oxy-Cope rearrangement. One of the many important contributions arose when, as an extension of the taxusin studies, a vinyl sulfide was utilized as an oxygen surrogate.[180] Thus, a direct comparison of the relative reactivity of **105** and **106** in the anionic oxy-Cope rearrangement was made possible.[181] Interestingly, both reactions were complete in just 5 minutes, but required substantially different temperatures for this process. These results clearly demonstrate the large reactivity effects that subtle changes can have on the course of the reaction, with the sulfide

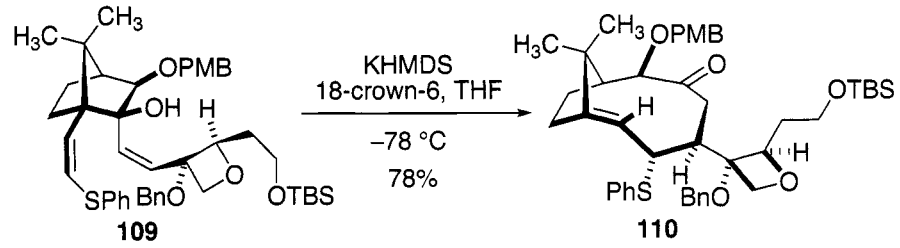
functional group offering enhanced reactivity in the 6-position of the dienol system.[182,183]



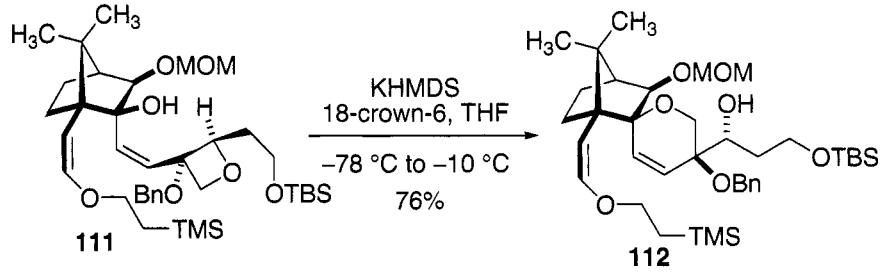
105 X = OCH_2CH_2TMS 0 °C; 71% : **107**

106 X = SPh −78 °C; 85% : **108**

A consequence of these substitution dependent rates can be seen in the comparison of the attempted anionic oxy-Cope rearrangement of **109** and **111**.[181] While **109** proceeds efficiently to give the Cope product **110**, **111** appears to decompose via an intramolecular backside opening of the neighboring oxetane ring to give **112**.



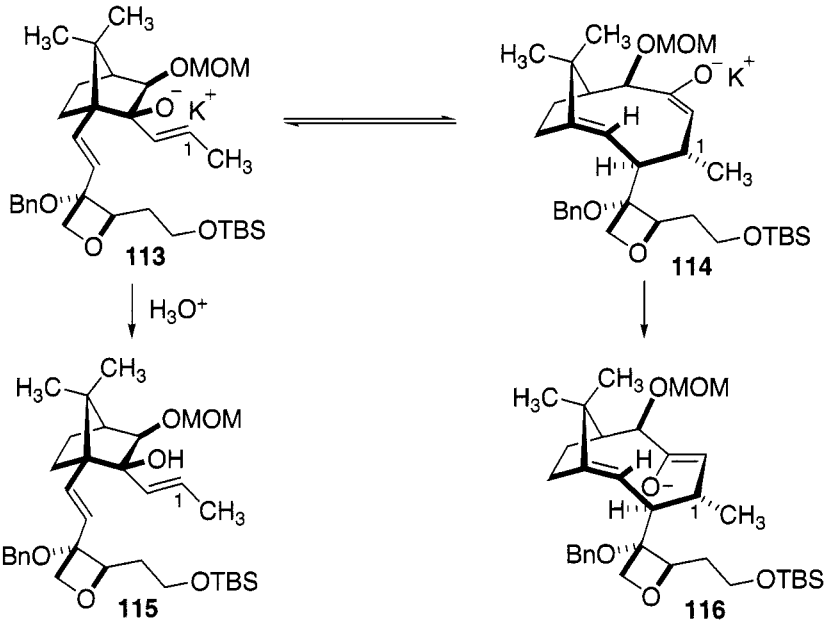
109 **110**



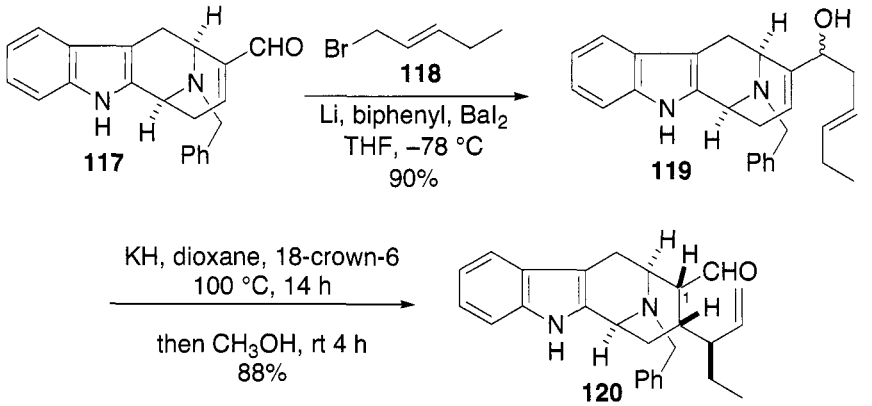
111 **112**

Another noteworthy event from these studies was the discovery of the first reversible anionic oxy-Cope rearrangement.[184] The oxy- and anionic oxy-Cope rearrangements are largely thought to be irreversible processes as a result of the significant difference in energy between the starting diene and the product enol or enolate, respectively. However, while investigating the sigmatropic rearrangement of potassium salt **113**, any attempts at quenching the reaction with aqueous acid resulted in the starting dienol, even though

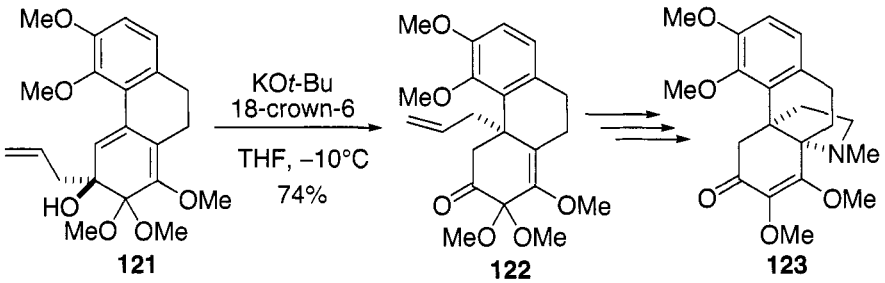
TLC evidence had suggested the reaction was complete. It was thus discovered that the equilibrium mixture preferentially protonated via **113**. However, in the presence of silica gel at higher temperature (0 °C), atropisomerization gave the more stable isomer **116**, resulting in the Cope rearrangement product after protonation. A compound lacking the C-1 methyl underwent facile rearrangement implying that an $A^{1,3}$ interaction between the methyl substituent and the bulky oxygenated side chain was the reason for the slow atropisomerization of **114**.



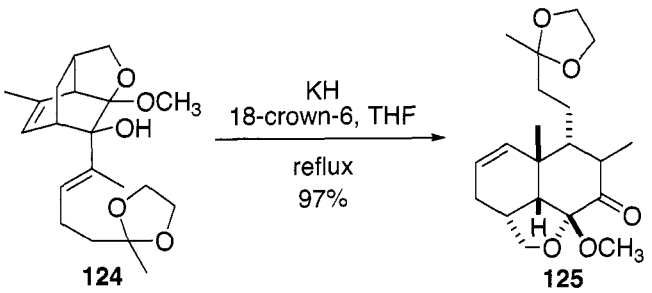
An impressive demonstration of the synthetic utility of the anionic oxy-Cope rearrangement comes from the Cook laboratories. Addition of the allylic carbanion of **118** provided the requisite dienol **119** for the Cope rearrangement. In a procedure that has found application in the synthesis of a number of related alkaloids, treatment of dienol **119** under standard conditions resulted in the facile rearrangement to **120**.[185] Originally, **120** was isolated in a 4:1 ratio with its C-1 diastereomer.[186] However, methanol workup resulted in epimerization to give exclusively **120** in 88% yield. Demonstrating the power of this transformation, this strategy has been utilized by Cook for the synthesis of several indole alkaloids, including talpinine, talcarpine, alstonerine, ajmaline, alkaloid G, norsuaveoline, (–)-(*E*)16-epiaffinisine, (+)-(*E*)-16-epinormacusine B and (+)-dehydro-16-epiaffinisine, amongst others.[187–194]



The anionic oxy-Cope also featured predominantly in the synthesis of the alkaloid (±)-hasubonine (**123**), bearing a structural resemblance to the morphine alkaloids.[193] Following the Grignard addition of an allyl group to give trienol **121**, standard conditions were utilized to effect rearrangement to **122** at low temperature and in good yield. The synthesis of **123** was completed in just three steps, and should be amenable to synthesis of other members of the family.

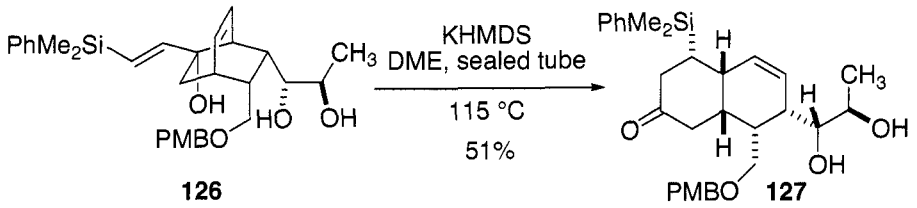


Liao and coworkers used the anionic oxy-Cope rearrangement as a key step in their synthesis of (±)-bilosespenes A and B, molecules which have demonstrated cytotoxicity against a variety of tumor cell lines.[194] Specifically, their strategy relies on the use of a general four step process, featuring an intramolecular Diels–Alder and anionic oxy-Cope rearrangement for synthesis of the *cis*-decalin core. In the final step of this process, the Cope rearrangement of **124** was effected under standard conditions to give **125** in nearly quantitative yield.



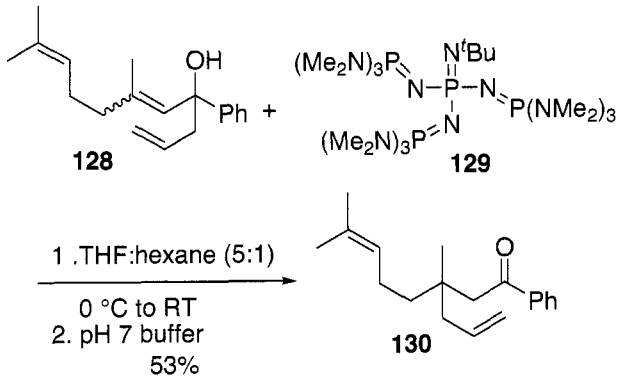
124 125

The related anionic oxy-Cope rearrangement of **126** to **127** was utilized for preparation of the *cis*-decalin ring system of superstolides A and B.[195]



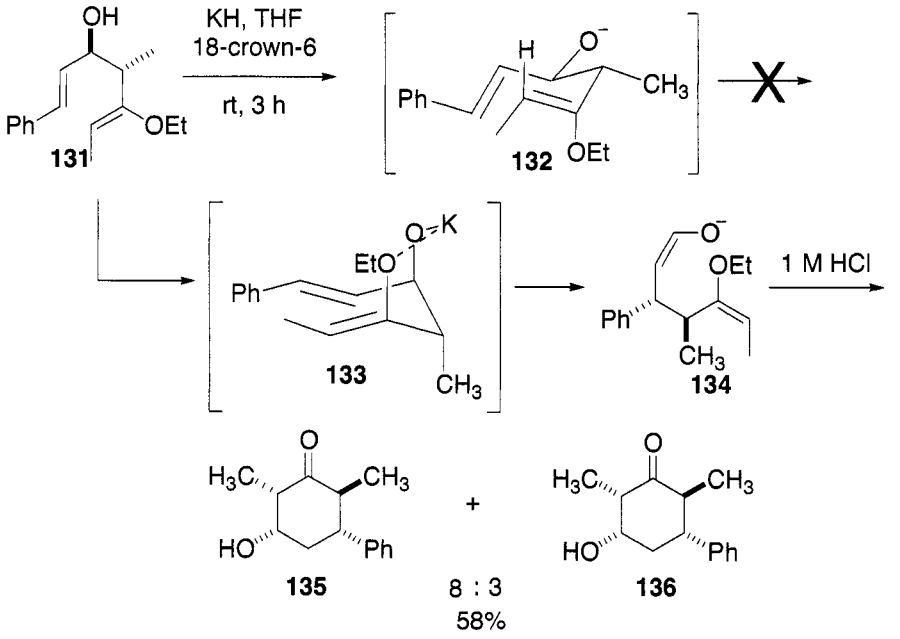
126 **127**

In 2000, Hartley demonstrated the first use of a neutral, uncharged, metal-free base for this transformation.[196] Treatment of dienol **128** with phosphazine super-base **129** resulted in facile rearrangement, which proceeded at or below room temperature, to provide **130**. Because of the highly delocalized nature of the positive charge[197] upon deprotonation, the resulting alkoxide is effectively naked, and thus enables the efficient rearrangement. This easy to handle and commercially available base provides a viable alternative to the organic insoluble and highly reactive potassium hydride, which is typically used in this transformation.

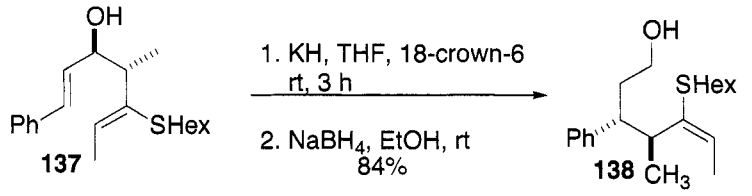


128 **129** **130**

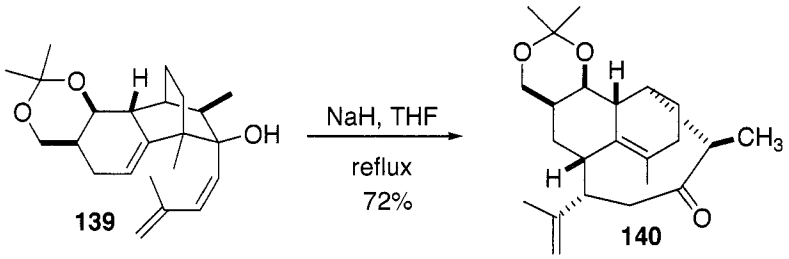
An interesting example of a chelation controlled anionic oxy-Cope rearrangement was provided by Hartley and coworkers.[198] Treatment of **131** was expected to promote rearrangement via transition state **132** with the alkoxide and methyl substituents in the equatorial position. However, 1,3-chelation between the ethoxy substituent and the potassium alkoxide caused preordering of the ground state, resulting in rearrangement to give **134**. Work-up of the resulting enolate **134** resulted in formation of β-hydroxy cyclohexanones **135** and **136**, demonstrating the anionic oxy-Cope as part of a general strategy for formation of these compounds.[199]



In contrast, anionic oxy-Cope rearrangement of a related compound, differing only in the replacement of the alkoxy group with a sulfide, proceeds as expected with no apparent chelation control. Thus, subjection of **137** to similar conditions results in the formation of **138** after reductively quenching the reaction.

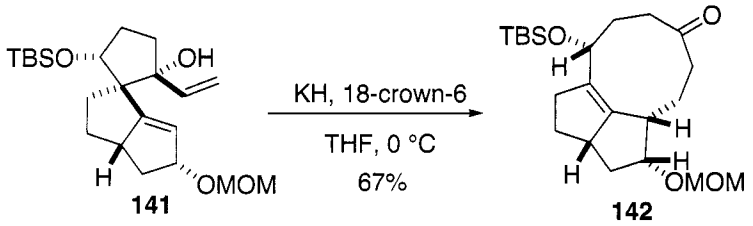


A common use of the Cope rearrangement is the synthesis of medium-sized rings, which are present in a variety of natural products. One example is the synthesis of the carbocyclic skeleton of the fungal diterpenoid vinigrol, a compound possessing a variety of potential medicinal uses. Sodium hydride was found to be preferential to potassium hydride in promoting the anionic oxy-Cope rearrangement of **139** to provide **140**.[200] An interesting facet of these studies revealed that isopropyl (in lieu of isopropenyl) substitution prevents the Cope rearrangement from occurring.[201] The preference for isopropenyl substitution has been observed previously,[85,202] and is thought to be a consequence of the electronic stabilization of the transition state, rather than a matter of steric hindrance.[203]



139 140

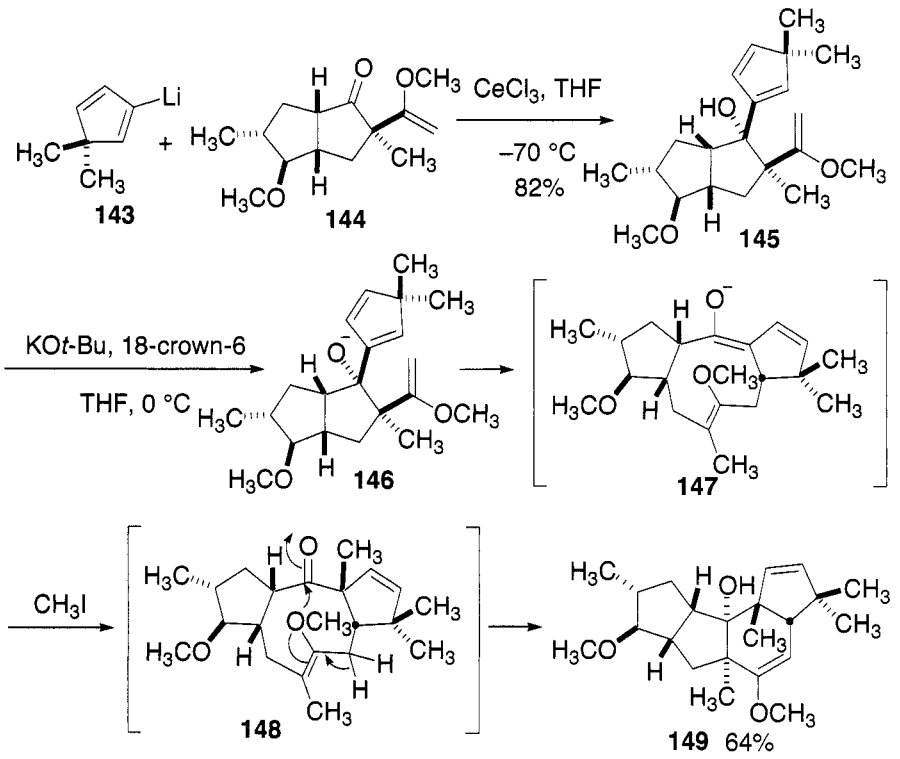
In a related process, the synthesis of the aquariolide ring system featured a similar ring expansion utilizing the Cope rearrangement.[204] Treatment of **141** under typical conditions resulted in the smooth preparation of **142**.



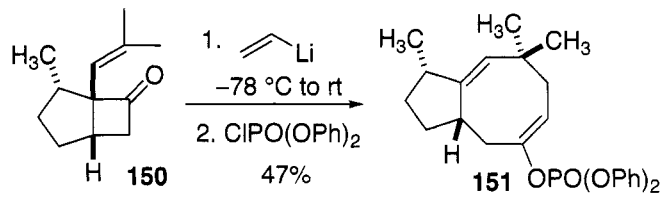
141 142

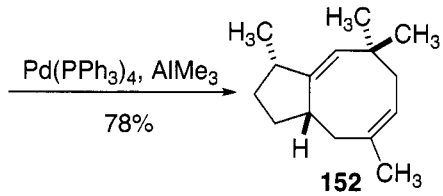
The synthetic utility of the anionic oxy-Cope rearrangement is dramatically increased when it is used in tandem with other C–C bond forming reactions. One of the most impressive demonstrations of this comes from the Paquette laboratory. Efforts which led to the synthesis of the tricyclic diterpenoids jatrophatrione and citlalitrione began with addition of the organocerium reagent derived from alkenyllithium **143** to ketone **144**.[205,206] The anionic oxy-Cope rearrangement, carried out under standard conditions, resulted in enolate **147**. At this point addition of CH_3I resulted in enolate alkylation on the β-face to give the ketone **148**, which immediately

undergoes a transannular ene cyclization resulting in **149**. This impressive combination of reactions, occurring in a single pot, was achieved in a very respectable 64% yield.

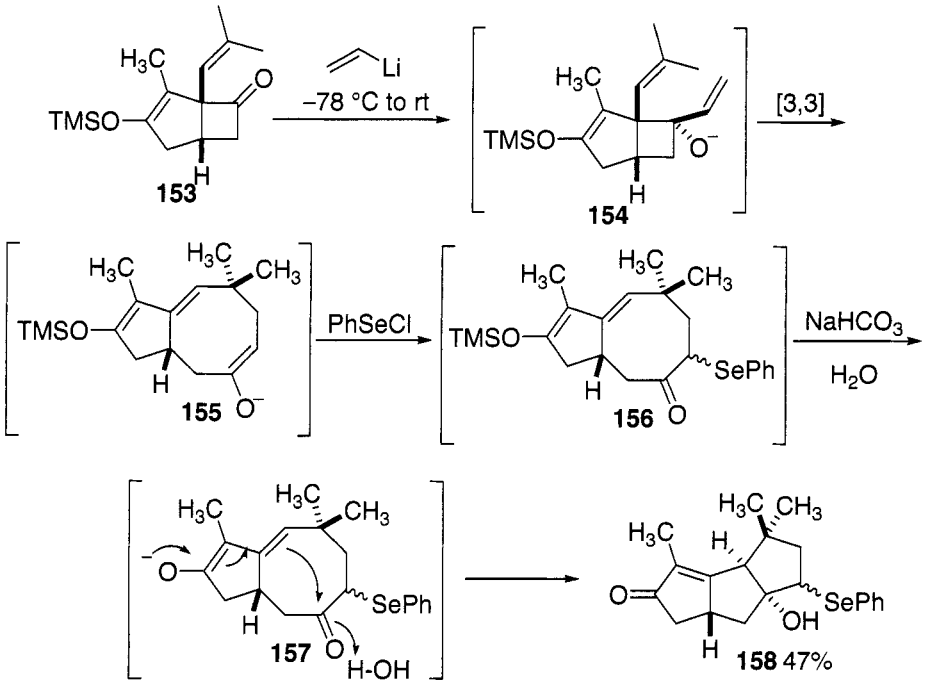


Moore and coworkers have made significant contributions to natural product synthesis involving reactions which are utilized in tandem with the anionic oxy-Cope.[207,208] In an elegant synthesis of (±)-precapnelladiene, addition of vinyllithium to **150** was followed by sigmatropic rearrangement to give the enolate, which was subsequently trapped as its diphenyl phosphate derivative **151**.[209] Completion of the synthesis was then accomplished by a palladium catalyzed coupling reaction to give **152**.



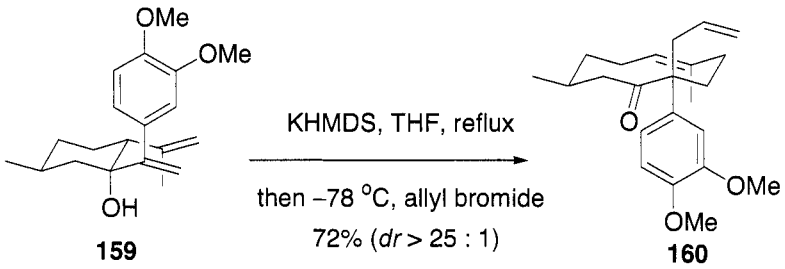


Using suitably functionalized ketones in the reaction above allows for the formation of stereochemically complex and highly functionalized polyquinanes with reactive handles for future manipulation. In one of the more impressive demonstrations of what has proven to be a general reaction, addition of vinyllithium produces the anionic oxy-Cope substrate **154**.[209] Following the sigmatropic rearrangement, the enolate is trapped to provide the α-phenylselenyl ketone **156**. Addition of water to the reaction mixture results in hydrolysis of the enolsilane revealing an enolate which then undergoes a transannular ring closure to provide **158**.

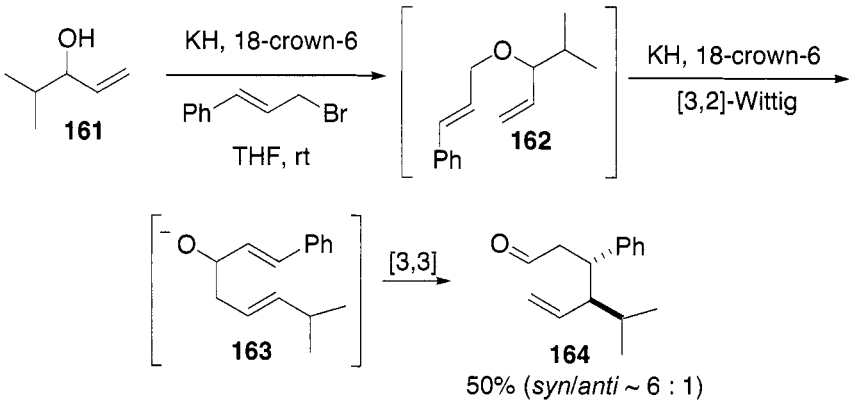


A formal synthesis of (–)-mesembrine, a serotonin reuptake inhibitor, also features the tandem anionic oxy-Cope rearrangement/enolate trapping sequence. This reaction has proven to be quite general, even for the stereoselective formation of quaternary carbon centers. As illustrated below, anionic oxy-Cope rearrangement under standard conditions results in an

enolate which is trapped with allyl bromide to give **160** in very high yield. The product **160** can then be elaborated to (–)-mesembrine in 9 steps.[210]

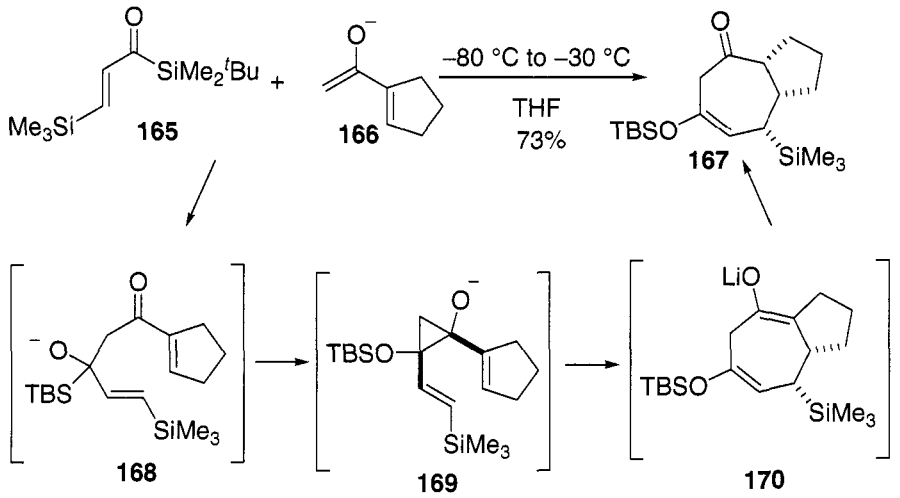


A double tandem etherification/[2,3]-Wittig/anionic oxy-Cope rearrangement sequence has been utilized in a short synthesis of tetrasubstituted tetrahydropyrans containing five stereocenters.[211] The sequence begins with alkylation of alcohol **161** giving **162**. Treatment of **162** with additional base results in the [3,2]-Wittig rearrangement yielding **163** which immediately undergoes anionic oxy-Cope rearrangement to give aldehyde **164** upon protonation of the resulting enolate.

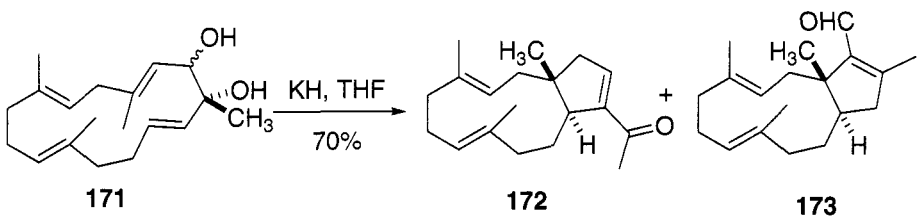


Originally thought to proceed via a tandem enolate addition/Brook rearrangement/Michael addition, the [3 + 4]-annulation utilizing α,β-unsaturated acylsilanes represents a powerful methodology for the stereoselective synthesis of functionalized 7-membered rings.[212,213] Extensions of this methodology as well as mechanistic explanations of the stereochemical results have suggested an alternate mechanism featuring an anionic oxy-Cope rearrangement.[214] Following enolate addition to acylsilane **165**, alkoxide **168** undergoes a Brook rearrangement. Trapping of the resulting anion via formation of the divinyl cyclopropane **169** results immediately in the anionic oxy-Cope rearrangement to give lithium enolate

170. Finally, hydrolysis of the enolate provides **167** in a reaction that has proven to be quite general for a number of substrates.

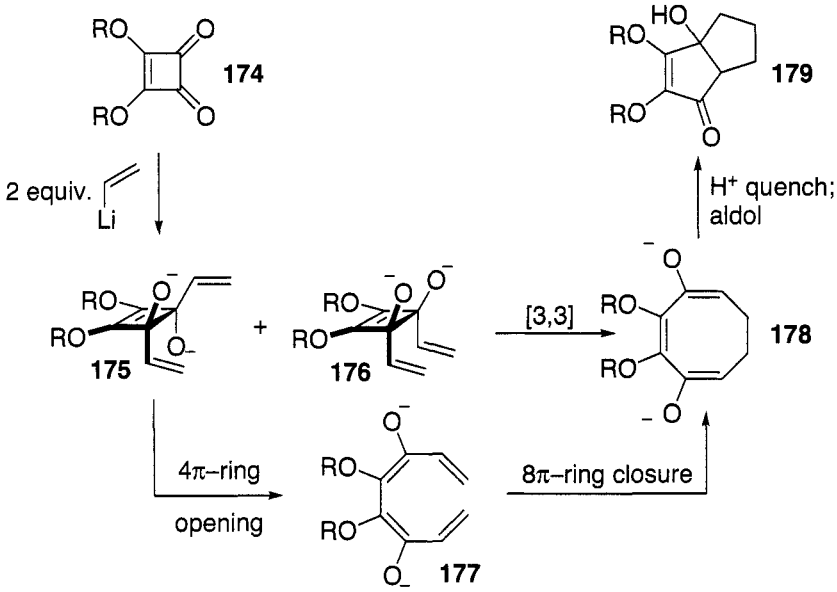


Another related reaction which has found utility in natural product synthesis is the dianionic oxy-Cope rearrangement. An example of this is seen in the syntheses of (±)-palominol and (±)-dolabellatrienone by Corey.[215] Diol **171** was deprotonated with excess base, resulting in the Cope rearrangement, which was followed immediately by an intramolecular aldol addition to give a 1 : 1 mixture of **172** and **173** in good yield.

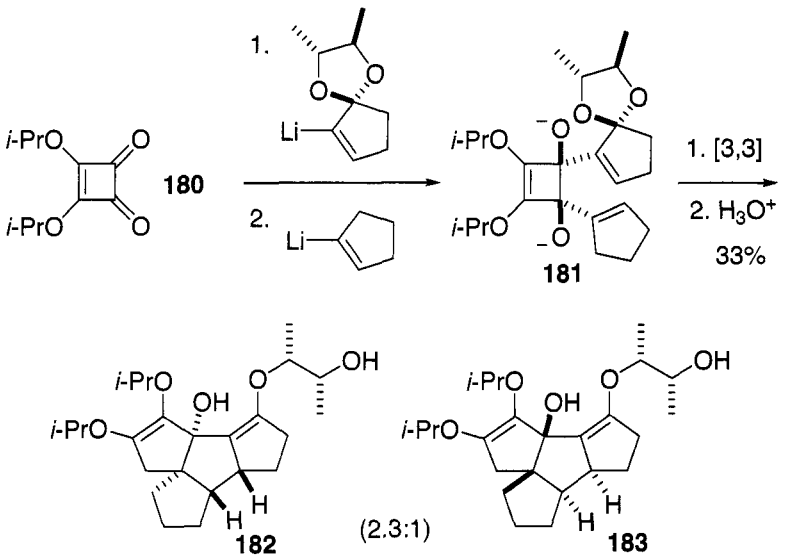


One area that has attracted significant attention is the dianionic oxy-Cope rearrangement of dienes prepared via addition of alkenyl anions to squarate esters such as **174**. Depending on the stereoselectivity of the initial addition reactions, two different processes can take place. The preferred mode of reaction of *trans*-adduct **175** features a conrotatory 4π electrocyclic ring opening to give **177** which is followed by 8π conrotatory ring closure to give cyclooctatriene **178**. On the other hand, *cis*-adduct **176**, due to the proximity of the alkene termini, is able to undergo the dianionic oxy-Cope rearrangement to give the cyclooctatriene **178** directly. The resulting triene **178** typically undergoes an intramolecular aldol reaction to give structurally

complex polycyclic products such as **179**. While the carbon skeleton of either pathway is similar regardless of which mechanism, and therefore which starting material (**175** or **176**) is employed, the Cope pathway proceeds through a strictly defined boat-like transition state and thus results in more predictable stereochemical arrangements. Originating primarily in the Paquette laboratory, a tremendous amount of work has been directed at these systems, both in terms of their application to complex molecule synthesis, but also in studying how subtle changes in strategy can make the Cope pathway more favorable.[216,217]

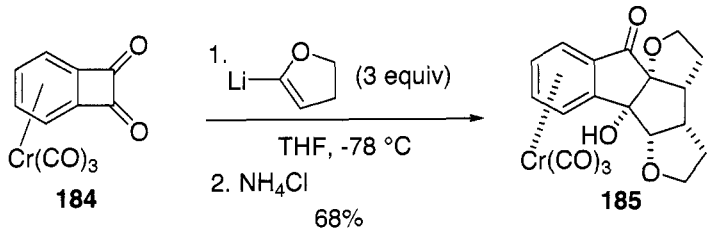


While *trans*-addition to squarate esters to provide **175** is the overwhelmingly preferred pathway, examples have come to light where the *cis*-addition is competitive.[218,219] In all of these cases, the presence of a nearby ethereal oxygen has been implicated in directing addition to the same face, although this hypothesis is seen by some as overly simplistic. The example below reveals the high level of complexity that can be obtained via this process. Sequential addition of alkenyllithium reagents is followed by the dianionic oxy-Cope rearrangement of *cis*-adduct **181** which precedes intramolecular aldol addition to give **182** and **183**,[217] the structures of which were unambiguously determined by X-ray crystallography.



Another major contributor to this research area has been the Butenschön laboratories, whose focus has been on the double addition of alkenyllithium reagents to benzocyclobutenedione chromium complex **184**.[220,221] Whereas the addition of alkenyllithium reagents to the squarate esters used in the Paquette studies favor the *trans*-addition pathway, addition to **184** gives exclusively *syn*-addition products, enabling them to undergo facile dianionic oxy-Cope rearrangements.[222,223] In a similar fashion, the diketones produced are well situated to undergo intramolecular aldol additions.

An impressive demonstration of this reaction is illustrated by the double addition to **184** at low temperature.[224] Following the sigmatropic rearrangement and intramolecular aldol addition, racemic **185** is produced in good yield.

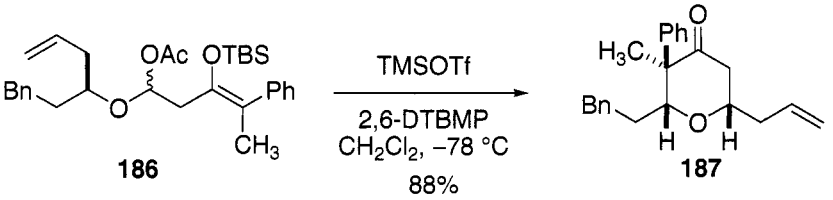


2-Oxonia-Cope

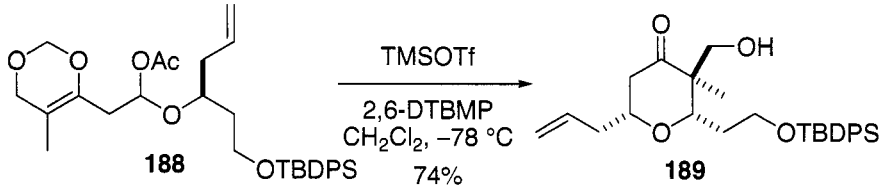
A number of research groups have published studies focusing on the oxonia-Cope rearrangement and how it competes, mechanistically, with other

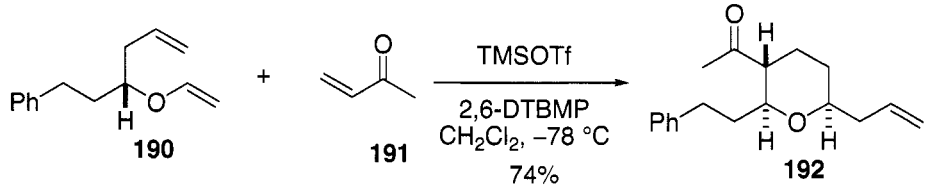
transformations.[225–230] Led by Rychnovsky, several research groups have managed to utilize this reaction as a general tool for synthetic endeavors.[231–236]

The oxonia-Cope has emerged as a powerful tool for the synthesis of tetrahydropyranones bearing quaternary centers. Beginning with acetate **186**, treatment with TMSOTf results in formation of an oxocarbenium ion, which rapidly equilibrates via the Cope rearrangement.[237] The latent silyl ether functionality is properly situated to trap the oxonium ion resulting from this rearrangement to provide **187** in good yield, as a single isomer.



This transformation, referred to as the 2-oxonia-Cope/Prins cascade has been successfully utilized to prepare, quite efficiently, the C18–C25 segment of lasonolide A,[238] a sponge metabolite with potent activity against A-549 human lung carcinoma. In contrast to the previous example, the resulting oxocarbenium generated from the oxonia-Cope rearrangement of **188** is trapped by the enol ether, hydrolysis of which results in ketone **189**.



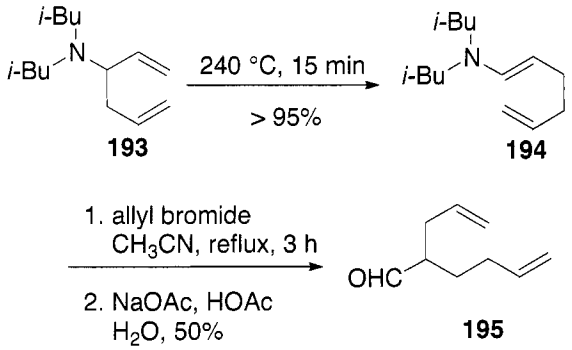


The oxonia-Cope rearrangement is also a key aspect of the Mukaiyama–Michael cascade reaction developed by Rychnovsky, which results in the formation of tetrahydropyran rings with high levels of stereoselectivity. As demonstrated in the example below, the Lewis acid promoted conjugate addition of enol ether **190** results in an intermediate oxocarbenium ion, formation of which is followed by Cope rearrangement.

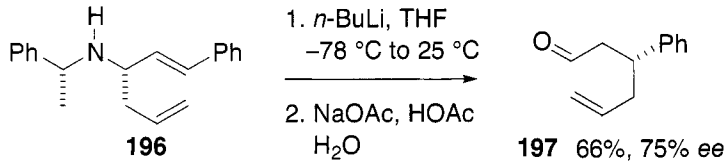
The resulting oxocarbenium ion is trapped by the enolate from the initial Michel addition completing the synthesis of **192** as a single isomer.

Amino-Cope

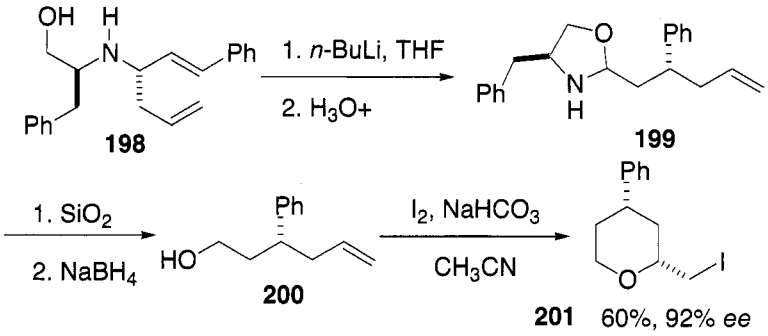
The amino-Cope variant has seen limited use in synthetic endeavors. Lead by the efforts of Allin and coworkers,[239] the synthetic potential of this reaction has only begun to be appreciated. Given the ease of preparation of suitably functionalized 3-amino-1,5-dienes, and the synthetic utility of the resulting enamine products in C–C bond forming processes, the amino-Cope should eventually prove to be a powerful methodology. In one of the limited examples of such a strategy, the amino-Cope rearrangement of **193** has been coupled with alkylation of the resulting enamine **194** to give aldehyde **195** upon hydrolysis. The use of bulky *N*-isobutyl substituents prevented decomposition of the enamine intermediate **194** by *N*-allylation.



As expected, the anionic amino-Cope rearrangement proceeds rapidly and has been shown to produce a significant level of asymmetric induction when using chiral, non-racemic substrates in the rearrangement. In what is believed to be the first asymmetric amino-Cope, rearrangement of lithiated-**196** occurs at room temperature and provides **197** in 75% *ee* and moderate yield following hydrolysis.[240] This result is rationalized by concerted rearrangement through an ordered chair-like transition state in which the amino group prefers an equatorial orientation. However, calculations by Houk and coworkers[58] suggest a non-concerted, dissociative mechanism for rearrangements of this type.

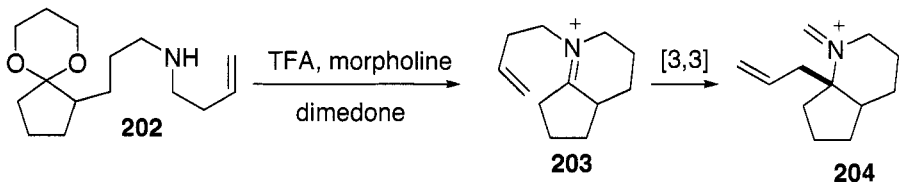


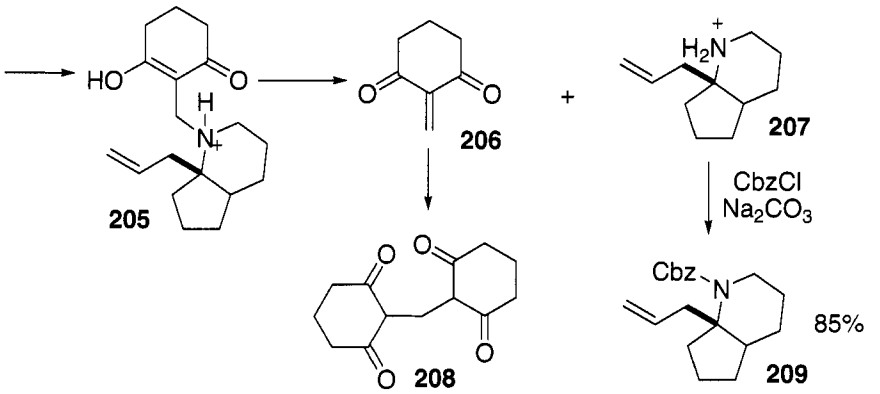
The synthetic utility of the process described above can be seen in the elaboration of **198** to give the enantiomeric tetrahydropyran **201**, suitably functionalized for further elaboration.[241] Following deprotonation of **198**,[242] rearrangement occurs to give **199**. Hydrolysis of **199** and reduction of the resulting aldehyde gives **200** in 94% *ee*. Electrophilic addition of iodine and cyclization resulted in **201** as the major diastereomer.



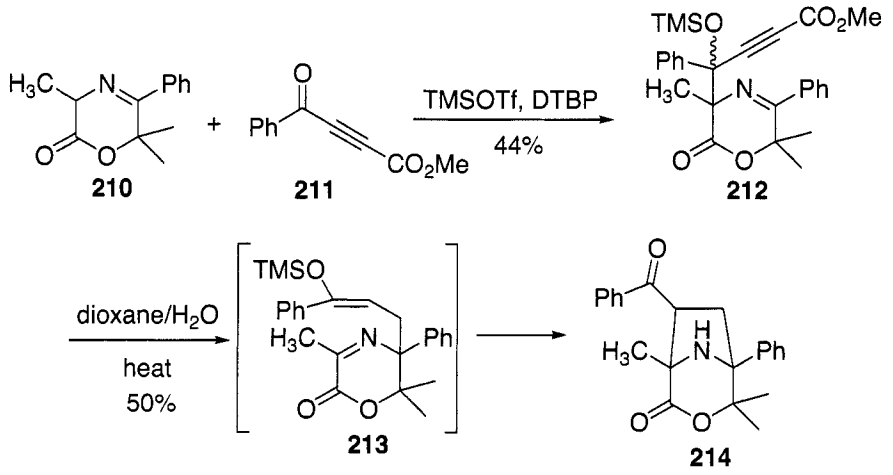
2-Aza-Cope

As a reversible process, the synthetic utility of the 2-aza-Cope rearrangement is limited by the fact that, with rare exception,[243–245] neither side of the equilibrium is favored by a significant amount. In spite of this, it has become a valuable synthetic tool.[246–254] Many of the methods developed drive the equilibrium by either trapping[255–259] or cleaving one isomer preferentially.[256,260–263] A recent report utilizes the trapping of a more reactive iminium ion by the nucleophilic addition of dimedone as show below.[264] Heating of **202** in the presence of acid results in the formation of iminium ion **203**, suitably situated to undergo sigmatropic rearrangement to yield **204**. While dimedone could react with either iminium isomer **203** or **204**, the steric hindrance in **205** likely prevents this reaction, driving the equilibrium to **204**. The dimedone adduct **205** eventually decomposes to give 2-methylenyldimedone **206**, which dimerizes via Michael addition of a second molecule of dimedone.

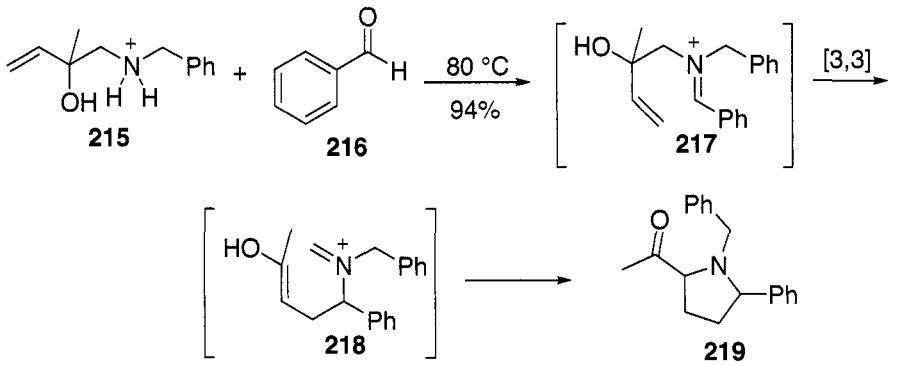




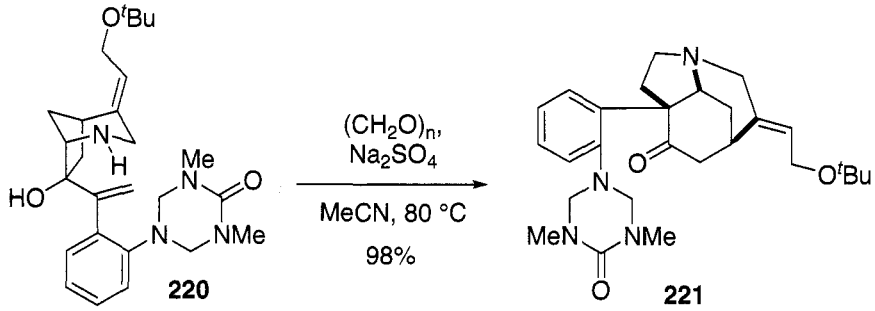
A formal [3 + 2]-cycloaddition reaction was developed featuring an aza-Cope rearrangement followed by an intramolecular Mukaiyama reaction to trap the resulting imine.[265] Initially, compound **212** was prepared by a Mukaiyama aldol reaction between **210** and **211**. This was followed by the 2-aza-Cope rearrangement of **212**, resulting in **213**. Following an intramolecular Mukaiyama aldol addition, **214** is produced in moderate yield.



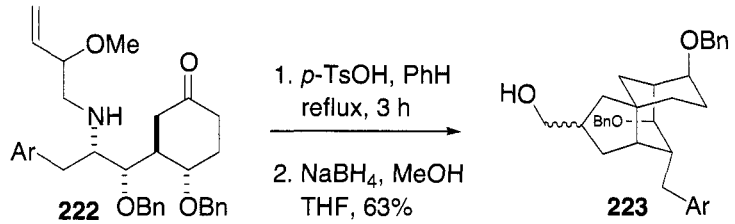
A process that has been popularized and utilized extensively by Overman and coworkers involves a tandem 2-aza-Cope rearrangement followed by trapping of the resultant isomer by a Mannich reaction. First demonstrated in 1979,[266] this has become a powerful methodology that has found substantial utility in alkaloid synthesis.[267–283] The reaction between **215** and benzaldehyde results in formation of iminium ion **217**, which undergoes the 2-azonia-Cope rearrangement to give iminium ion **218**. Trapping of **218** by the enol functionality results in pyrrolidine **219**.



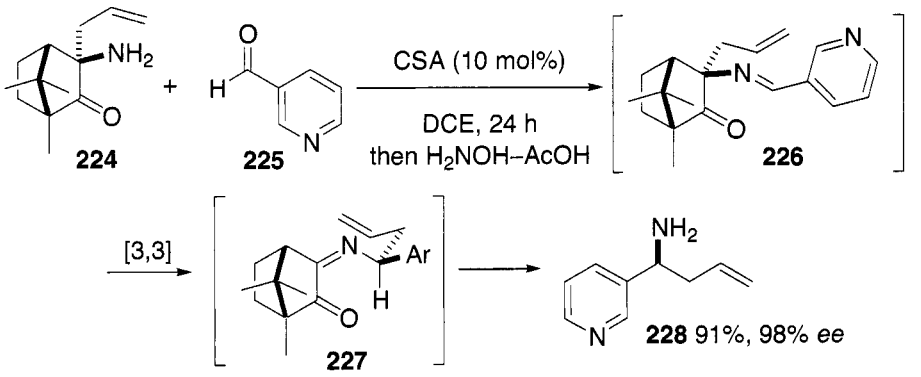
One of the more impressive demonstrations of this reaction was in the landmark total synthesis of strychnine by Overman and coworkers.[284] Treatment of **220** with formaldehyde resulted in an iminium ion which underwent the tandem 2-aza-Cope rearrangement/Mannich sequence to give **221** which was elaborated to (–)-strychnine in six more steps.



Brummond has impressively utilized the similar transformation of **222** to **223** in a formal synthesis of the highly active immunosuppressant (–)-FR901483.[285,286] Initial formation of the iminium ion results in the cationic 2-aza-Cope rearrangement which is followed by Mannich cyclization to give **223** upon reduction with sodium borohydride.

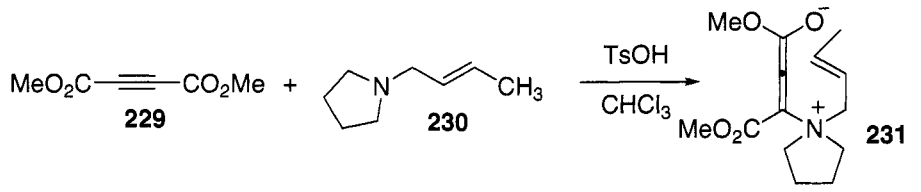


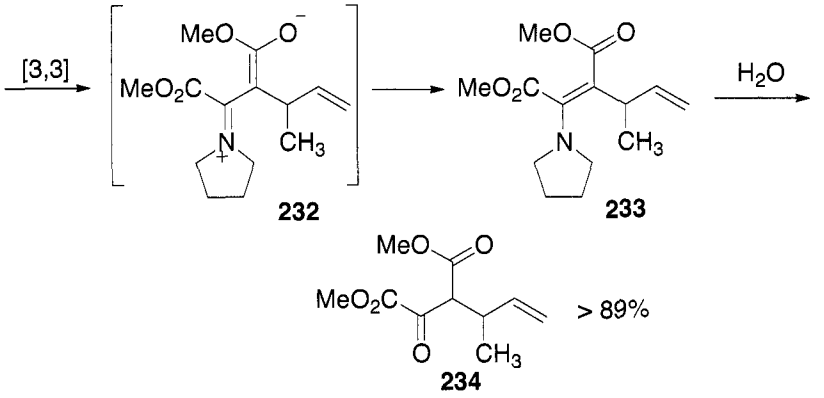
An elegant method for the synthesis of optically active homoallylic primary amines features the 2-aza-Cope rearrangement. α-Aminoketone **224** is used as the chiral source for enantioselective transfer of the aminoallyl group. Following imine formation with aldehyde **225**, sigmatropic rearrangement is followed by hydrolysis of the resulting imine, producing **228** and regenerating the diketone from which **224** is prepared in a single step.

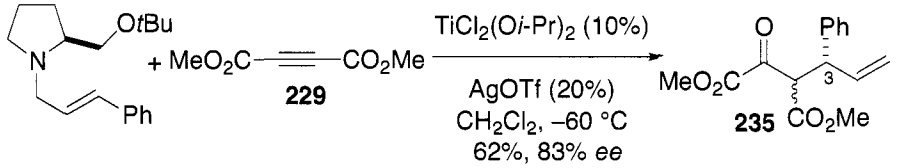


3-Aza-Cope

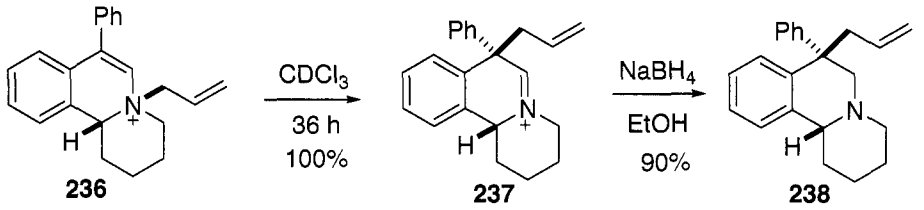
Due to the harsh conditions required for effecting reaction,[287] the 3-aza-Cope (also regarded as the amino-Claisen) has received little synthetic attention. However, recent efforts have sought to increase the utility of this process.[287-293] A creative approach to this reaction comes from the work of Vedejs and coworkers.[294] Their approach utilizes an acid-catalyzed Michael addition of allylic amines, such as **230**, resulting in the formation of **231** which immediately undergoes aza-Cope rearrangement to give **233**. Hydrolysis then provides **234**. This reaction has proven to be quite general for a number of compounds, and, when utilizing a chiral, non-racemic allylamine under Lewis acid catalysis conditions, results in high levels of stereoselectivity, as evidenced by the formation of **235** from **229** in 83 % *ee* at C-3. In a related fashion, MacMillan and co-workers have effected the 3-aza-Cope rearrangement of intermediates derived from Michael addition of allylic amines to allenoate esters.[295]







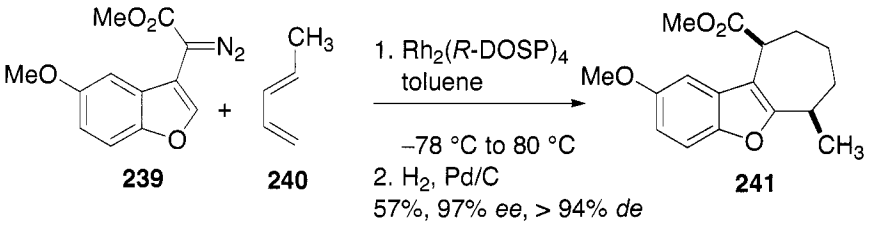
Maryanaoff and McComsey[296] have more directly utilized the 3-aza-Cope rearrangement for preparation of quaternary carbon centers via transfer of an allyl group from a quaternary ammonium salt. As illustrated below, reaction of **236** proceeds smoothly in what is predominantly a [3,3]-sigmatropic process to give **237**. Reduction of the iminium ion **237** provides **238**.



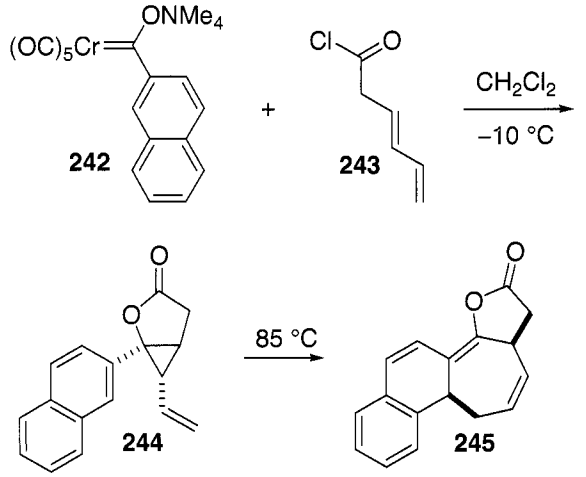
Cyclopropyl-Cope

In recent years, the synthetic utility[297] of the cyclopropyl-Cope rearrangement has expanded exponentially as a result of new chiral organometallic catalysts which allow for the efficient, stereoselective formation of the required *cis*-divinylcyclopropanes.[298–301] One of the leaders in this area is Davies, who has repeatedly demonstrated the successful tandem cyclopropanation/Cope rearrangement between vinyldiazoacetates and dienes for the synthesis of functionalized seven-membered rings.[302,303]

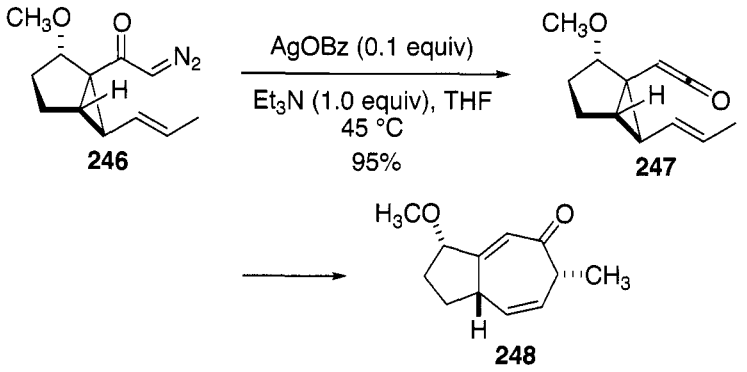
The reaction, which represents a formal [4 + 3]-cycloaddition has been broadly applied[304–309] and when coupled with chiral dirhodium catalysts,[310,311] results in products with high enantiomeric excess. This reaction was recently applied by Davies and coworkers[312] in an elegant synthesis of a late stage intermediate in the Dansihefsky[313] synthesis of frondosin B. Enantioselective cyclopropanation of **240** by the rhodium carbenoid of **239** is followed by heating to effect the Cope rearrangement which results, after hydrogenation, in **241**. The formal synthesis of frondosin B was thus completed in four more steps. In a similar manner, the synthesis of racemic tremulenolide A and tremulenediol A featured the tandem cyclopropanation/Cope rearrangement as a key step.[314] Iwasawa and coworkers have recently delineated a similar approach involving a $W(CO)_5$(thf) catalyzed intramolecular cyclopropanation/Cope strategy.[315]



The synthesis of cycloheptane fused lactones has been accomplished through a variation of this paradigm, using Fischer carbene complexes for cyclopropanation.[316] Acylation of complex **242** sets the stage for the intramolecular cyclopropanation to give lactone **244**. A diastereoselective aromatic-cyclopropyl-Cope rearrangement then occurs to provide racemic **245**. This reaction has been successfully applied with electron-rich benzene and furan aromatic ring systems.

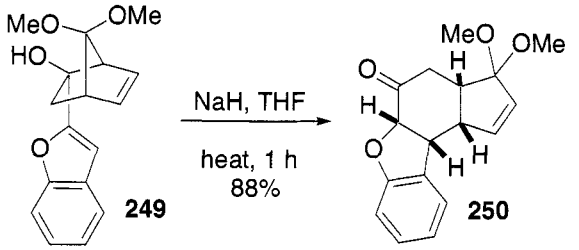


The Stoltz group[317] has developed a novel extension of the cyclopropyl-Cope rearrangement for the stereoselective synthesis of functionalized cycloheptadienones.[318] The process begins with irradiation of diazoketone **246** resulting in Wolff rearrangement to cyclopropylketene **247**. Ketene **247** immediately undergoes the Cope rearrangement resulting in cycloheptadienone **248**, highly functionalized for future elaboration.

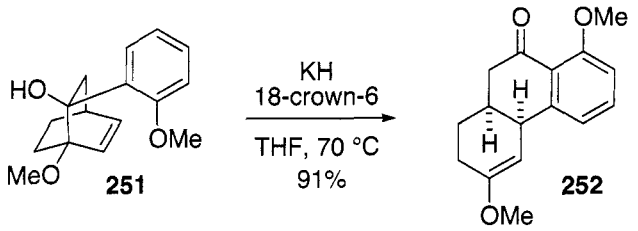


Aromatic-Cope

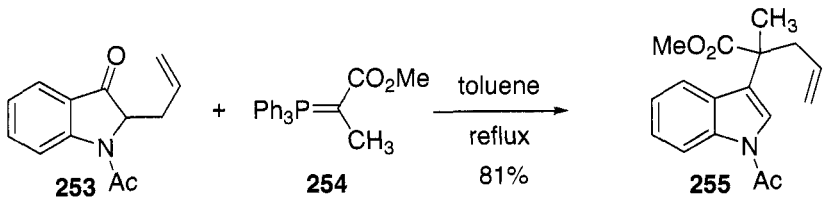
One of the first examples of the use of the aromatic-Cope rearrangement in synthesis was developed in the Jung laboratories toward the synthesis of (±)-coronafacic acid. Featuring the participation of a benzofuran as the aromatic partner in an anionic oxy-Cope rearrangement, the reaction of **249** proceeds to give the tetracyclic product **250** as a single diastereomer.



Compared to the example above, the participation of benzene in the aromatic-Cope rearrangement has been more difficult to achieve. However, it has recently been utilized for the preparation of helicenes[319,320] and other polycyclic compounds.[321] One of the first and most impressive demonstrations of this reaction was utilized in the synthesis of tricyclic compounds such as **252**. As above, the anionic oxy-aromatic-Cope rearrangement of **251** proceeded in excellent yield to give **252**, resulting from rearomatization of the benzene ring.



As a result of the inherent difficulty in achieving the aromatic-Cope rearrangement, Kawasaki and coworkers creatively used the formation of an aromatic molecule to drive what has been referred to as the reverse aromatic-Cope rearrangement to synthesize 3-indoleacetic acid derivatives. As illustrated below, Wittig reaction of **253** results in a 1,5-diene which immediately undergoes the Cope rerrangement to give the aromatic indole **255** in high yield.



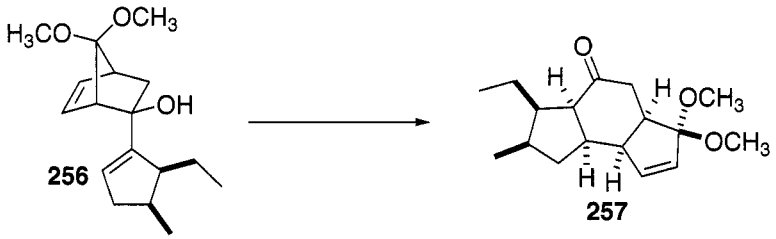
1.1.3.6 Experimental

Protypical Cope

Synthesis of 68:[111]

Diene **67** (105 mg) was dissolved in 1,2-dichlorobenzene (3 mL) and heated to reflux temperature overnight. Upon cooling, the solvent was removed in vacuo and the residue purified by silica gel column chromatography (eluted with 1 : 1 hexanes/EtOAc) to provide the white crystalline product, **68** (92 mg, 88%).

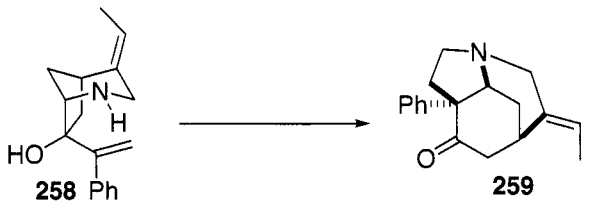
Anionic Oxy-Cope



(3a*R,5a*S**,6*R**,7*R**,8a*R**,8b*S**)-6-Ethyl-3a,4,5a,6,7,8,8a,8b-octahydro-7-methyl-*as*-indacene-3,5-dione 3-(dimethyl acetal) (257).**[174]

Potassium hydride (236 mg, 5.92 mmol) was preweighed into a 100 mL round-bottomed flask under argon. Tetrahydrofuran (40 mL) was added and the solution was cooled to 0 °C. Alcohol **256** (1.30 g. 4.68 mmol) dissolved in 20 mL of the same solvent was slowly added and the reaction mixture was stirred at room temperature for 2.5 h. The solution was recooled to 0 °C and 10 mL of water was added. After 30 min of continued agitation and extraction with ether (3 × 40 mL), the combined organic phases were washed with brine (2 × 40 mL) and dried. Concentration gave a residue which was crystallized from pentane to give 832 mg (64%) of **257** as white needles. The mother liquor was subjected to MPLC on Florisil (elution with 7% ethyl acetate in petroleum ether) to recover an additional 104 mg of **257** (total yield, 72%).

2-Aza-Cope



(*E*)-2-Ethylidene-7-phenyl-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (259).[276]

To a solution of the amino alcohol **258** (35 mg, 0.14 mmol) in acetonitrile (2.0 mL) was added sequentially Na_2SO_4 (25.3 mg, 0.18 mmol), formaldehyde (4.5 mg, 0.15 mmol), and camphorsulphonic acid (30.2 mg, 0.13 mmol). This solution was heated to reflux for approximately 45 min then cooled to room temperature. The solution was then diluted with CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried (K_2CO_3) and concentrated. Purification of the residue by radial chromatography (1

mm plate, 95:5 $CHCl_3$:CH_3OH, 1% triethylamine) gave 34.3 mg (90%) of the azatetracycle **259** as a clear colorless oil, which was 96% pure by capillary GC analysis.

1.1.3.4 References

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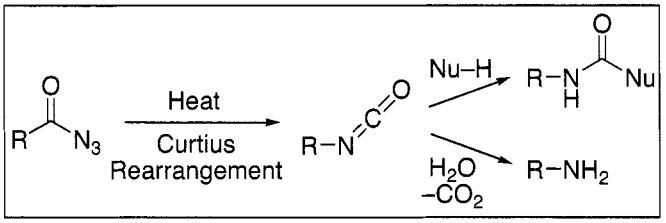
1.1.4 Curtius Rearrangement

Christian M. Rojas

1.1.4.1 Description

Alkyl-, vinyl-, and aryl-substituted acyl azides undergo thermal 1,2-carbon-to-nitrogen migration with extrusion of dinitrogen — the Curtius rearrangement — producing isocyantes. Reaction of the isocyanate products with nucleophiles, often *in situ*, provides carbamates, ureas, and other *N*-acyl derivatives. Alternatively, hydrolysis of the isocyanates leads to primary amines.

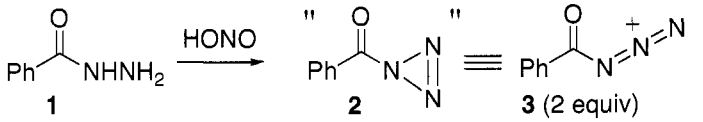


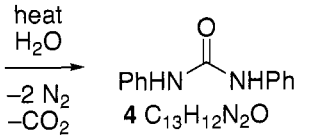
During the more than 110 years since its discovery, chemists have explored the details of the Curtius rearrangement and applied it in synthesis. They have addressed mechanistic questions common to many other rearrangements: Is the process concerted or stepwise? How is stereochemistry at the migrating group affected? The Curtius rearrangement provides a way to replace a carboxyl group with amine functionality, a transformation of pronounced synthetic value. Streamlined preparation of the starting acyl azides, alternative methods that avoid isolation of these potentially unstable acyl azides altogether, and improved ways to intercept the isocyanate products, including metal-catalyzed reactions, have added to the preparative utility of the Curtius rearrangement. Because of the vast literature on the Curtius rearrangement, including many excellent review articles,[1–12] this chapter, while describing some classic examples, will emphasize recent applications of the reaction, including its application in synthetically challenging, highly functionalized molecular frameworks.

1.1.4.2 Historical Perspective

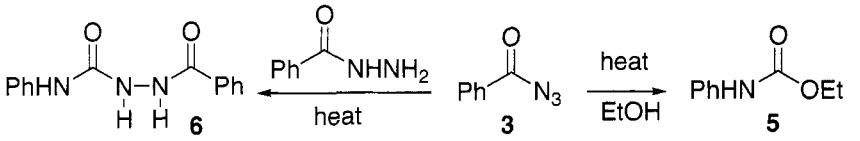
During the 1890s, Thomas Curtius studied the preparation and reactions of acyl azides. For example, treatment of benzoylhydrazine (**1**) with nitrous acid provided benzoyl azide,[13] which Curtius represented as **2**, consistent

with the then-accepted cyclic azido structure. In the presence of water, heating benzoyl azide liberated molecular nitrogen and carbon dioxide and gave an organic product $C_{13}H_{12}N_2O$ that Curtius showed was diphenylurea.[14] This established the carbon-to-nitrogen change in connectivity of the original acyl substituent during the reaction. The same urea product resulted when Curtius heated benzoyl azide in the presence of aniline.





Heating benzoyl azide with ethanol or benzoylhydrazine gave the corresponding urethane (**5**) or benzoylphenyl semicarbazide (**6**), respectively. The explosive diacyl azide **8**, prepared from fumaric acid-derived **7**, underwent double rearrangement in ethanol to the dicarbamate **9**.[14]

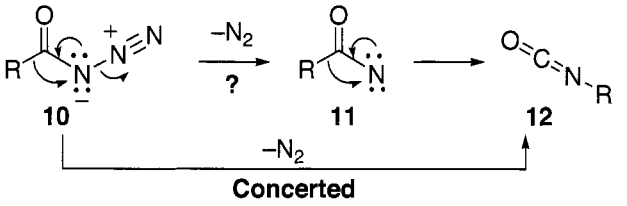


Providing ready conversion of a carboxyl to an amino group (including amines functionalized as ureas or urethanes) Curtius's rearrangement became a well-known and widely applied reaction. In 1946, Peter Smith published an extraordinarily comprehensive review of the Curtius rearrangement, aiming to catalogue every example of the reaction through April 1945.[1] That heroic compilation, with 454 references, included over 750 compounds used as starting materials for Curtius rearrangement sequences.

1.1.4.3 Mechanism

Concertedness of the rearrangement:

Although early proposals by Stieglitz[15] and Jones and Hurd[16] invoked a "univalent nitrogen derivative"[15] as an intermediate in the Curtius rearrangement, mechanistic studies support C → N migration occurring in concert with extrusion of molecular nitrogen (**10** → **12**) as opposed to initial formation of a nitrene (**11**, singlet or triplet).[3,4] Nitrene-trapping attempts were unsuccessful.[17] Radical intermediates are not involved,[6] as Curtius rearrangements of benzoyl azide[18] or α-benzyl propionyl azide[19] were not affected by the presence of triphenylmethyl radical, and less than 1% polymerization of added acrylonitrile was observed during rearrangement of benzoyl azide.[20]



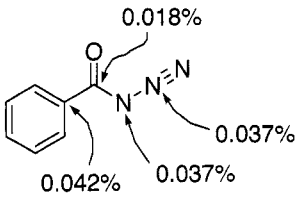
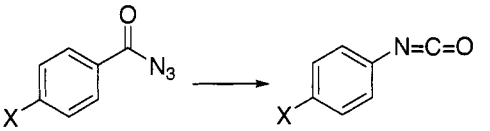


Figure 1: Kinetic isotope effects in Curtius rearrangement



X	k (s^{-1} at 60 °C)	$\Delta H^{\dagger}$ (kcal/mol)	$\Delta S^{\dagger}$ (eu)
H	3.03×10^{-5}	27.8	+4.1
NO_2	2.14×10^{-5}	28.3	+4.7
OMe	2.065×10^{-5}	28.0	+3.9

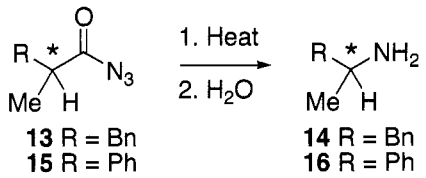
Figure 2: Rate constants and activation parameters for Curtius rearrangement of benzoyl azides

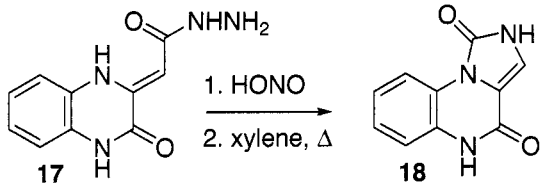
An extensive survey of solvent effects in the Curtius rearrangement of benzoyl azide revealed no clear relationship between rate and solvent polarity as measured by either dielectric constant or dipole moment.[21] Carbon- and nitrogen kinetic isotope effects were observed at the migrating carbon, the carbonyl carbon, and both the α and β nitrogens of the azide group, consistent with a concerted mechanism (Figure 1).[22,23] The effect of varying the electronics of the migrating group was small.[24,25] For example, *p*-nitro-

and *p*-methoxy benzoyl azides underwent rearrangement to the isocyanates with very similar first-order rate constants and activation parameters (Figure 2).[3] Since all other evidence indicates a concerted rearrangement, the small electronic effects suggest an asynchronous transition state, dominated by release of nitrogen.[3]

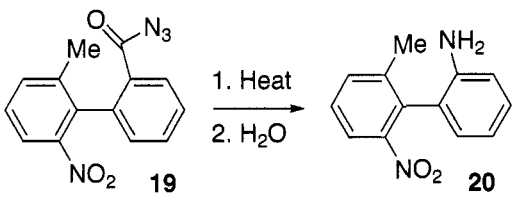
Stereochemistry at the migrating carbon:

From the perspective of synthetic utility (see *Section 1.1.4.4*), a crucial mechanistic feature of the Curtius rearrangement is that migration of sp^3 carbons occurs stereospecifically, with retention of configuration.[6] Wallis showed that the product from rearrangement of enantiomerically enriched α-benzyl propionyl azide **13** remained optically active.[26] Kenyon and co-workers proved that preservation of optical activity corresponded to retention of configuration by studying rearrangement of **15**. The product **16** was obtained with > 99% retention of stereochemistry.[27–29]





In migration of sp^2 carbons, alkene geometry is preserved. This is often not apparent from the isolated product, because the resulting enamine is hydrolyzed to the corresponding aldehyde or ketone. However, retention of alkene stereochemistry is observed where the stereochemistry of the vinyl isocyanate can be inferred, as in the Curtius rearrangement starting from acyl hydrazine **17**, where the intermediate isocyanate was trapped to yield heterocycle **18**.[30,8] While opportunities do exist for double bond isomerization in the vinyl isocyanate derived from **17**, additional examples (cf. **9**, **60**, **62**, **90**, **95**, and **101**) illustrate the generality with which alkene geometry is preserved in the Curtius rearrangement of α,β-unsaturated acyl azides.



An unusual mode of stereospecificity was demonstrated in Bell's elegant experiment with optically active biphenyl **19**. Retention of optical activity in the Curtius rearrangement to **20** indicated that the migration occurred with continuous intimate contact between the phenyl group and the C–N fragment, preventing rotation around the biphenyl linkage throughout the course of the rearrangement.[31]

Catalysis by Lewis- and Brønsted acids:

Lewis acids can accelerate the Curtius rearrangement.[32,6] The reactions studied were first order in Lewis acid when excess azide was used and first order in azide with excess Lewis acid. The Lewis acid was not consumed in the reaction. Various Lewis acids, including $GaCl_3$ and $AlCl_3$ were effective. The proposed mode of catalysis was activation of the acyl azide by rapid and reversible pre-complexation with the Lewis acid, followed by rearrangement to the isocyanate with release of the catalyst (Figure 3).

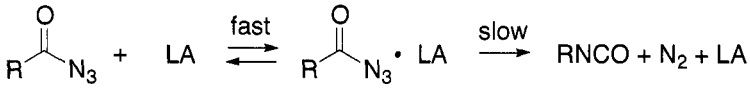
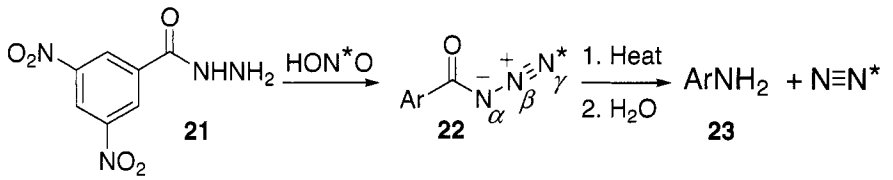


Figure 3. Lewis acid catalysis of the Curtius rearrangement

Brønsted acids, including glacial acetic acid, aqueous acetic acid, and sulfuric acid in glacial acetic acid also accelerate the Curtius rearrangement.[33,6] In glacial acetic acid alone or in glacial acetic acid with added H_2SO_4, Hammett studies of substituted benzoyl azides showed little dependence on the substituents. The mechanistic scenario would be analogous to the Lewis acid-catalyzed picture, with a rapid pre-equilibrium between the acyl azide and its protonated form, favoring the neutral form, followed by rearrangement.[6] The Brønsted-acid-catalyzed Curtius rearrangement, then, may represent the rate-determining step of the closely related Schmidt rearrangement.[6]



Which nitrogen of the azide is retained?

An experiment using **22**, isotopically labeled at the γ position with ^{15}N, demonstrated that the terminal nitrogen atom of the acyl azide is, in fact, lost in the extruded nitrogen molecule during the Curtius rearrangement.[34] This result ruled out possible mechanisms involving exchange of the α and γ nitrogens of the acyl azide and is consistent with a 1,2-carbon-to-nitrogen shift in formation of the isocyanate.

1.1.4.4 Synthetic Utility

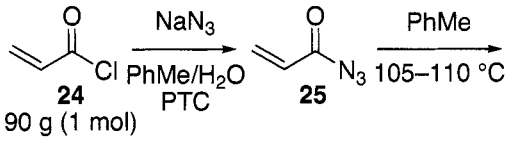
From a synthetic perspective, the power of the Curtius rearrangement involves the ready conversion of a carboxyl group to nitrogen functionality. Furthermore, the nature of that nitrogen functionality can be controlled by the way in which the direct product of the Curtius rearrangement—the isocyanate—is manipulated. An extremely wide scope of carboxylic acid substrates, once converted to the acyl azides, successfully undergo Curtius rearrangement: aromatic, vinyl, alkyl, cyclic, heterocyclic. The site of the resulting amino functionality is determined with high reliability, including stereochemistry. This section provides a representative range of examples. Some of the most commonly used synthetic variants of the Curtius rearrangement, including the Shioiri and Weinstock variants, differ in how the acyl azides are generated from carboxylic acid starting materials. Examples of those protocols are found in the *Variations and Improvements Section (1.1.4.5)*.

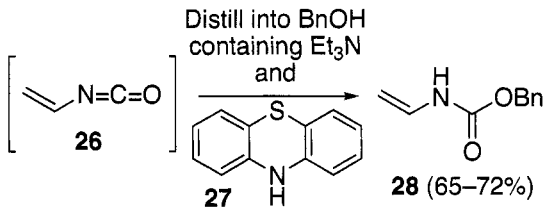
Acyl azides from acid hydrazides:

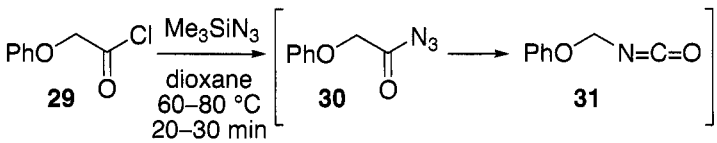
In the early literature, including the pioneering studies of Curtius himself, acyl azides were prepared from carboxylic acids via treatment of the derived acid hydrazides with nitrous acid. This method is less commonly used in contemporary synthesis but still appears occasionally in the literature. Examples were shown for compounds **1**, **7**, **17**, and **21** in the earlier sections above.

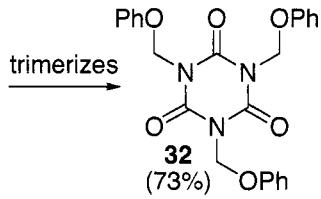
Acyl azides from acid chlorides:

Activation of the carboxylic acid as the acyl chloride permits direct reaction with azide anion to form the acyl azide substrates for Curtius rearrangement. Sodium azide is commonly used, and the reaction has been used on the process chemistry scale for the synthesis of benzyl-*N*-vinyl carbamate.[35] Acryloyl chloride was combined with sodium azide in a biphasic system with phase-transfer catalysis (PTC), providing acyl azide **25**. Upon heating, Curtius rearrangement provided vinyl isocyanate, which was distilled directly into benzyl alcohol containing phenothiazine (**27**) to inhibit polymerization of **26** and triethylamine to catalyze addition of the alcohol to the isocyanate. The vinyl carbamate product **28** was isolated by crystallization. As the author clearly pointed out, preparation and reaction of acyl azides, particularly on large scales, require appropriate safety precautions.





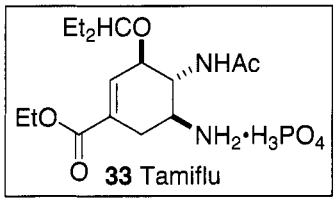


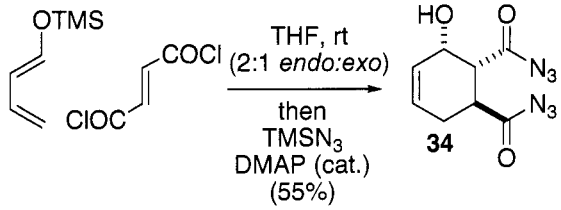


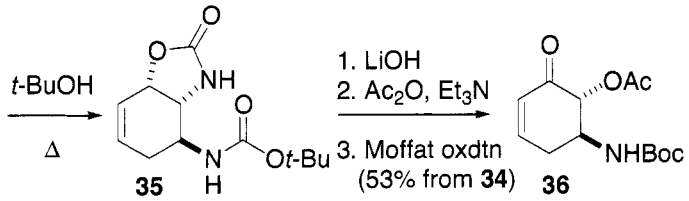
Trimethylsilylazide is a convenient, organic solvent-soluble, thermally stable source of azide anion. Kricheldorf investigated its use in the

Curtius rearrangement with various acid chlorides,[36] including phenoxy acetyl chloride. Heating in dioxane provided **32** the trimer of isocyanate **31**, formed by rearrangement of acyl azide **30**.

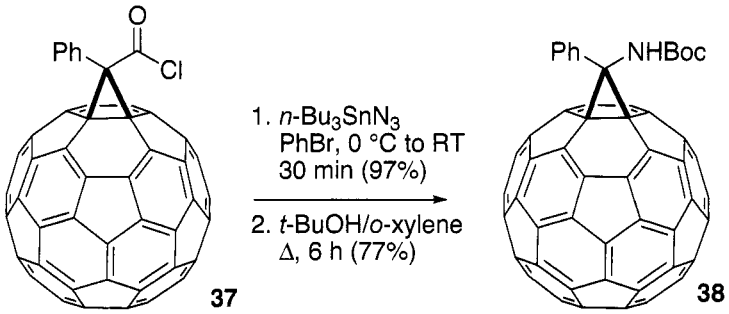
In a recent route to the influenza-treating drug Tamiflu (**33**), chloride displacement from the product of a fumaryl chloride Diels–Alder reaction provided bis acyl azide **34**. Heating in *tert*-butanol produced double Curtius rearrangement. One of the isocyanates was trapped in intramolecular fashion, providing the oxazolidinone, while the other resulted in the Boc group of product **35**, which was advanced toward Tamiflu precursor **36**.[37] In an earlier example, trimethylsilyl azide was used in a Curtius route to various 1,2-dihydroxy-4,5-diamino cyclohexane derivatives, prepared as possible antitumor agents.[38]







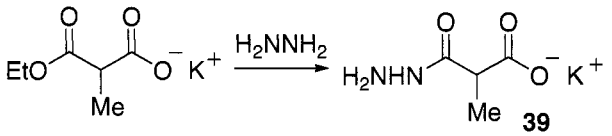
Curtius rearrangement precursors can also be prepared from acyl chlorides using tributylstannyl azide. An alkylamino fullerene derivative **38** was prepared from acyl chloride **37**, for example.[39] Application of the Curtius rearrangement in C_{60} chemistry also highlights the utility of this venerable reaction in new contexts.

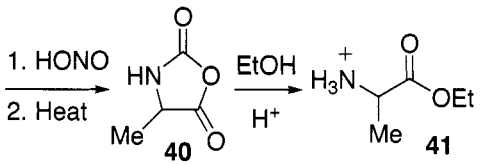


37 38

Amino Acids:

α-Amino acids are accessible via the Curtius rearrangement. The acyl azides derived from α-cyanoacids provide the corresponding isocyanates upon heating. Acid hydrolysis leads to the amino acids.[1] An alternative, developed early by Curtius, is to use the monoester of a malonic acid derivative to prepare the mono acid hydrazide **39**. Azotization and rearrangement led to **40** upon intramolecular trapping of the isocyanate, and ethanolysis provided alanine ethyl ester.[40]



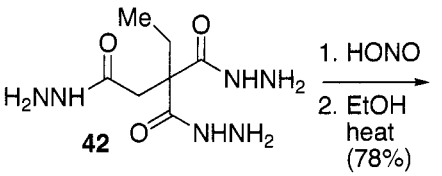


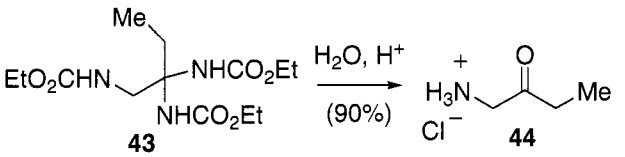
More recent Curtius rearrangement-based approaches to amino acids have typically employed variants such as the Shioiri and Weinstock methods. Examples are provided in the *Variations and Improvements Section.*

Polyamines:

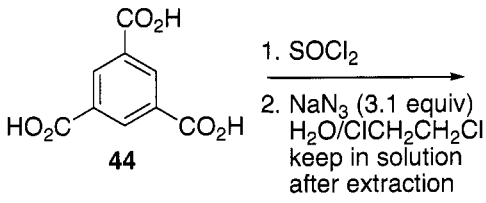
As suggested by the Tamiflu example shown above (cf., diazide **34**), the Curtius rearrangement opens the possibility for polyamine synthesis from polycarboxylic acids. When two carboxyl groups are attached to the same carbon, hydrolysis of the rearrangement product provides aldehydes or ketones. Tricarboxylic acid hydrazide **42**, for example, served as the starting

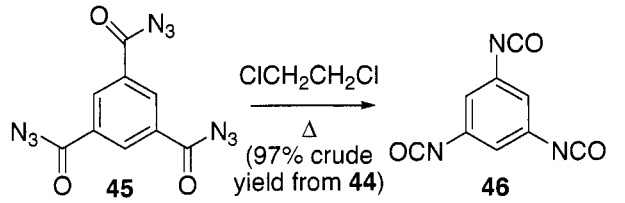
point for a triple Curtius sequence. Acid hydrolysis of the resulting triurethane **43** provided α-amino ketone salt **44**.[41]





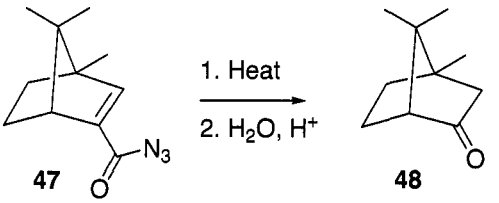
Caution is required with poly acyl azide intermediates. The triazide precursor to **43** is explosive, for example.[41] Curtius also first reported conversion of mesic acid to 1,3,5-benzenetricarbonyl triazide (**45**),[42] but this material is explosive in the solid state. Isolation of the solid triazide can be avoided by using 1,2-dichloroethane as the solvent and keeping the intermediate in solution throughout the procedure. After drying over magnesium sulfate, heating at reflux in the same 1,2-dichloroethane solvent yields the tris isocyanate **46**.[43] Because of these safety concerns, alternative Curtius-type methodology is preferred for such systems. For example, conversion of mesic acid to a tris urethane derivative of 1,3,5-aminobenzene was achieved using the Shioiri modification[44] (see *Variations and Improvements Section* for the Shioiri process).





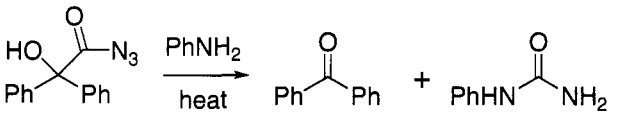
α,β-Unsaturated acyl azides:

These azides undergo Curtius rearrangement to vinyl isocyanates, which are prone to polymerization.[1,2] Where polymerization does not interfere, hydrolysis of the vinyl isocyanate provides aldehydes or ketones via the enamine. Bornylene carbonyl azide (**47**) yielded epicamphor (**48**) via the Curtius rearrangement–hydrolysis sequence.[45,1]



47 **48**

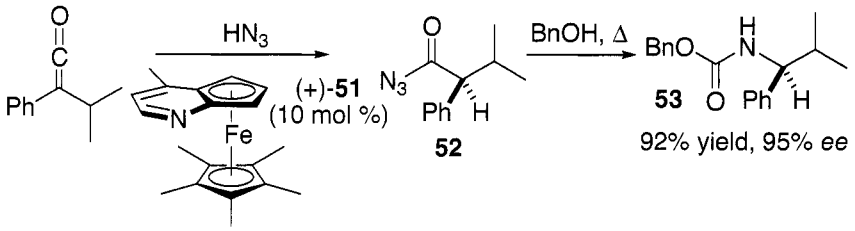
The Curtius rearrangement of *α,β*-unsaturated acyl azides preserves double bond geometry. The vinyl isocyanate can be trapped by nucleophiles rather than hydrolyzed. Examples capitalizing on the Shioiri and Weinstock procedures are discussed in the *Variations and Improvements Section* (see **60**, **62**, and **90**).



49 **50**

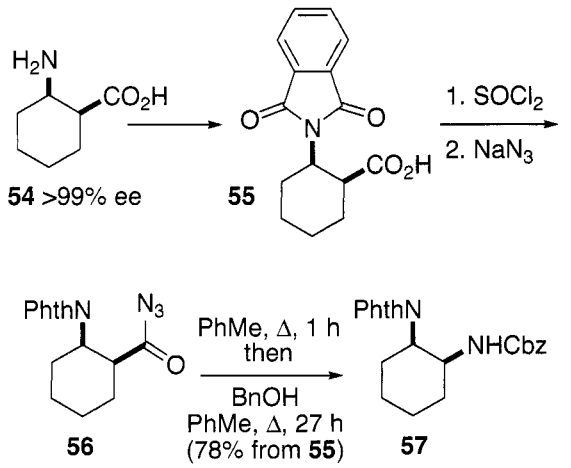
α-Hydroxy acyl azides:

Curtius rearrangement of these azides leads to ketones via loss of an isocyanic acid (HN=C=O) equivalent, which can be trapped *in situ* as shown for **49** where benzophenone resulted and addition of aniline to the isocyanic acid gave urea **50**.[46,1] *α*-Alkoxy- and *α*-amino acyl azides, meanwhile, are precursors to hemiaminals and bisaminals, respectively. Examples in complex natural product synthesis are shown for **81** and **66** in the *Variations and Improvements Section.*



Asymmetric routes to chiral amines:

Because of the stereospecific retention of configuration in the Curtius rearrangement, the reaction can play a key role in the asymmetric preparation of chiral amines, provided that the acyl azide precursor is available in enantiomerically enriched form. For example, Fu developed chiral ferrocene derivative **51** as a catalyst for enantioselective addition of hydrazoic acid to ketenes, giving α-chiral acyl azides (e.g., **52**).[47] Subsequent Curtius rearrangement and trapping of the isocyanate with an alcohol gave urethanes, including **53**, in high enantiomeric excess. The isocyantes could also be hydrolyzed to the amines.



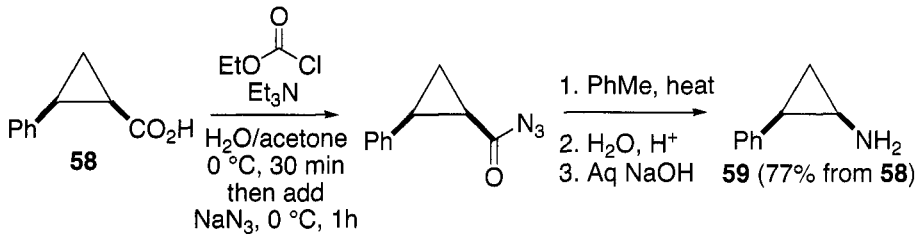
An asymmetric approach to differentially substituted *cis*-1,2-diamino cyclohexanes also utilized the Curtius rearrangement.[48] The chiral diamine products are components of biologically active small molecules and useful as conformationally restricted peptide-like scaffolds. β-Amino acid **54** was prepared in enantiomerically pure form using asymmetric reductive amination and converted to phthaloyl-protected β-amino acyl azide **56**. Curtius rearrangement, followed by addition of benzyl alcohol and further heating provided chiral *cis*-1,2-diamine **57** with orthogonal *N*-protection.

Preservation of stereochemistry upon rearrangement is the key in these applications of the Curtius process in asymmetric synthesis. Additional examples featuring this stereospecificity, particularly directed toward natural product synthesis, are found in the *Variations and Improvements Section.*

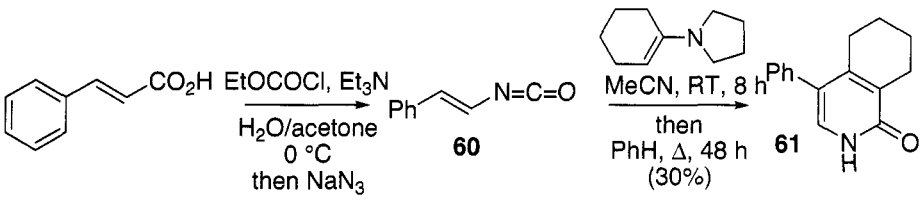
1.1.4.5 Variations and Improvements

Weinstock Conditions:

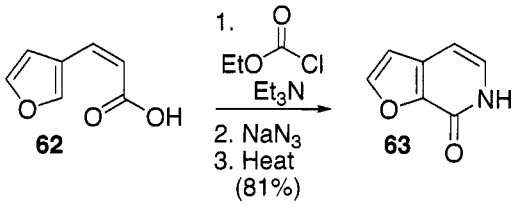
The acyl azides required for Curtius rearrangement can be prepared under mild conditions via mixed carboxylic-carbonic anhydrides.[49] The original 1961 report detailed preparation of racemic *cis*-2-phenylcyclopropylamine.[50] Treatment of carboxylic acid **58** with ethyl chloroformate and base in aqueous acetone provided the mixed anhydride, which was treated *in situ* with sodium azide. The crude acyl azide was isolated by extractive workup and underwent Curtius rearrangement, followed by acid hydrolysis. After raising the pH, the free base **59** was obtained in good overall yield.



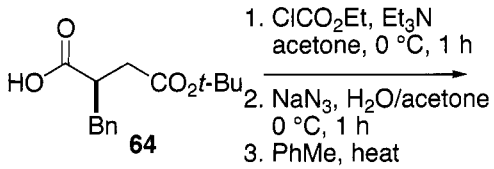
While it does not avoid isolation of the acyl azide, at least in crude form, Weinstock's method has found wide application in synthesis. Rigby and Balasubramanian used Curtius-generated vinyl isocyanates as 2-pyridone precursors, applying the Weinstock conditions to *trans*-cinnamic acid, for instance.[51] Although the stereospecificity of the sp^2 carbon migration is not necessarily reflected in the ultimate pyridone product, the *trans*-double bond geometry of the starting acid was faithfully transmitted to the vinyl isocyanate **60**. Reaction of the isocyanate with a cyclohexanone enamine and cyclization provided 2-pyridone **61**.

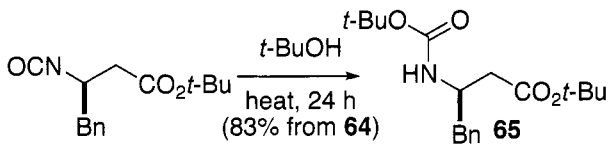


Another vinyl isocyanate was involved in the Curtius-mediated synthesis of furanyl heterocycle **63**.[52,8] The acyl azide precursor was obtained from (*Z*)-alkenyl carboxylic acid **62** using the Weinstock conditions. Upon Curtius rearrangement, the pendant furan cyclized onto the resulting (*Z*)-vinyl isocyanate.

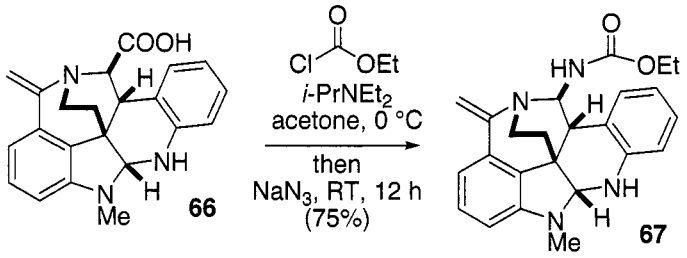


The Weinstock variant of the Curtius rearrangement has also found application in amino acid synthesis. For example, a route toward *β*-amino acids employed a chiral auxiliary to prepare alkylated succinic acid monoester **64** in enantiomerically enriched form. Under the Weinstock conditions, smooth rearrangement to the isocyanate occurred, and, without isolation, this was heated with *tert*-butyl alcohol, providing the Boc-protected *β*-amino ester **65**.[53]



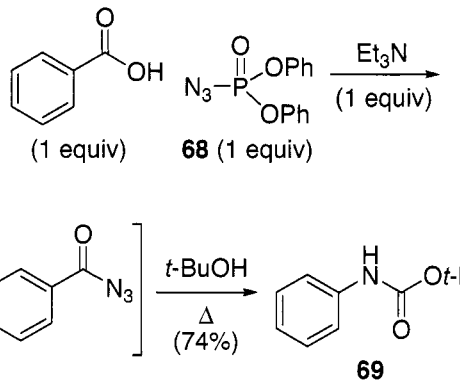


The ethoxy group liberated upon formation of the mixed anhydride can become incorporated into the rearranged product. An impressive example in the area of natural product synthesis involved rearrangement of highly functionalized *α*-amino acid **66** to *N*-acyl bisaminal **67**, containing the hexacyclic core structure of the cytotoxic *Penicillium* metabolite communesin B.[54] In contrast to the isocyanic-acid-extruding reaction of *α*-hydroxy acyl azide **49**, Curtius rearrangement of *α*-amino and *α*-alkoxy substrates provides routes to stable bisaminals (e.g., **67**) and hemiaminals. Further examples are highlighted later in this article (see **73** and **82**).

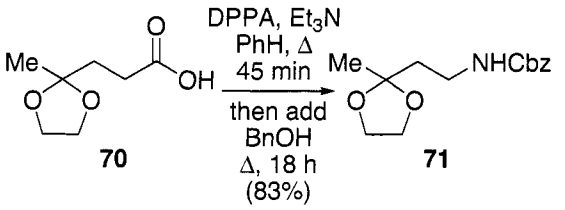


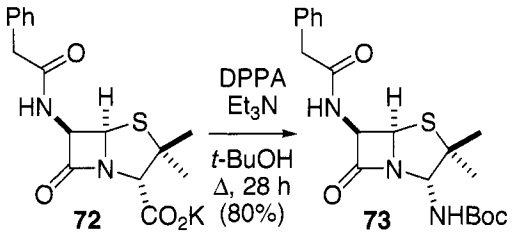
Shioiri–Ninomiya–Yamada modification:

Carboxylic acids are converted to Curtius-rearranged urethanes in one pot using diphenylphosphoryl azide (DPPA, **68**), triethylamine, and an alcohol.[11]

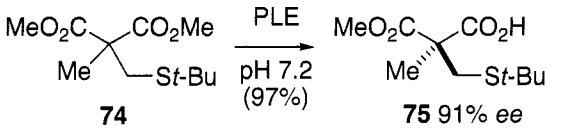


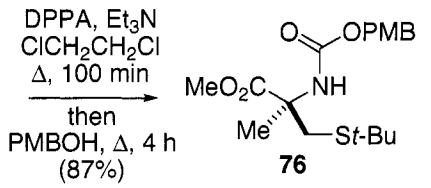
First reported by Shioiri, Ninomiya, and Yamada in 1972,[55] this procedure is the most important synthetic variant of the Curtius rearrangement. It is general for both aromatic and aliphatic carboxylic acids. Activation of the carboxyl by DPPA and addition of azide generates the acyl azide *in situ*, but it is not necessary to isolate that intermediate as it rearranges directly under the reaction conditions. The resulting isocyanate reacts with added alcohol, which is either included in the reaction mixture from the start or can be added once the Curtius rearrangement has occurred. Starting from benzoic acid, the *tert*-butyl carbamate of aniline (**69**) was prepared in good yield, and a benzyl carbamate-protected amine **71** was efficiently produced from carboxylic acid **70**.[56] It is noteworthy that a bis *N*-acyl aminal product **73** resulted from application of the Shioiri conditions to penicillin G potassium (**72**).





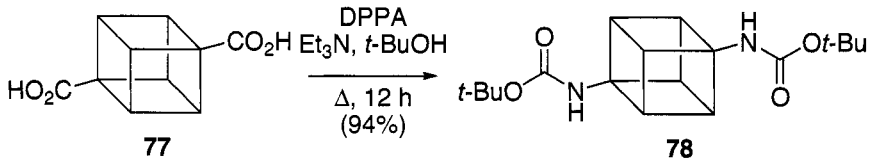
The Shioiri procedure was used recently in an asymmetric synthesis of protected forms of the α-disubstituted-α-amino acid 2-methylcysteine. Desymmetrization of dialkylated dimethylmalonate **74** with pig-liver esterase (PLE) provided monoacid **75** in good enantiomeric excess. Curtius rearrangement under the Shioiri conditions provided the *p*-methoxybenzyl carbamate **76**.[57]





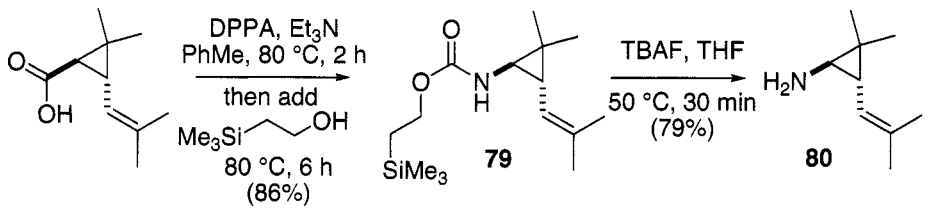
Because the Shioiri modification avoids isolation of the intermediate acyl azide, it is particularly well suited for cases in which the azide intermediate would be particularly unstable. The case of 1,3,5-benzenetricarbonyl azide (**45**) was mentioned earlier. Another instance is the diacyl azide derived from 1,4-cubane dicarboxylic acid: "An early attempt to prepare diaminocubane via Curtius rearrangement of the diacyl azide was abandoned when the first sample of the crystalline azide exploded violently."[58] However, the Shioiri–Ninomiya–Yamada conditions smoothly

converted 1,4-cubane dicarboxylic acid (**77**) to bis urethane **78** in excellent yield.[58]



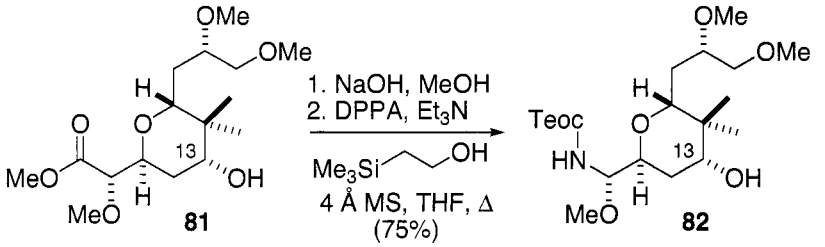
77 **78**

Using *tert*-butanol or benzyl alcohol in the carbamate-forming step provides Boc- and Cbz-protected amines, respectively, as shown in examples above. For many substrates, these protecting groups are readily cleaved under acidic, basic, reducing, or oxidizing conditions. For cases where neither Boc nor Cbz protection is compatible with the substrate or synthetic route, however, Poulter developed the use of 2-trimethylsilylethanol, leading to 2-(trimethylsilyl)ethoxycarbonyl (Teoc) protected amines.[59] For example, *trans*-chrysanthemic acid underwent Shioiri-modified Curtius rearrangement to Teoc-protected product **79**, and the carbamate was readily cleaved with fluoride, affording amine **80** in good yield.

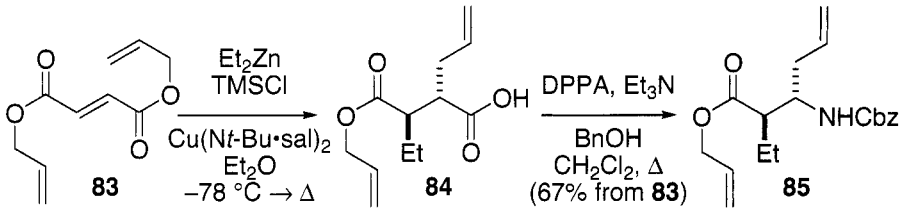


79 **80**

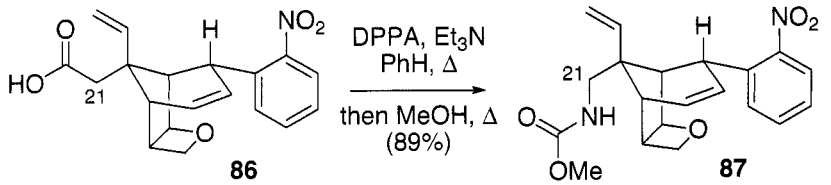
Rawal applied the Poulter procedure in the total synthesis of pederin, an example that also highlights the power of the Curtius rearrangement for installation of an acyclic hemiaminal.[60] Saponification of α-methoxyester **81** and DPPA-mediated acyl azide formation led to rearranged *N*-acyl hemiaminal **82**, a strategy pioneered by Roush and Marron[61] in their approach to the structurally closely related mycalamide and onnamide systems. In the Rawal example, the reaction occurred smoothly in the presence of a free neopentyl alcohol group at C13.



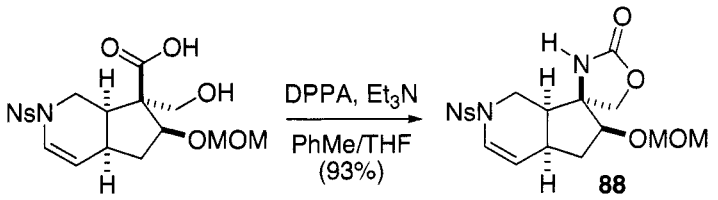
A diastereoselective β-aminoester synthesis utilized Shioiri conditions for the Curtius rearrangement of carboxylic acid **84**,[62] generated by conjugate addition to bis allyl fumarate **83** and subsequent Ireland–Claisen rearrangement. The Curtius rearrangement preserved the relative configuration at the stereogenic centers, and the product β-aminoester **85** was produced in Cbz-protected form.

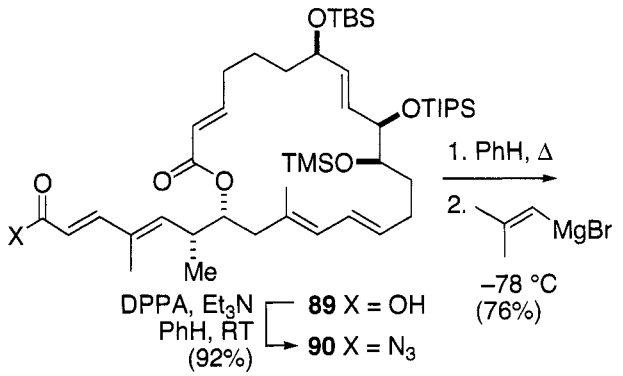


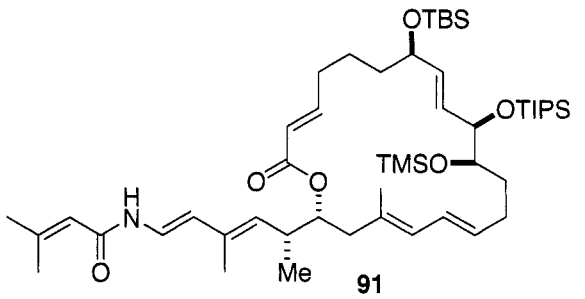
The mild, efficient, one-pot conditions of the DPPA-mediated Curtius rearrangement are often optimal for complex molecule synthesis. In Danishefsky's total synthesis of gelsemine, for example, the carboxyl group of **86** was used to introduce the C21–N bond in the form of methyl carbamate **87**, obtained in excellent yield without disturbing the oxetane ring.[63] From a strategic perspective, the power of the Curtius rearrangement is that it permits the carboxyl group, or a lower-oxidation-state carboxyl precursor, to act as a surrogate for the amino functionality, postponing introduction of nitrogen to a later stage of the synthesis. In the case of gelsemine, the Curtius substrate **86** already included all but one of the carbons of the natural product.



Additionally, Fukuyama took advantage of the stereospecific nature of the Curtius rearrangement in applying the Shioiri modification toward preparation of the core of anti-tumor natural product altemicidin.[64] Here, the nitrogen was incorporated at a fully substituted stereogenic center, and the isocyanate intermediate trapped by the pendant hydroxyl, providing oxazolidinone product **88**. In the natural product, the methylene of the oxazolidinone becomes a carboxyl group, so that the Curtius rearrangement enabled incorporation of an α-disubstituted-α-amino acid.





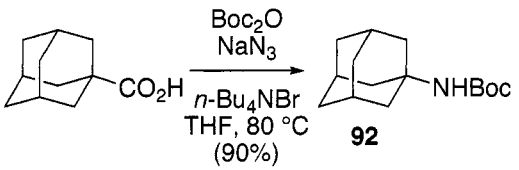


Preservation of alkene geometry in the Curtius rearrangement was a key feature in De Brabander's remarkable application of Shioiri methodology in the total synthesis of palmerolide A.[65] Conversion of carboxylic acid **89** to dienyl acyl azide **90** utilized DPPA, and Curtius rearrangement to the (*E*)-

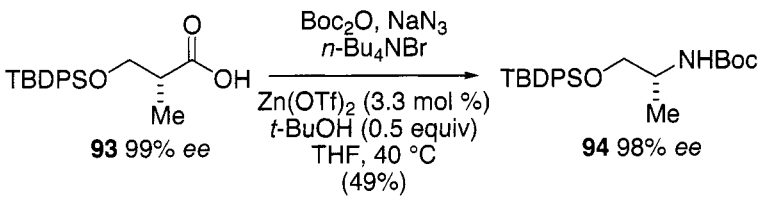
vinyl isocyanate was followed by addition of 2-methylpropenyl Grignard. The sequence installed the sensitive *N*-acyl dienamine group of **91** with complete stereocontrol in a highly functionalized substrate. From this late-stage Curtius sequence it was only three chemical steps to the natural product.

Lebel modification:

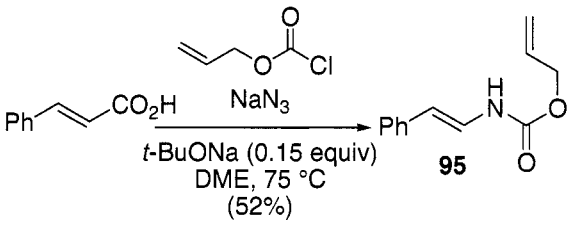
Use of di-*tert*-butyl dicarbonate (Boc_2O) and sodium azide with a phase-transfer agent enabled the one-pot Curtius rearrangement of aliphatic carboxylic acids to Boc-protected amines.[66,10] Mechanistically, Lebel and co-workers suggested an analogy to the Shioiri conditions, with *in situ*-generated *tert*-butyl azidoformate playing the role of DPPA by activating the carboxyl group and providing the source of azide for forming the acyl azide intermediate.

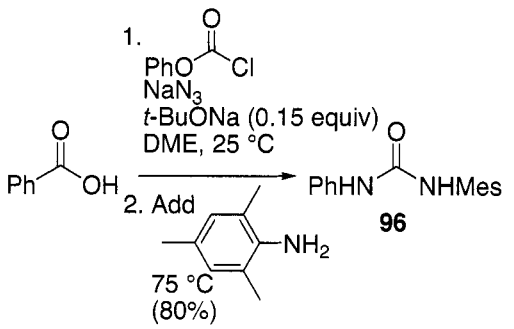


The reaction of 1-adamantane carboxylic acid proceeded smoothly at 80 °C, providing Boc-protected amine **92** in high yield, but the slow step of the process was addition of the *tert*-butoxy nucleophile (butoxide or butanol) to the isocyanate intermediate. Of numerous catalysts and conditions screened to accelerate that addition, zinc triflate in tetrahydrofuran solvent proved optimal, allowing the process to occur smoothly at 40 °C for a range of alkyl carboxylic acids. In some cases, such as the stereoretentive conversion of α-methyl-β-siloxy propionic acid **93** to Boc-protected chiral amine **94**, inclusion of additional *tert*-butanol was required. Catalysis was proposed to occur via an isocyanate-derived, zinc-complexed carbamoyl bromide. The Lebel conditions were also applied to malonate monoesters as a route to α-disubstituted-α-amino acids.

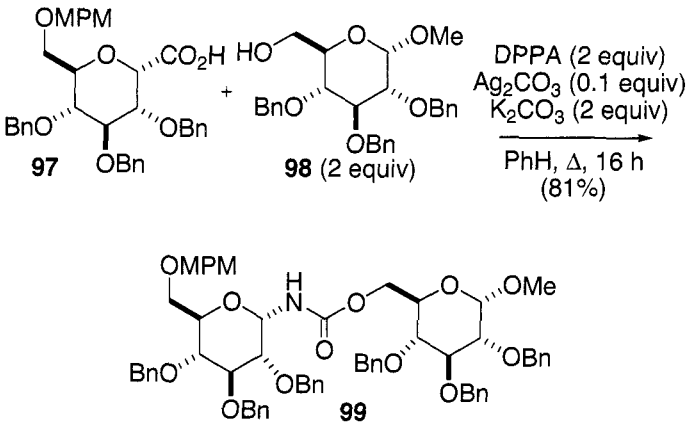


By substituting chloroformates for di-*tert*-butyl dicarbonate, Lebel extended her protocol to aromatic carboxylic acids.[67] In addition, DME was a better solvent than THF for these substrates, and a substoichiometric amount of *tert*-butoxide was included as a base. Again, an azidoformate intermediate, formed in this case by reaction of azide with the chloroformate, was suggested as the species that reacted with the carboxylic acid to generate the acyl azide. Depending on the chloroformate used, Curtius-rearranged amines with allyl-, benzyl-, and trichloroethyl carbamate protection were prepared in one pot from aromatic carboxylic acids. For example, *trans*-cinnamic acid provided *N*-alkenyl allyl carbamate **95**, with retention of olefin geometry. By using phenyl chloroformate, which releases the relatively less nucleophilic phenoxy group upon acyl azide formation, amine nucleophiles could be added to trap the isocyanate product of the Curtius rearrangement, providing a synthesis of ureas such as **96**.



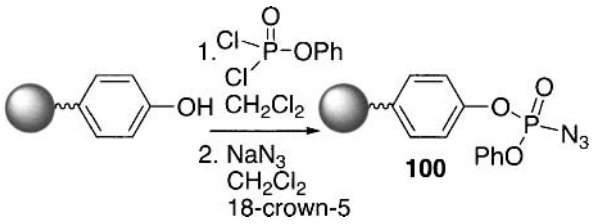


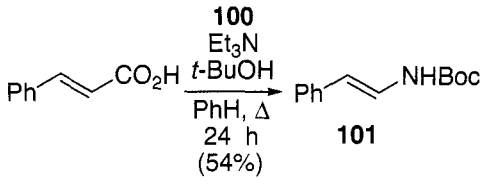
As in Lebel's zinc-mediated reactions of aliphatic acids, overcoming the sluggish reactivity of the intermediate isocyanates was an impediment in studies by Ikegami to apply the Curtius rearrangement for glycoconjugate synthesis. However, silver-ion catalysis and inclusion of potassium carbonate as base enabled coupling of sugar alcohols such as **98** with isocyanates derived from sugar carboxylic acids (e.g., **97**) under Shioiri conditions, efficiently producing urethane-linked disaccharide **99**.[68] Ikegami has also applied this approach in oligosaccharide synthesis.[69]



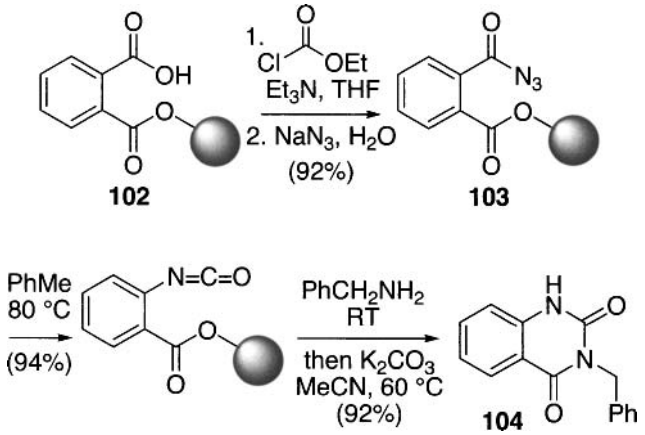
Polymer supported:

Reagents and reactants on solid supports have been utilized for the Curtius rearrangement. Lu and Taylor developed a polymer-bound phosphoryl azide to replace DPPA in Shioiri-type Curtius rearrangements. This methodology addressed a shortcoming of the Shioiri methodology, phosphorus byproducts that are difficult to separate from the desired Curtius products.[70] Attachment of the phosphoryl azide to a phenol resin gave polymer-bound reagent **100**, which was storable for periods of over one month. Shioiri–Curtius rearrangement of various acids, including *trans*-cinnamic acid, proceeded smoothly using **100**, providing *trans*-vinyl isocyanate **101** stereospecifically. The polymer-bound phosphorus-containing byproducts were removed by filtration at the end of the reaction.

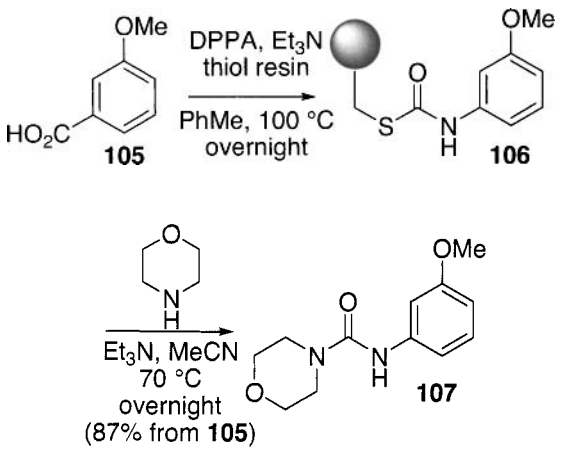




The carboxylic acid starting material has also been attached to polymer support.[71,72] For example, reaction of phthalic anhydride with polyethylene glycol (PEG, molecular weight 3400), provided soluble, polymer-attached phthalate monoester **102**. The free carboxyl was converted to the acyl azide using Weinstock conditions. Interestingly, the PEG support seemed to facilitate phase transfer in the reaction of sodium azide with the mixed anhydride intermediate. Curtius rearrangement of the polymer-bound acyl azide **103** occurred smoothly in hot toluene, and the resulting isocyanate could be reacted with various primary amines, giving ureas. Cleavage from the PEG support occurred upon treatment with base, as the distal urea nitrogen cyclized onto the ester carbonyl, releasing the quinazoline-2,4-dione product (e.g., **104**).[71]

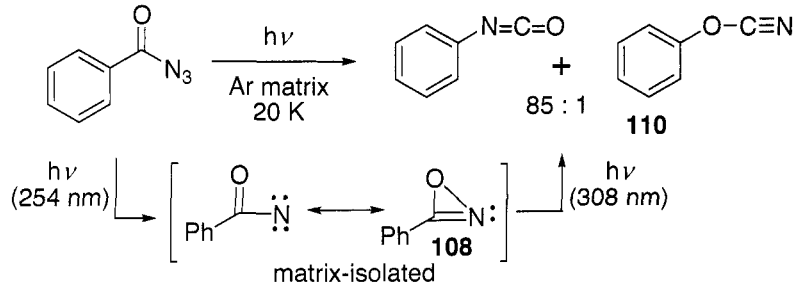


Another approach has been to react the isocyanate product from Curtius rearrangement with a solid-supported nucleophile.[73,74] The Curtius rearrangement of various carboxylic acids under Shioiri conditions was conducted in the presence of thiol-on-silica, an odorless resin. The resulting support-bound thiocarbamates, such as **106**, were washed and dried and could be stored. Their reaction with amines released urea products from the resin in high purity even without further purification. An example with morpholine as the nucleophile yielded urea **107** in excellent overall yield from the starting carboxylic acid. In essence, the resin-bound thiocarbamates served as readily prepared and handled isocyanate equivalents, increasing the potential of the Curtius rearrangement for diversity-targeted synthesis.[74]



Photochemically induced:

Photolysis of acyl azides generates isocyantes, apparently via two distinct routes: a concerted path as for the thermal Curtius rearrangement and also through the intermediacy of a singlet acyl nitrene. Early studies, including those by Lwowski, however, indicated that photochemical rearrangement of pivaloyl azide did not appear to involve a nitrene intermediate.[4,75,76] The yield of isocyanate was unchanged upon switching from the nitrene-trapping solvent cyclohexene to methylene chloride. Lwowski concluded that nitrene formed in the photochemical reaction goes on to non-Curtius products and is not an intermediate *en route* to isocyanate.

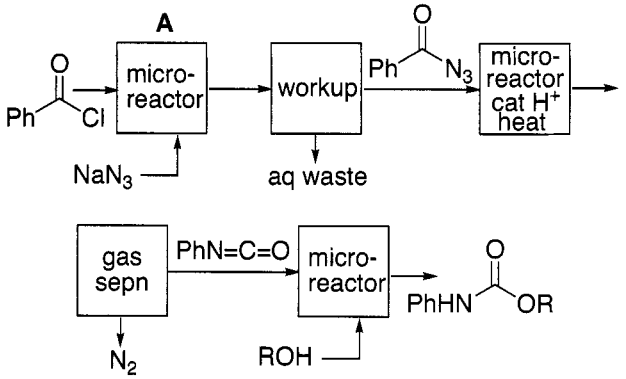


More recent matrix isolation studies on benzoyl nitrene, however, did show conversion to the isocyanate.[77] Calculations show that the acyl nitrene has oxazirene (**108**) character and that this O–N interaction stabilizes the singlet state of the nitrene.[78] Interestingly, a reexamination of benzoyl nitrene, trapped in an argon matrix and irradiated at 308 nm, revealed that in addition to phenyl isocyanate, a small amount of phenyl cyanate (**110**) was formed.[79] Direct irradiation of benzoyl azide (254 nm) also generated the

small amount of phenyl cyanate, but none of the phenyl cyanate formed under thermal Curtius rearrangement conditions.

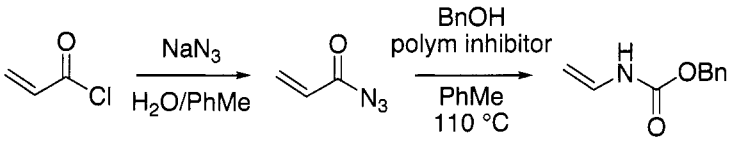
In a microfluidic system:

Formation of the acyl azide, Curtius rearrangement, and subsequent isocyanate trapping provided a fascinating model system for development of multistep synthesis in microfluidic reactors.[80] Benzoyl chloride and sodium azide (aqueous solution adjusted to pH 9) were combined in the first microreactor (**A**), workup occurred in an in-line separator module, and the resulting acyl azide was introduced into a heated microreactor where Curtius rearrangement to phenyl isocyanate occurred. Catalysis of the rearrangement with a solid-phase acid catalyst lowered the temperature necessary for efficient rearrangement. Dissolved nitrogen was removed by passing through a gas-impermeable membrane. Finally, the resulting isocyanate stream was split for separate reaction with various alcohols, generating the final carbamate products. On this proof-of-concept scale, the microfluidic reactor system could be run continuously for 6–7 days, generating 80–120 mg of carbamate products per day.

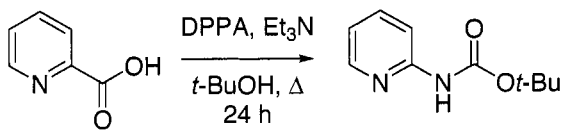


The application of a reaction first reported in the early 1890s to cutting-edge development of microfluidic reactor technology nearly 120 years later encapsulates the mechanistic traits, synthetic versatility, and overall appeal of the venerable and ever-intriguing Curtius rearrangement.

3.3.3.6 Experimental



Benzyl-*N*-vinyl carbamate.[35]
A 1-L reactor was charged with 68.4 g (1.05 mol) of sodium azide, 200 mL of water, 200 mL of toluene, and 0.09 g of Adogen 464 (methyltrialkylammonium chloride). The mixture was cooled with stirring in ice-water bath, and 90 g (1 mol) of acryloyl chloride was added drop-wise over a period of 1.5 h at 0–5 °C. After the addition, the mixture was stirred for 45 min. The organic phase was separated and stored at 0–5 °C until used. A 1-L flask was equipped with a variable speed pump, mechanical stirrer, temperature controller, a 4-in column packed with ceramic saddles, distillation head, spiral condenser (cooled with 10–15 °C water), and receiver. The flask was charged with 150–200 mL toluene and 0.5 g phenothiazine. The toluene solution was heated to 105–110 °C. The receiver was charged with 86 g (0.8 mol) of benzyl alcohol, 0.05 g of phenothiazine, and 0.1–0.3 g triethylamine. This mixture was cooled in ice and stirred. A solution of acryloyl azide (1 mol) prepared as described above was pumped into the distillation flask over a period of 4–5 h, maintaining a pot temperature at 105–110 °C with a heating mantle. The vapor temperature varied, depending on the rate of addition of the azide, but was in the range of 80–100 °C. The distillate was collected directly in the benzyl alcohol mixture. After the addition of acryloyl azide, the distillation continued to distill out 10–20 mL of toluene. The receiver was then isolated from the distillation set up, and its contents were stirred at 0–5 °C for 1–2 h. The product mixture was then stripped in vacuo to a weight of 200–250 g. To the residue was added 300–350 mL heptane and cooled with stirring to 15 °C. A few seed crystals of benzyl-*N*-vinyl carbamate were added, and the mixture was stirred for 2–3 h. The product was filtered, washed with heptane, and dried in vacuo. Yield 115–128 g (65–72%).



tert-Butyl-_N_-(2-pyridyl)carbamate.[56]

A mixture of pyridine-2-carboxylic acid (1.23 g), diphenylphosphoryl azide (2.75 g), and triethylamine (1.05 g) in *t*-BuOH (30 mL) was stirred at reflux for 23 h. The mixture was evaporated, and the residue was dissolved in benzene (250 mL). The solution was successively washed with 5% aq citric acid (30 mL), water (15 mL), satd aq $NaHCO_3$ (30 mL), and brine (15 mL). Drying followed by evaporation gave a yellow solid, which was recrystallized from EtOAc–EtOH–hexane to give a high melting compound (0.025 g, mp > 300 °C). The mother liquor was chromatographed (hexane-$CHCl_3$-EtOAc, 20:4:1) to give the carbamate (1.42 g, 73%).

3.1.4.7 References

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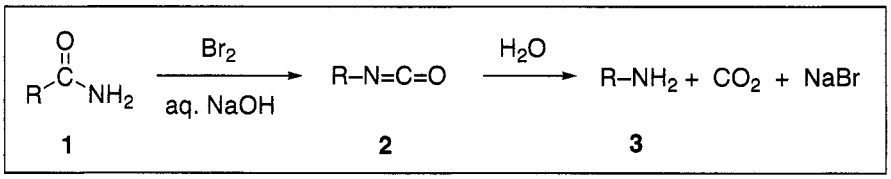
1.1.5 Hofmann Rearrangement

Gordon W. Gribble

1.1.5.1 Description

The Hofmann Rearrangement (HR), which is often called the Hofmann Reaction or Hofmann Degradation but should not be confused with the Hofmann Elimination, describes the multistep transformation of a primary carboxamide **1** to a primary amine **3** via an intermediate isocyanate **2** under the action of bromine and sodium hydroxide.[1–7] As will be shown, many variations of this rearrangement are known and widely used today.



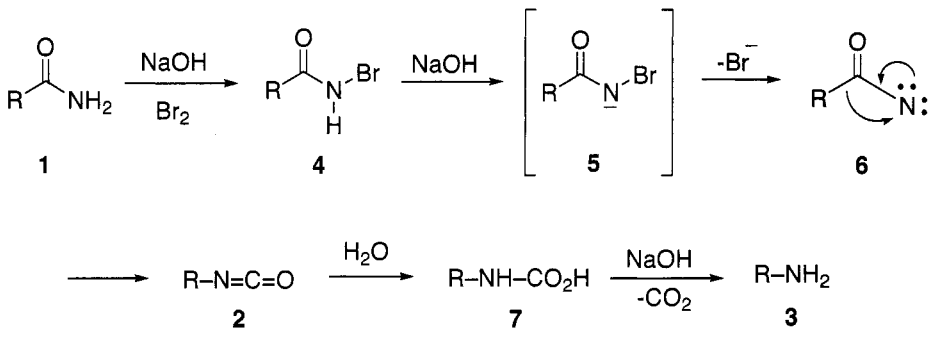
1.1.5.2 Historical Perspective

More than 100 years ago, Hofmann reported in a series of papers the conversion of primary amides to amines with bromine in aqueous sodium hydroxide.[8] The occasional side reaction leading to nitrile formation was also observed by Hofmann.[8d,e] Another early observed side reaction is the formation of ureas from the combination of isocyanate with unreacted amide. This particular side reaction can be circumvented by employing sodium methoxide in place of sodium hydroxide to afford the corresponding methyl carbamate, which upon distillation from calcium hydroxide affords the corresponding primary amine, as first described by Jeffreys.[9]

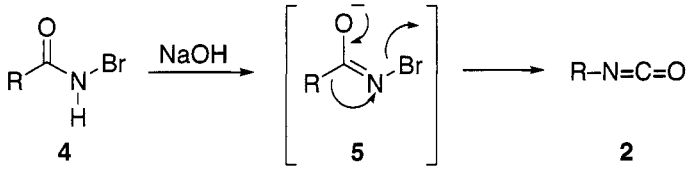
1.1.5.3 Mechanism

Although the basic mechanism of the HR seems established,[1–7] the details of the formation of isocyanate **2** have been of long standing interest.[10–15] Thus, following base-catalyzed bromination of the amide to give *N*-bromoamide **4**, one can envision base-induced elimination of HBr from **4** to give a nitrene **6** followed by intramolecular rearrangement to an isocyanate **2**. Subsequent reaction with water affords an unstable carbamic acid **7** that loses carbon dioxide to give amine **3** (Scheme 1). Alternatively, *N*-bromoamide **4**, upon deprotonation to amidate **5**, can be imagined to form isocyanate **2** directly (Scheme 2).

Scheme 1



Scheme 2



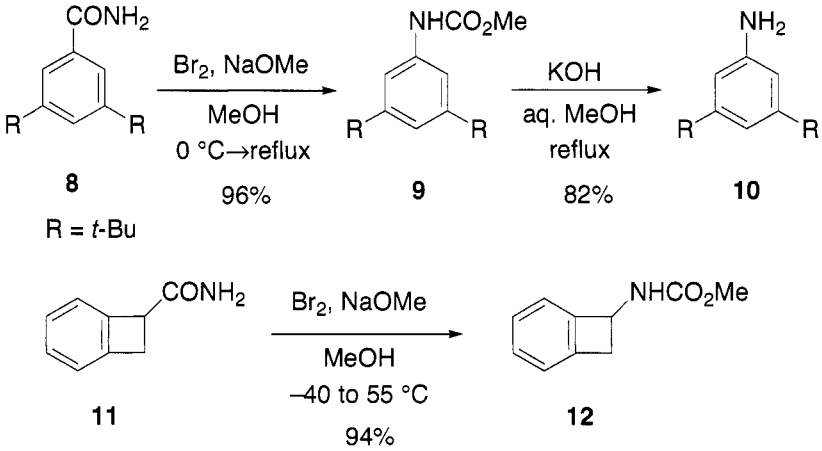
Early mechanistic studies demonstrated that there is no rearrangement within the alkyl migrating group; for example, the HR of *t*-butylacetamide affords neopentylamine and not the rearranged *t*-amylamine.[10] Furthermore, the rate of the HR starting from *N*-bromobenzamides is a function of benzene ring substitution; electron-donating substituents greatly facilitate the rearrangement, and the authors conclude that the rate-determining step is loss of bromide from the amidate **5**.[11] Arguments against the intermediacy of nitrene **6** are that hydroxamic acids (RCONHOH) are not isolated, as might be expected as products of the HR.[12] An elegant doubly labeling study of the HR of a mixture of *m*-$DC_6H_4CONH_2$ and $C_6H_5CON^{15}H_2$ established the intramolecularity of the migration of the phenyl group to the nitrogen.[13] A detailed study of the HR of both *N*-bromobenzamides and *N*-chlorobenzamides strongly supports a concerted mechanism (Scheme 2) for these substrates.[14] Notably, kinetic isotope effects in the HR of phenyl-1-^{14}C and carbonyl-^{14}C labeled *N*-chlorobenzamides provide compelling evidence for the concerted nature of these reactions.[14d] Interestingly, such isotope effects are not observed in the related Wolff and Schmidt rearrangements, but are observed in the Beckmann rearrangement.[14d] Intermediate *N*-bromoamidate **5** (R = Ph) can be generated by photolysis of benzoyl azide in the presence of lithium bromide, but this species does not yield an isocyanate under these conditions.[15]

In summary, the evidence would appear to favor a concerted mechanism (Scheme 2), involving as the rate-determining step the migration of the R group to the nitrogen of **5** affording isocyanate **2** directly.

1.1.5.4 Variations and Improvements

Unlike many name reactions, the HR has evolved into a myriad of variations, some of which have supplanted the original Hofmann method in both importance and utility.

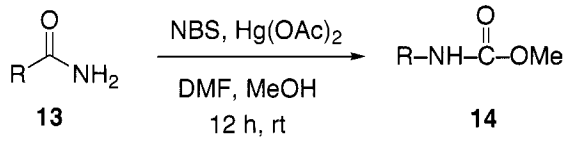
The aforementioned Jeffreys modification[9] using Br_2/NaOMe has been extended by Nagai *et al.*[16] (**8**→**10**) and Radlick (**11**→**12**).[17]



Both sodium bromite ($NaBrO_2$)[18] and benzyltrimethylammonium tribromide[19] can be used instead of bromine to effect the HR. Interestingly, the employment of bromine and NaOH under phase-transfer conditions interrupts and terminates the reaction at the isocyanate stage with aliphatic primary amides.[20] Bromine with the monosodium salt of ethylene glycol has been used in the HR of poly(acrylamide).[21] Sodium hypochlorite (Cl_2, NaOH) is frequently employed in the HR and an early example is that of Schneider.[22] A triphasic system of sodium hypochlorite, sodium bromide, and tetrabutylammonium hydrogen sulfate is effective in converting primary acetamides to nitriles.[23] Sodium hypochlorite and methanol using potassium fluoride on alumina as a base converts amides to methyl carbamates in excellent yield.[24]

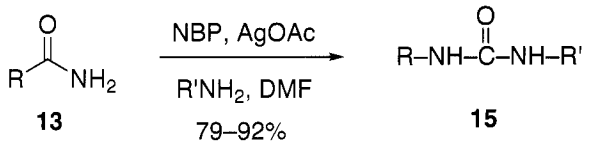
Another source of bromine in the HR is *N*-bromosuccinimide (NBS), which was first employed by Jew *et al.* in combination with mercuric acetate or silver acetate to convert primary amides **13** to carbamates **14**.[25] These workers also used 1,3-dibromo-5,5-dimethylhydantoin (dibromatin) in place of NBS with comparable success. Similarly, the combination of *N*-

bromophthalimide (NBP) and silver acetate in the presence of methanol effects the same HR,[26a] and in the presence of added amines, ureas are obtained (**13**→**15**).[26b] The use of NBS, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and methanol in the HR leading to methyl carbamates avoids the use of toxic mercuric acetate and expensive silver acetate.[27] The mechanism of the NBS HR has been studied in some detail, with the conclusion that the actual oxidizing agent is *N*-bromosuccinamic acid dipotassium salt.[28]



13 **14**

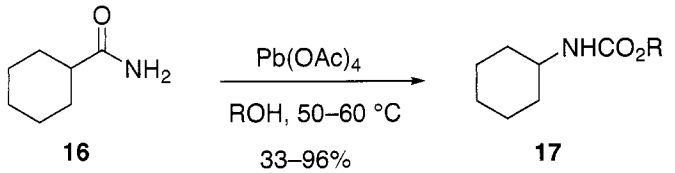
R = *n*-C_7H_{15}, *n*-C_9H_{19}, *n*-$C_{15}H_{31}$, *c*-C_6H_{11}, *t*-Bu, Bn, Ph, 4-NO_2Ph, 2-EtPh, 2-MePh, 2-ClPh, 3-pyridyl



13 **15**

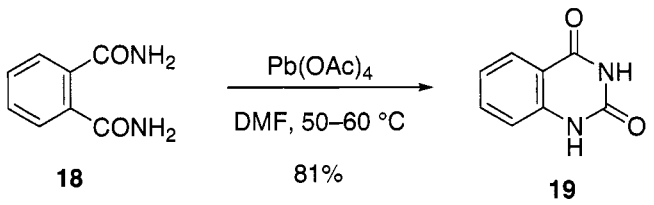
R = Bn, Ph, *c*-C_6H_{11}, *n*-C_5H_{11}, *n*-C_7H_{15}; R' = Ph, Bn, *c*-C_6H_{11}

An early variation of the classic HR is the use of lead tetraacetate (LTA) to accomplish the rearrangement of primary amides to carbamates via the intermediacy of isocyanates. Discovered independently by Beckwith[29] and Baumgarten,[30] the reaction is proposed to involve nitrene **6** leading to isocyanate **2** (Scheme 1).[31] Thus, in the presence of LTA, cyclohexyl amide (**16**) is converted to methyl carbamate **17**,[29c] phthalamide (**18**) forms dioxoquinazoline **19**,[29d] and amide ester **20** yields amino acid **22** after hydrolysis of carbamate **21** with retention of configuration.[30b]

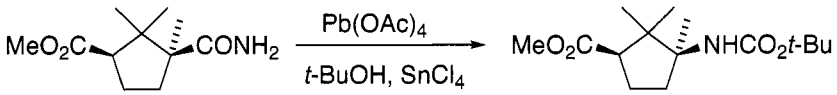


16 **17**

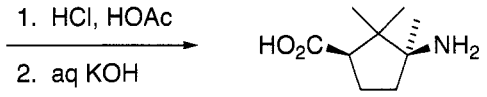
R = Me, Et, *c*-C_6H_{11}, *t*-Bu



18 19

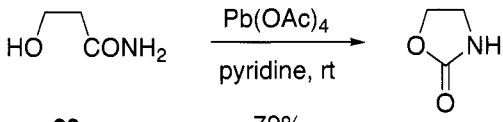


20 21



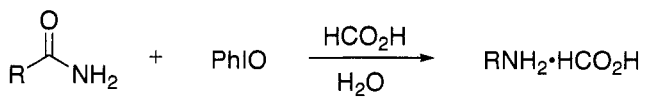
22

Simons has found that LTA in pyridine provides for a synthesis of 2-oxazolidinones (**24**) from β-hydroxy primary amides **23**.[32]



23 **24**

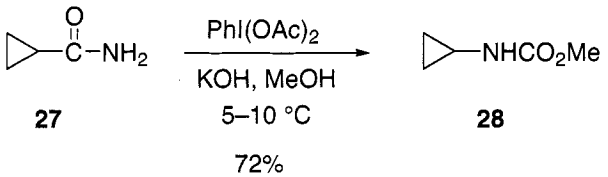
Perhaps inspired by the 1903 discovery by Tscherniac that phthalimide affords anthranilic acid upon exposure to iodosobenzene (iodosylbenzene),[33] several workers have explored different hypervalent iodine reagents in what has become the most widely adopted variation of the HR. Iodosobenzene[34] itself continues to find use; e.g., **25**→**26**,[35] although hypervalent iodine derivatives are more frequently employed (*vide infra*).



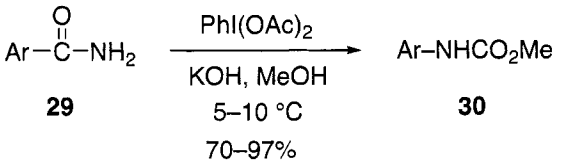
25 70–90% **26**

R = Bn, 4-MeOBn, $PhCH_2CH_2$, n-C_5H_{11}, i-$C_3H_7CH_2$, t-Bu

The readily available iodosobenzene diacetate ($PhI(OAc)_2$, diacetoxyiodobenzene)[36] also effects the HR under mild conditions;[37,38] for example, **27**→**28** and **29**→**30**.[38] A mechanism for these reactions is proposed to involve the formation of $PhI(OMe)_2$, which reacts with the amide to form RCONHI(OMe)Ph that subsequently rearranges to the usual isocyanate intermediate under the influence of base.[38,39]



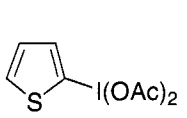
27 **28**



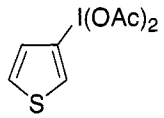
29 **30**

Ar = Ph, 2-pyridyl, 3-pyridyl, 6-quinolyl, others

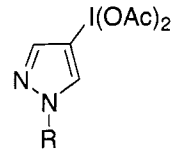
The preparation and limited HR studies of a series of diacetoxy iodoheterocycles (**31**–**34**) have been described,[40] but no advantage of these reagents over $PhI(OAc)_2$ is evident from this study.



31

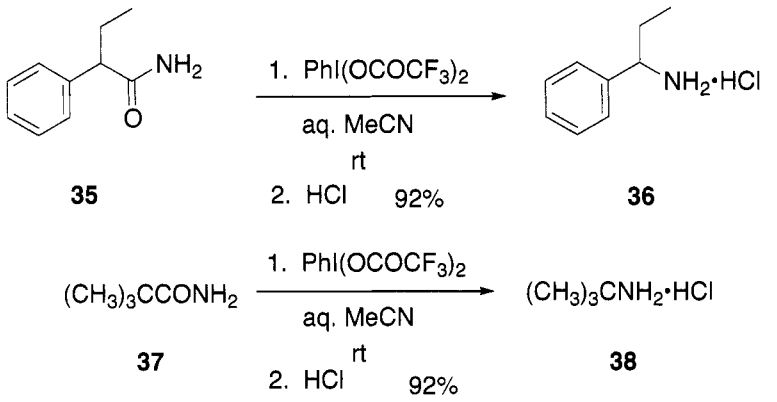


32

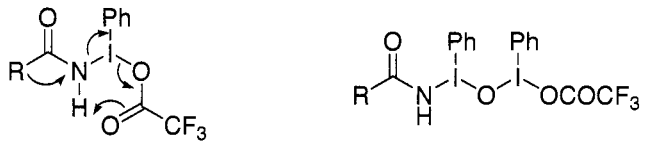


33 (R = Ts)
34 (R = Tf)

Loudon and co-workers have found that the somewhat less stable iodosobenzene bis(trifluoroacetate) ($PhI(O_2CCF_3)_2$) also effects the HR of aliphatic amides to amines under mild conditions and without having to isolate the isocyanate intermediate.[41] Aromatic amines are further oxidized by $PhI(O_2CCF_3)_2$ and cannot be synthesized in this fashion. Two examples are shown (**35**→**36** and **37**→**38**).[41a,b] Because at least five different acronyms have been used for this reagent (PIFA, BTIB, BTI, TIB, TBIB), including two different acronyms in the same paper (!), none is used here.

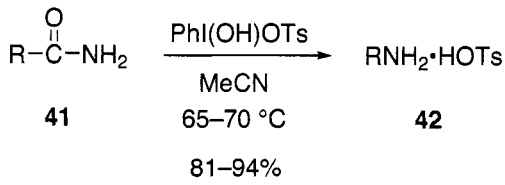


A mechanistic study of the $PhI(O_2CCF_3)_2$-HR has led to the speculation that the key intermediate may be either **39** or **40**, which rearranges in typical fashion to the isocyanate.[41c]

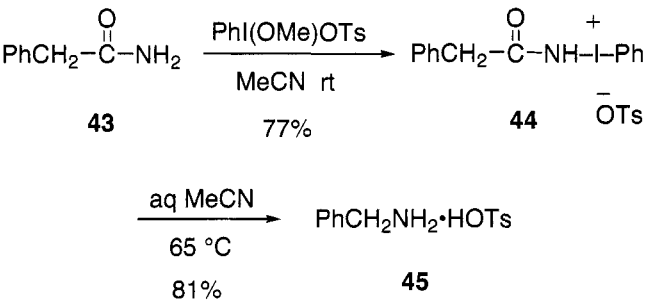


39 **40**

A related reagent to $PhI(OAc)_2$ and $PhI(O_2CCF_3)_2$ is [hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs), which has the advantage over $PhI(O_2CCF_3)_2$ of improved stability and which is especially useful for the HR of long-chain primary amides.[42] A similar HR reagent is [methoxy(tosyloxy)iodo]benzene (PhI(OMe)OTs), which has increased solubility in acetonitrile over that of PhI(OH)OTs.[43] Examples of these HR transformations are given here (**41** → **42** and **43** → **44** → **45**).[42,43] Intermediate **44** could be isolated and characterized, and when it is heated in chloroform, the expected benzyl isocyanate is isolated.[43]

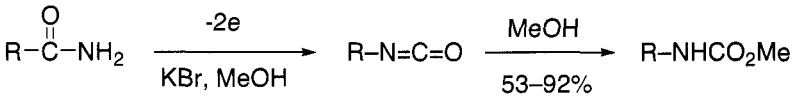


R = *n*-$C_{12}H_{25}$, *n*-$C_{13}H_{27}$, *n*-$C_{14}H_{29}$, *n*-$C_{15}H_{31}$, *n*-$C_{16}H_{33}$, *n*-$C_{17}H_{35}$, *n*-$C_{21}H_{43}$



43 **44** **45**

A final variation of the HR is an electrochemical method described by Shono *et al.* (e.g., **46→48**).[44] This novel HR involves the oxidation of bromide to bromine and the reduction of potassium ion to potassium, which generates potassium methoxide, resulting in typical HR conditions. In some cases the isocyanate is the major product.



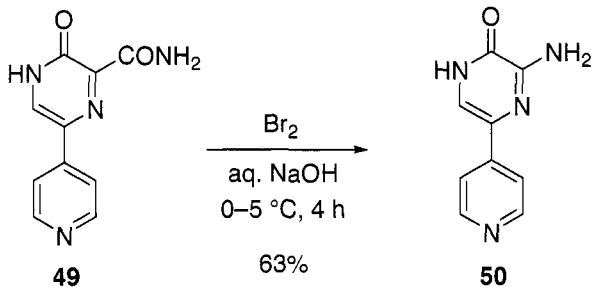
46 **47** **48**

R = *n*-Pr, *c*-C_6H_{11}, *n*-C_8H_{17}, Bn, *t*-Bu

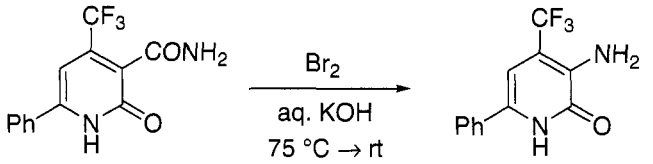
1.1.5.5 Synthetic Utility

Bromine and Hydroxide

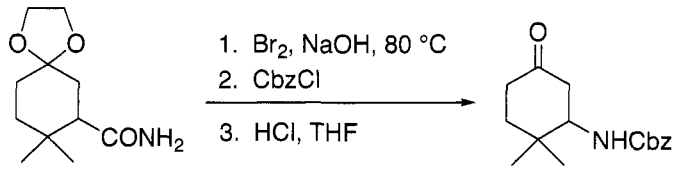
Given the plethora of new and "improved" methods, it is perhaps surprising that the original Hofmann conditions still find utility. Thus, the action of bromine and sodium hydroxide solution effects the conversion of 3-acetamidothiophene to 3-aminothiophene derivatives (70–82%),[45] 6-fluoropicolinamide to 2-amino-6-fluoropyridine (87%),[46] 2-azidobenzamide to 2-azidoaniline (49%),[47] *N*-α-tosylasparagine to 2-(*S*)-tosylamino-β-alanine on a multi-kilogram scale (70%),[48] 3-(4'-methoxyphenyl)-2-methyl-propanamide to 2-amino-1-(4'-methoxyphenyl)propane (75%),[49] 2,2,5,5-tetramethyl-3-carbamoylpyrrolidine-1-oxyl to 2,2,5,5-tetramethyl-3-amino-pyrrolidine-1-oxyl (52%),[50] 2-fluorobenzamide-d_4 to 2-fluoroaniline-d_4 (53%),[51] and ^{18}F-labelled pyridinecarboxamides to ^{18}F-labelled amino-pyridines (20–30%).[52] Some additional examples are illustrated below (**49→50**;[53] **51→52**;[54] **53→54**;[55] **55→56**;[56] and **57→58**[57]).



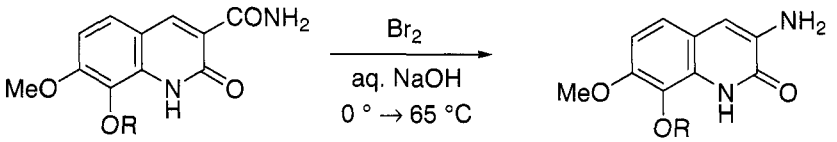
49 50



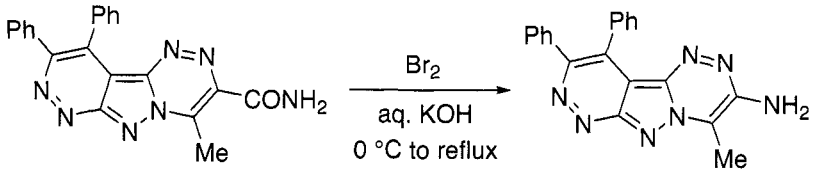
51 52



53 54



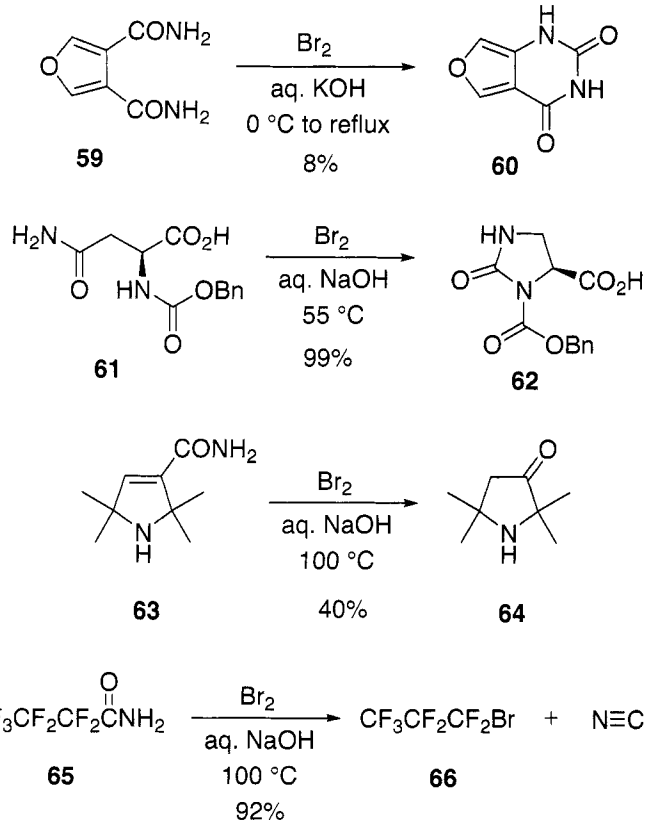
55 R = *n*-C_5H_{11} 56



57 58

As illustrated earlier (**18**→**19** and **23**→**24**), the intermediate isocyanate can often be ambushed by a proximate nucleophile. Thus, 3,4-furandicarboxamide (**59**) yields **60** upon treatment with bromine/potassium hydroxide, albeit in low yield.[58] This isocyanate-trapping tactic has been

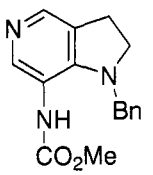
used by several workers to cleave asparagine peptides[59] and to prepare imidazolidin-2-ones;[60–62] for example, **61**→**62** on a 60 gram scale.[62b] In contrast, as mentioned earlier, *N*-α-toxylasparagine is smoothly converted to 2-(*S*)-tosylamino-β-alanine, the normal HR product.[48] A standard HR represents a simple route to pyrrolidin-3-one **64**.[63] The HR of perfluorinated amides can afford an unusual cleavage product, e.g., **66**, and cyanate ion (which is isolated in 69% yield), presumably via fragmentation of the corresponding *N*-bromoamidate.[64]



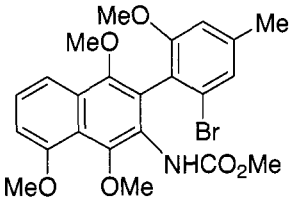
Bromine and Alkoxide

The modification of the HR that employs alkoxide, often methoxide, is usually an efficient route to carbamates. For example, methyl carbamates **67**–**72** are synthesized from the corresponding primary amides using bromine and sodium methoxide. Carbamate **68** is used in a synthesis of phenanthroviridin aglycon,[66] and cyanoester **70** is a key feature in the commercial synthesis of the DuPont herbicide azafenidin.[68] Carbamate ester

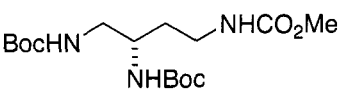
71 is obtained with 98% *ee* from a malononitrile and is an important precursor of (*S*)-α-methyldopa.[69]



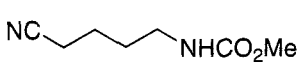
67 (50%)[65]



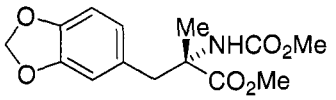
68 (81%)[66]



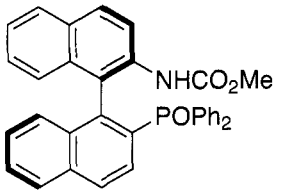
69 (68%)[67]



70 (94%)[68]

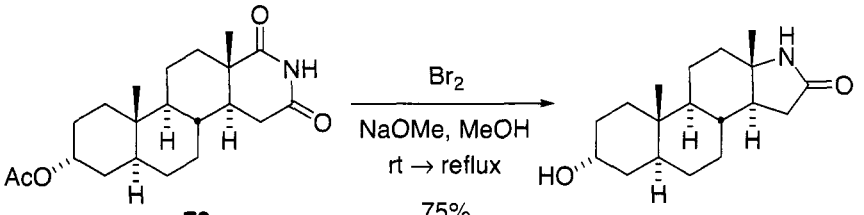


71 (73%)[69]

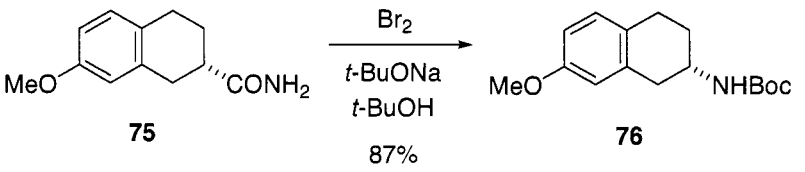


72 (94%)[70]

The combination of bromine and sodium methoxide has been used to effect the HR of amide- to amino-functionalized single-wall carbon nanotubes.[71] Azasteroid **73** yields lactam **74** on treatment with bromine/sodium methoxide,[72] and amide **75** produces BOC-protected amine **76** with bromide and sodium *tert*-butoxide.[73]



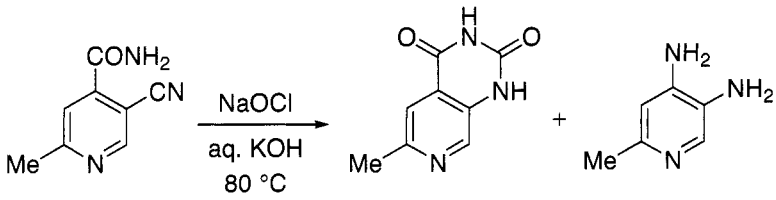
73 **74**



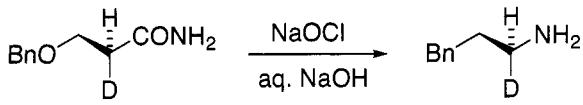
75 **76**

Sodium Hypochlorite

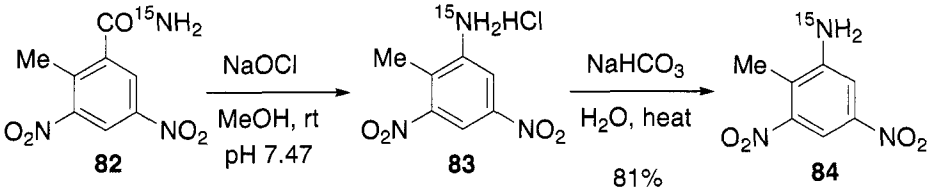
The ease of handling and availability of bleach (chlorox; sodium hypochlorite) has led to several applications of this venerable variation of the HR. An early example of the use of sodium hypochlorite is the conversion of cyanoamide **77** to a mixture of methyldioxycopazoline (**78**) and 2-methyl-4,5-diaminopyridine (**79**).[74] In the stereospecific conversion of amide **80** to **81** it is found that sodium hypochlorite is superior to sodium hypobromite, because the latter conditions effect benzylic bromination negating an efficient HR.[75] Careful adjustment of pH prevents the otherwise facile hydrolysis of amide **82** to the corresponding carboxylic acid, thus allowing for the HR to give amine **84**.[76] Intermediate *N*-chloroamide **83** can be isolated in quantitative yield after the chlorination step. This method also affords a synthesis of ^{15}N-labelled 4-amino-2,6-dinitrotoluene. A new application of the HR is the conversion of 1,1-disubstituted ureas (**85**) to the corresponding hydrazines **86**.[77] All but two of the yields are in the range 50–85%; the two low yields involve 1,2,3,4-tetrahydrocarbazole-9-carboxamide and 1-(2-naphthyl)-1-phenylurea, which suffer from hydrolysis and C-1 chlorination, respectively. Sodium hypochlorite was superior to other HR conditions examined.

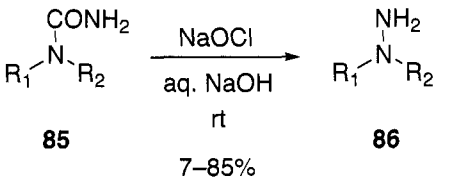


77 **78** (70%) **79** (5–10%)



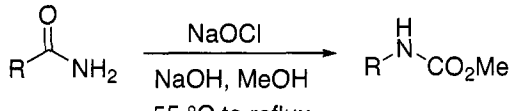
80 62% **81**



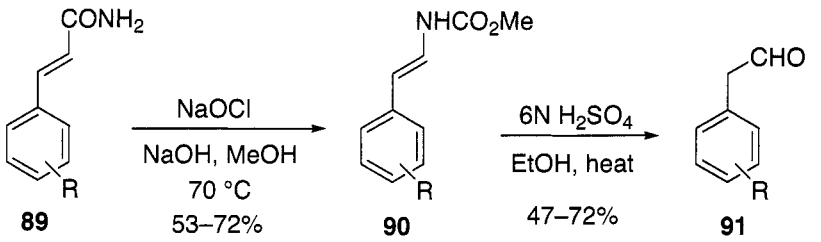


R_1 = 2-MeOPh, Ph, 2-NO_2Ph, 1- and 2- naphthyl, 3-ClPh, *c*-C_5H_{11}, Bn, Me
R_2 = 2-MeOPh, Ph; R_1,R_2 = piperidine

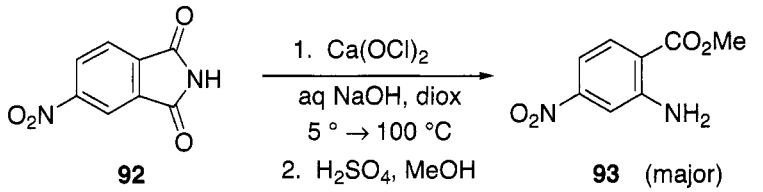
The use of freshly prepared sodium hypochlorite in methanol provides for an extremely efficient conversion of fatty acid amides **87** to methyl carbamates **88**, provided that the hypochlorite solution is added to the amide solution and with good stirring.[78] Lower yields obtain when the methanolic solution of amide is added to the hypochlorite solution. The methyl carbamates **90** resulting from the HR of cinnamamides **89** with methanolic sodium hypochlorite are hydrolyzed to the corresponding arylpropanals **91**.[79] Both nitro (e.g., **92**→**93**[80]) and azide groups (e.g., **94**→**95**[81]) are impervious to hypochlorite under the conditions of the HR. In the former example, methyl 2-amino-4-nitrobenzoate (**93**) and methyl 2-amino-5-nitrobenzoate (not shown) are formed in a 3:1 ratio.[80] As mentioned earlier the combination of sodium hypochlorite, methanol, and potassium fluoride on alumina is an excellent and versatile HR for a variety of amides; e.g., **96**→**97**.[24]

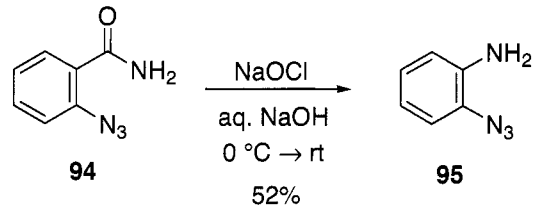


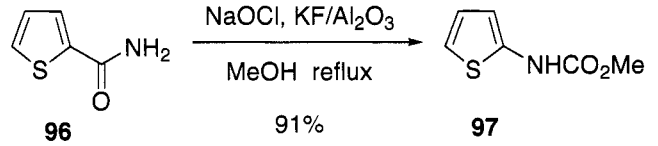
R = *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_9H_{19}, *n*-$C_{10}H_{21}$, *n*-$C_{11}H_{23}$, $CH_3(CH_2)_5CH(CH_2CH_3)$



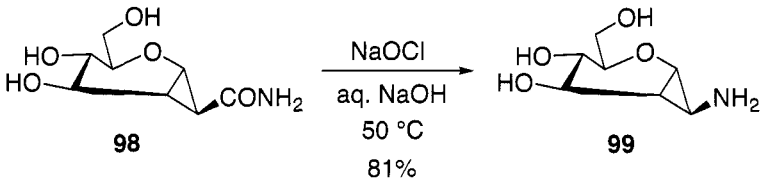
R = H, 4-Cl, 4-Br, 2-Cl, 2,6-Cl_2, 4-NO_2, 4-Me, 4-MeO, 3-NO_2, 4-CO_2H, 4-Ac, 3,4-$(MeO)_2$, 2,3,4-$(MeO)_3$, 3,4-(OCH_2O)





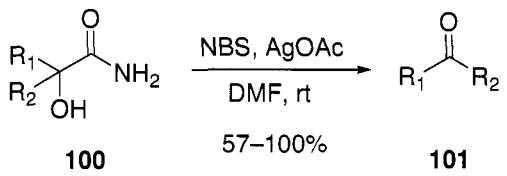


The HR using sodium hypochlorite has been applied to a synthesis of a key intermediate for a route to (+)-biotin,[82] and sodium hypochlorite also finds use in the preparation and HR of *N,N*-dichlorocarboxamide sugars.[83] The sodium hypochlorite variation of the HR has been extensively used to prepare poly(vinylamine) from polyacrylamide and related polymers.[84] One final application of sodium hypochlorite in a HR is the synthesis of glycoside hydrolase inhibitor **99**.[85]

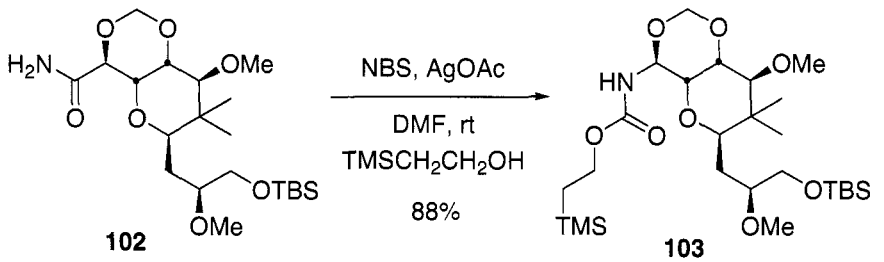


N-*Bromosuccinimide*

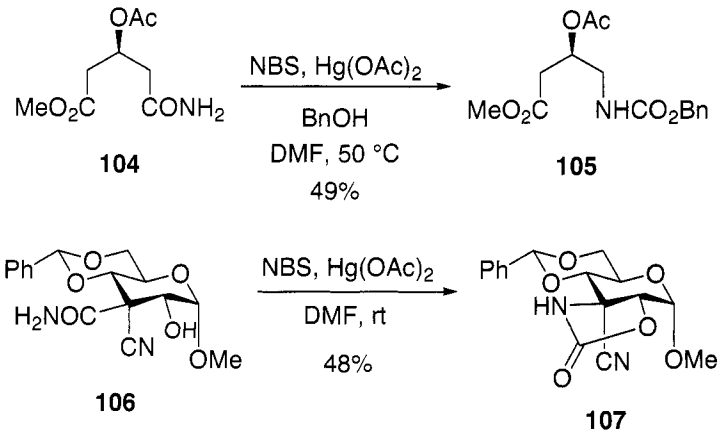
The discovery that *N*-bromosuccinimide (NBS) effects the HR[25–28] led to several applications of this variation towards synthetic targets. The original use of NBS in a HR involved mercuric acetate or silver acetate as a promoter of the rearrangement of the *N*-bromoamide to the isocyanate.[25,26] This combination of NBS and silver acetate converts the appropriate β- and γ-hydroxyamides to 2-oxazolidinones and 1,3-oxazine-2-ones,[86] respectively. In contrast, α-hydroxyamides **100** form ketones **101**,[87] presumably by "premature" fragmentation of the *N*-bromoamide. A synthesis of mycalamide B features a HR using NBS and AgOAc to convert amide **102** to carbamate **103** in 88% yield.[88] The use of $PhI(O_2CCF_3)_2$ affords **103** in 73% yield.



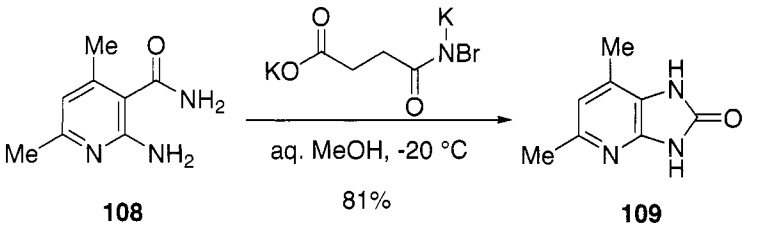
R_1 = Me, *n*-Bu, Bn, Ph; R_2 = *n*-$C_{11}H_{23}$, Ph, 4-EtPh, α-naphthyl, Bn



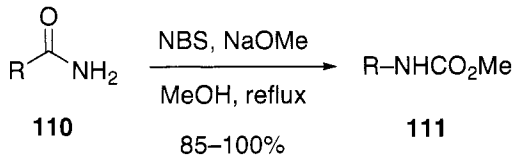
A synthesis of (*R*)-4-amino-3-hydroxybutanoic acid features the HR of ester amide **104** to benzyl carbamate **105** using NBS and mercuric acetate.[89] The alcohol corresponding to acetate **104** forms the expected 2-oxazolidinone under these conditions. Similarly, 2-oxazolidinone **107** is produced from glucopyranoside **106** upon exposure to NBS and $Hg(OAc)_2$.[90]



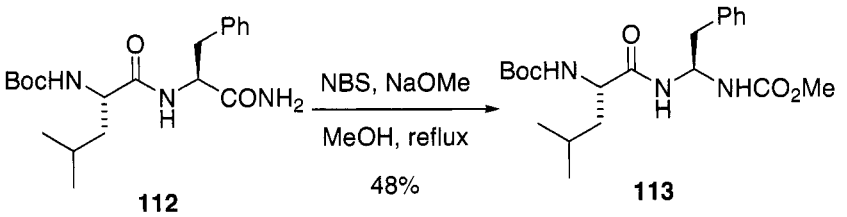
One can effect a HR with NBS in the presence of simple bases.[28] Thus, the combination of NBS and aqueous potassium hydroxide, which forms *N*-bromosuccinamic acid dipotassium salt,[28] converts 2-amino-4,6-dimethyl-nicotinamide (**108**) to 2-oxo-5,7-dimethylimidazolo[5',4':2,3]pyridine (**109**).[91] Comparable results are obtained using iodosobenzene diacetate.



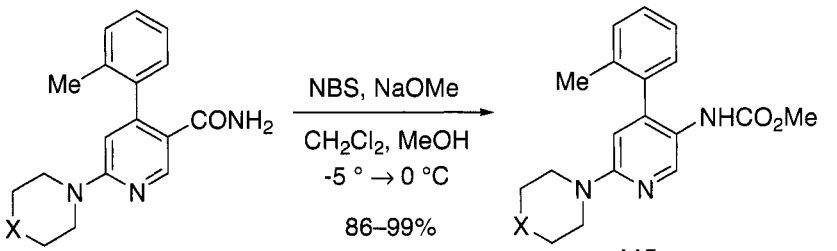
The union of NBS and sodium methoxide in the HR of amides leads to methyl carbamates, often in excellent yield (**110**→**111**;[92] **112**→**113**;[93] **114**→**115**[94]). It is suggested that the true brominating agent in these cases is $MeO_2CCH_2CH_2CON(Na)Br$.[92]



R = Ph, Bn, 4-MeOPh, 4-MePh, 4-ClPh, 4-CF_3Ph, *n*-$C_{15}H_{31}$, *n*-C_9H_{19}

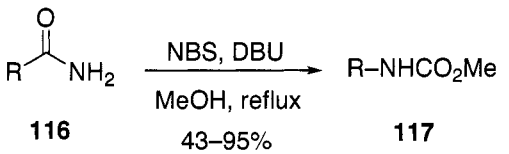


112 **113**



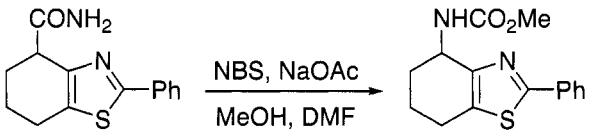
114 X = O, NMe **115**

Other bases used with NBS in the HR are DBU[27,95] (e.g., **116→117**),[27] sodium acetate (**118→119**),[96] and potassium acetate (**120→121**).[97] In the latter case, both NBS and AgOAc and $PhI(O_2CCF_3)_2$ afford lower yields of **121**.

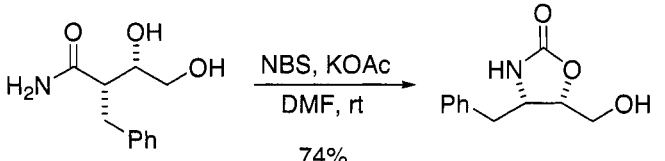


116 **117**

R = 4-MeOPh, 3,4-$(MeO)_2$Ph, 4-MePh, Ph, 4-ClPh, 4-NO_2Ph, Bn, *n*-C_9H_{19}, *n*-$C_{15}H_{31}$, 2,4-$(MeO)_2$Ph, 4-Me_2NPh



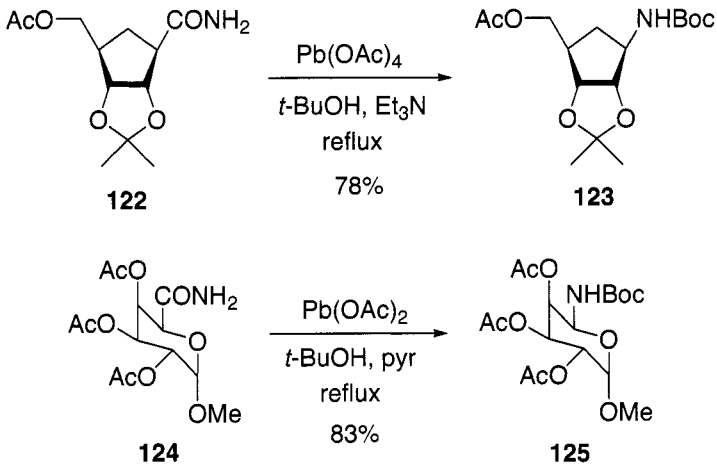
118 **119**



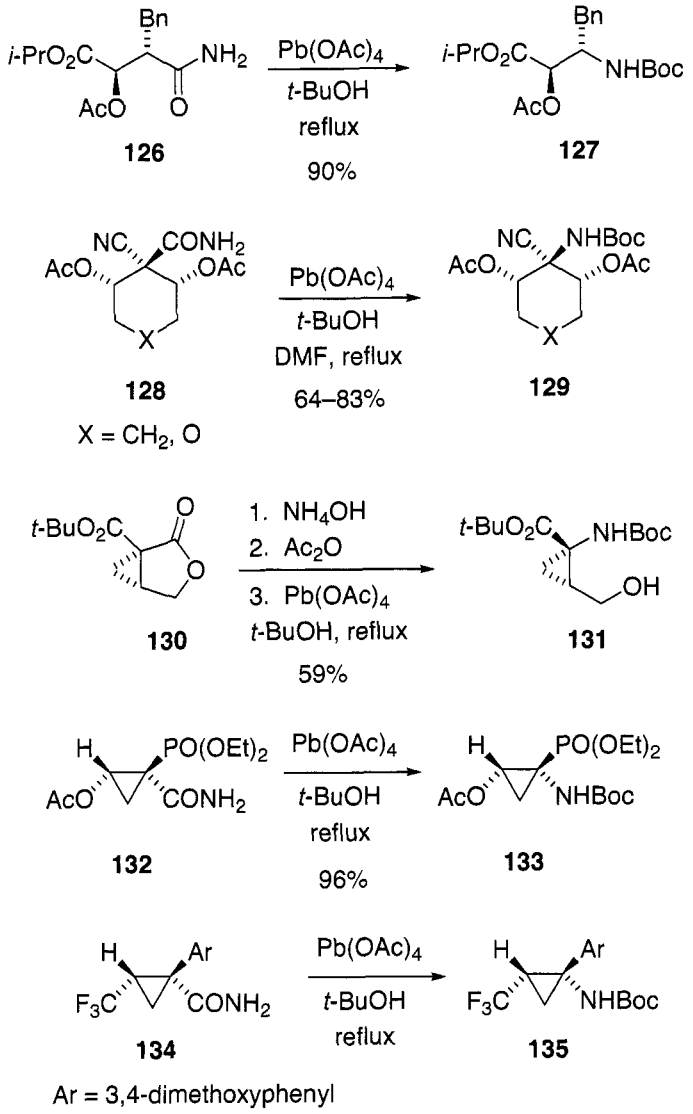
120 **121**

Lead Tetraacetate

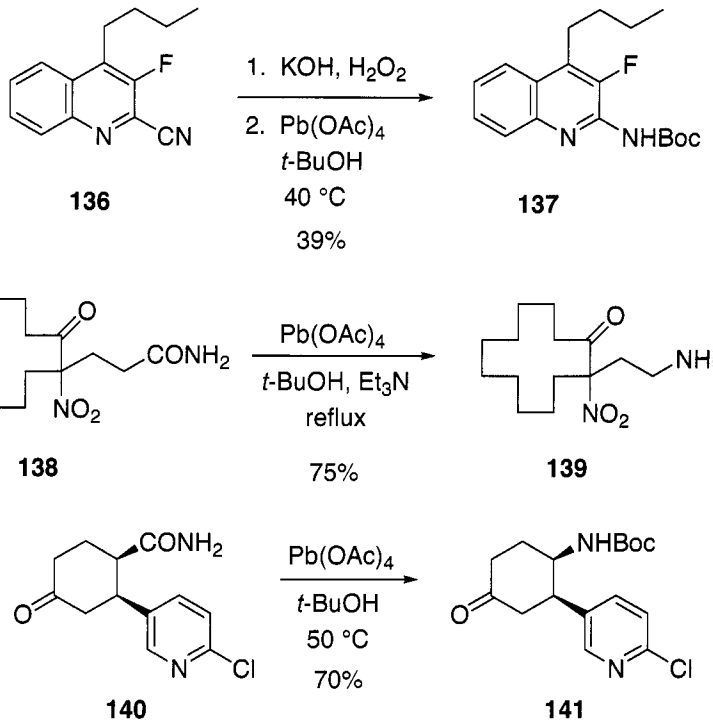
Despite the demonstrated success of NBS and the hypervalent iodine compounds as modern HR reagents, the classical variant lead tetraacetate[29,30] continues to find synthetic applications. A synthesis of the carbocyclic nucleoside (–)-aristeromycin features the conversion of amide **122** to Boc-protected amine **123**.[98] Similar tactics are used for syntheses of 6'-β-hydroxyaristeromycin,[99] 2',3'-dideoxy-2'-*C*-hydroxymethyl nucleosides,[100] an aminocyclopentanetrimethanol for the preparation of *xylo*-carbocyclic nucleosides,[101] 3-amino sugar derivatives,[102] Boc-protected amino-β-*L*-arabinopyranoside **125**,[103] and 2-amino-2-deoxyglycosides.[104] The latter study revealed that the HR employing bromine and sodium methoxide or sodium hydroxide gave much lower yields than did lead tetraacetate.



Lead tetraacetate is employed in the synthesis of nor-C-statine via the key step **126**→**127**.[105] The use of bromine in methanol or $PhI(O_2CCF_3)_2$ gives lower yields and impure product. Protected α-amino nitriles **129** are prepared from the corresponding amides **128** using LTA,[106] and this HR variation is a step in the conversion of cyclopropyl lactone **130** to carbamate **131**.[107] Likewise, Boc-protected cyclopropanephosphonate **133** is synthesized from **132** using LTA,[108] and **135** is an intermediate in a synthesis of a trifluoronorcoronamic acid employing LTA.[109]

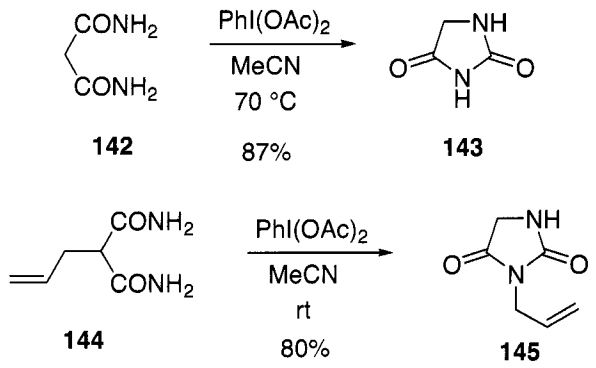


Some final HR applications that use LTA are the preparation of Boc-protected 2-amino-3-fluoroquinoline **137**[110] and 12-oxotetradecano-14-lactam precursor **139**.[111] The late stages of a synthesis of epibatidine (**140**→**141**) employ LTA.[112]



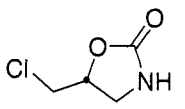
Iodosobenzene Diacetate

Iodosobenzene diacetate ($PhI(OAc)_2$) has a wide following amongst synthetic chemists and represents a robust and versatile HR reagent. An early application of $PhI(OAc)_2$ is the oxidative cyclization of diamides; for example, **142**→**143** and **144**→**145**, transformations that fail with LTA.[113]

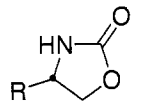


As seen earlier, a typical HR pathway where an internal nucleophile is present is cyclization. Several examples are shown for which each

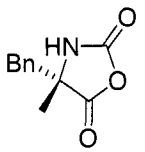
compound is derived from nucleophilic attack on an intermediate isocyanate formed from the corresponding primary amide and $PhI(OAc)_2$. The synthesis of **146** with NBS in DMF was lower yielding (63%). The starting amide for **154** is 2-amino-4,6-diphenyl-3-pyridinecarboxamide.



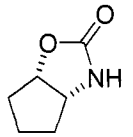
146 (92%)[114]



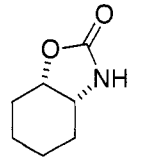
147, R = Me (84%)[115]
148, R = CH_2O*t*-Bu (74%)[115]



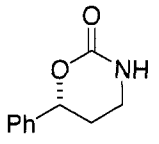
149[116]



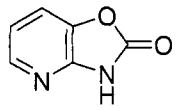
150 (93%)[117]



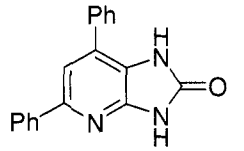
151 (94%)[117]



152 (83%)[118]

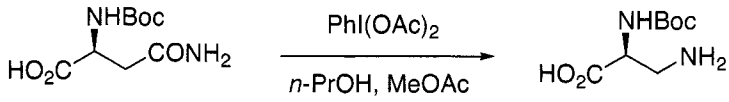


153 (68%)[119]



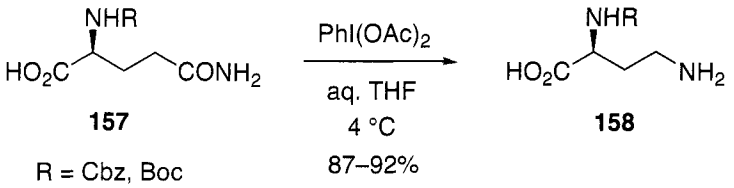
154 (52%)[119]

Whereas other HR conditions (hypochlorite, NBS/KOH, $PhI(O_2CCF_3)_2$) give poor to low yields, $PhI(OAc)_2$ produces **156** from *N*-Boc-asparagine **155** in 75% yield. This reaction can be scaled to hundred kilogram quantities for the synthesis of a platelet glycoprotein antagonist,[120] and it represents a general route to β-amino-L-alanine derivatives.[120b,121–123] Similar chemistry leads to 2,4-diaminobutanoic acids[124,125] (e.g., **157**→**158**).[124]



155 **156**

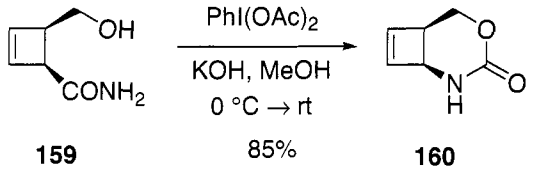
75%



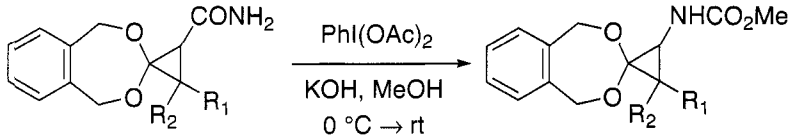
157 **158**

R = Cbz, Boc

En route to novel cyclobutene nucleosides, a HR on hydroxyamide **159** using $PhI(OAc)_2$ gives cyclic carbamate **160** with less than 2% of the methyl carbamate.[126] However, the use of $PhI(OAc)_2$ is a powerful route to alkyl carbamates from amides. Thus, the syntheses of α-aminocyclopropanone hydrates (**162**),[127] a precursor (**164**) to the influenza drug (–)-oseltamivir,[128] and indole carbamates **166**[129] all illustrate the power of $PhI(OAc)_2$ in the HR. The unsubstituted indole-3-acetamide **165** (R_1 = H) gives no HR product, but both thiopheneacetamides and pyrroleacetamides undergo this HR.[129] Amino heterocycles **167** and **168** are derived by base hydrolysis of the corresponding methyl carbamates (not isolated) from the HR using $PhI(OAc)_2$ on the corresponding amides.[130]

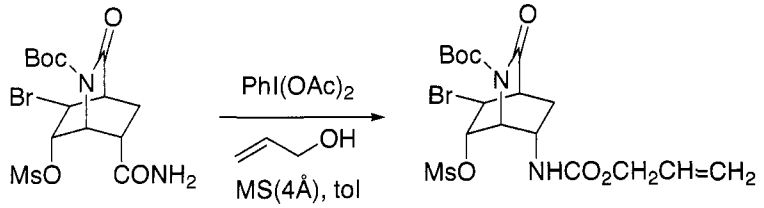


159 **160**

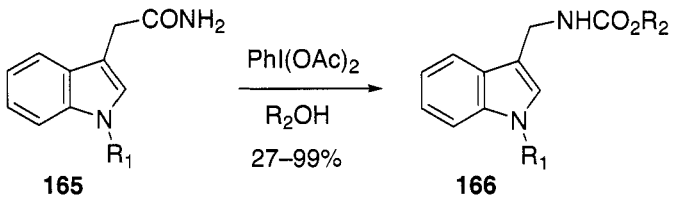


161 **162**

R_1 = H, Me; R_2 = H, Me, Et, Ph

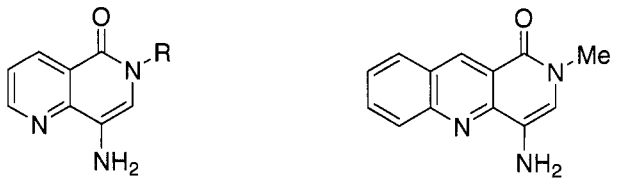


163 **164**



165 **166**

R_1 = Boc, Bn, Ts; R_2 = Me, Et, *i*-Pr, *t*-Bu, Bn



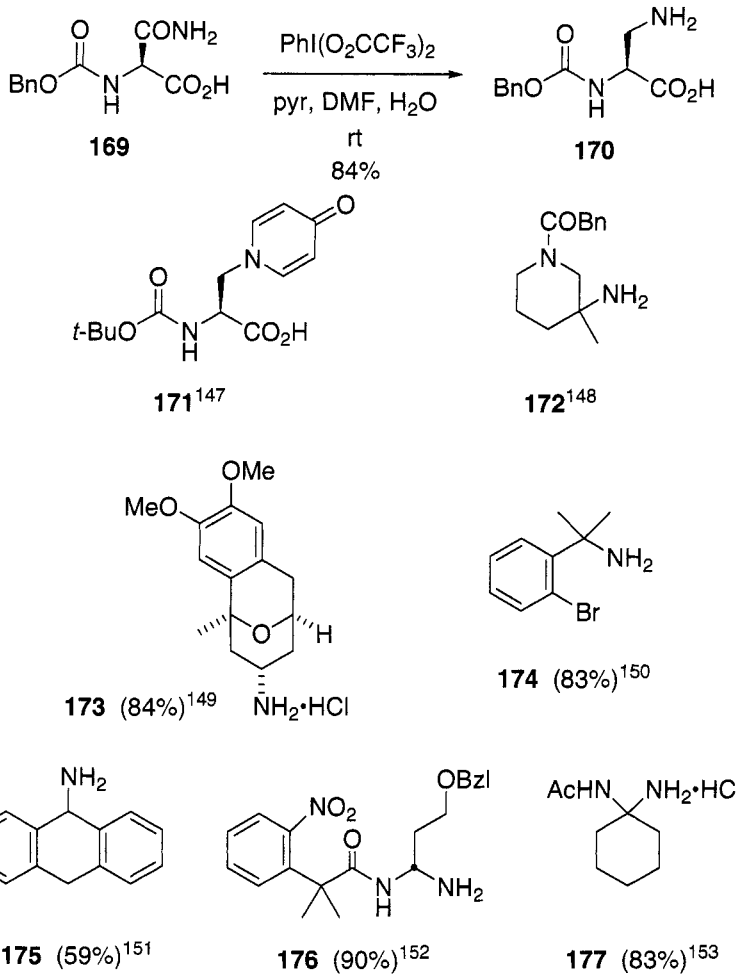
167 (68–86%) **168** (61%)

R = Me, 4-MeOPh

Iodobenzene Bis(trifluoroacetate)

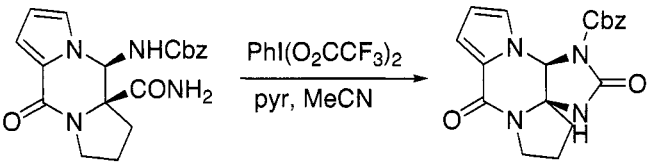
Like $PhI(OAc)_2$, the trifluoroacetoxy analogue, $PhI(O_2CCF_3)_2$, is an excellent reagent for the HR,[41] and it has seen wide utility despite its relative instability and the need to employ freshly prepared material. Loudon, the father of $PhI(O_2CCF_3)_2$ for use in the HR, was the first to demonstrate its ability to degrade carboxyl-terminal amino acid amides via a HR,[131] as was illustrated previously using $PhI(OAc)_2$. As such, this reagent has found extensive use in peptide chemistry for this specific cleavage protocol.[132–146] For example, *N*-benzyloxycarbonyl-L-asparagine (**169**) is smoothly converted to *N*-benzyl-oxycarbonyl-L-2,3-diaminopropanoic acid (**170**) with $PhI(O_2CCF_3)_2$.[132] Other applications of $PhI(O_2CCF_3)_2$ include the synthesis of modified enkephalins,[133b,134,138] modified bradykinins,[135] modified dermorphins,[136] new amino acid-based sweeteners,[137] the peptide antibiotic nisin,[139] amino acid chelators,[140] peptide nucleic acids,[142] peptides that pass through the blood-brain barrier,[143] peptide inhibitors of transglutaminase,[145] and polymyxin B component peptides.[146] This variation of the HR has also found use in the assay of peptides in bovine and porcine extracts,[141] and in the fluorescence derivatization of amidated amino acids following HR.[144] The Boc-analogue of **170** was synthesized using $PhI(O_2CCF_3)_2$ and converted to Boc-L-3-deoxymimosine (**171**) on reaction with 4*H*-pyran-4-one.[147] Other examples of the $PhI(O_2CCF_3)_2$-induced HR are shown below, each of which is derived from the corresponding amide. Aminopiperidine **172** was designed as a reduced amide dipeptide isostere,[148] **173** is a benzomorphan analogue,[149] and bromoamine **174** is a precursor to novel benzisoselenazolines.[150] Aminodihydroanthracene **175** is one of a series of potential serotonin

receptor ligands,[151] and nitro peptide **176** represents a class of new amine protecting groups.[152]

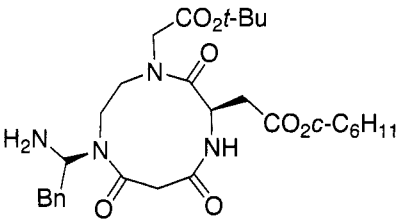


The HR using $PhI(O_2CCF_3)_2$ is featured in the total syntheses of the antibiotic pantocin B,[154] the tuberculostatic antibiotic capreomycin 1B,[155] and the marine sponge alkaloid (+)-dibromophakellstatin (the pentultimate step: **178→179**).[156] Adaptation of this HR to the solid phase (Merrifield polystyrene) led to the synthesis of a cyclic peptide containing the amino acid (*S*)-norarginine.[157] The use of $PhI(O_2CCF_3)_2$ also provides the novel 2,5,7-trioxo-1,4,8-triazadecane ring system (e.g., **180**) as a tetrapeptide β-turn mimetic,[158] and affords entry to phenylalanyl-4-aminocyclophosphamide conjugates as model prodrugs for proteolytic activation.[159] A series of amines **181** related to monodansylcadaverine were prepared using a HR with

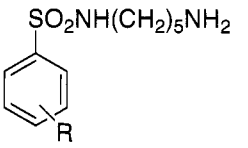
$PhI(O_2CCF_3)_2$.[160] This reagent also represents an excellent synthesis of 2-oxazolidinones and 1,3-oxazinan-2-ones; for example, **182**→**183** and **184**→**185**.[161]



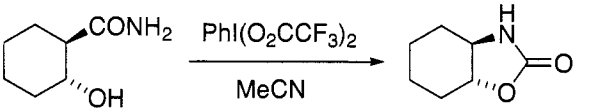
178 **179**



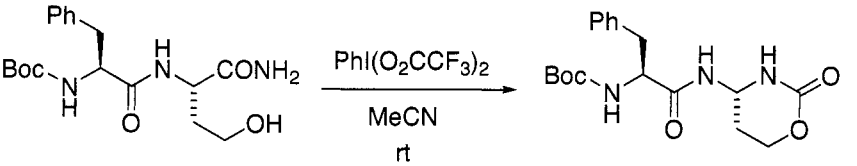
180



181
(R = H, 4-Br, 4-Me, 4-NO_2, 2,4,6-$(Me)_3$Ph, others)

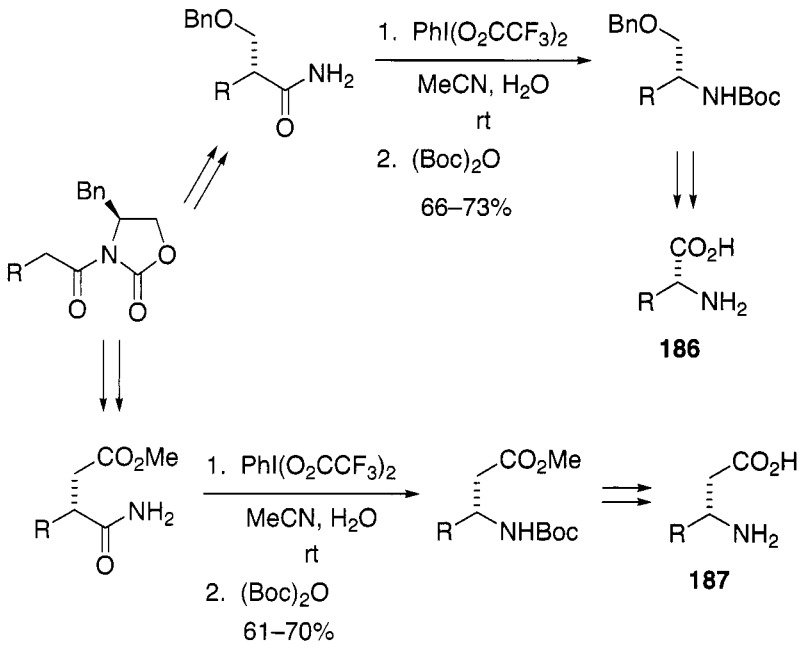


182 **183**



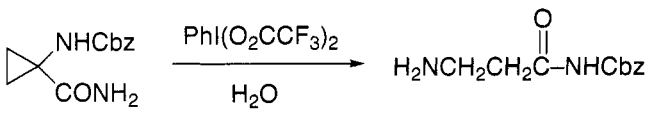
184 **185**

A protocol leading to both chiral α-amino acids **186** and β-amino acids **187** utilizing Evans' oxazolidinone methodology has been developed.[162]



R = Ph, Me, *i*-Pr, *n*-C_8H_{17}, *n*-$C_{16}H_{33}$, 8-Br-*n*-C_8H_{16}

Several other applications of $PhI(O_2CCF_3)_2$ in the HR of amino acids and peptides are known, including the synthesis of *L*-glutamic acid *p*-nitroanilide analogues,[163] *gem*-diamino derivatives on solid support,[164] urea pseudopeptides,[165] (*R*)-3,4-diaminobutanoic acid,[166] protected 2,3-diaminopropionic acids,[167] and *N*-aminoacyl-pyroglutamates.[168] Although most of these reactions of $PhI(O_2CCF_3)_2$ are predictable, an exception is the attempted HR of cyclopropyl amide **188** with $PhI(O_2CCF_3)_2$. This reaction leads instead to β-alanine derivative **189**[169] via a proposed mechanism involving ring expansion to a 2-pyrrolidinone, ring opening to an amido isocyanate, and formation of **189**.

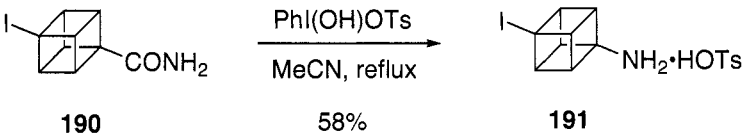


188 100% **189**

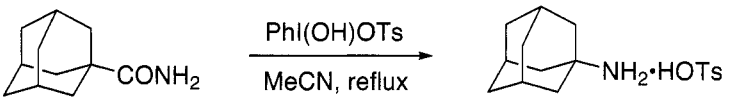
One clear advantage of $PhI(O_2CCF_3)_2$ over $PhI(OAc)_2$ in the HR is that the trifluoroacetic acid liberated from the former reagent can protonate the product amine, militating against urea and carbamate formation.

[Hydroxy(tosyloxy)iodo]benzene

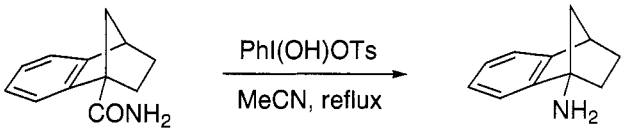
The relatively new hypervalent iodine reagent PhI(OH)OTs, which is more stable than $PhI(O_2CCF_3)_2$, has already proven to be an excellent HR reagent.[42,170] It is particularly useful for the conversion of long-chain amides to the corresponding amines (e.g., **41**→**42**).[42a,171] Moreover, PhI(OH)OTs has been employed for the synthesis of several polycyclic amines as shown for **190**→**191**,[172,173] **192**→**193**,[172] **194**→**195**,[174] **196**→**197**,[175] and **198**→**199**.[176] The addition of $PhI(OAc)_2$ to the reaction mixture leading to **197** is believed to regenerate PhI(OH)OTs.[175] Polymer-supported reactions with poly([4-hydroxy(tosyloxy)iodo]styrene) have been reported, e.g., **200**→**201**.[177] The yields are generally comparable to those obtained with PhI(OH)OTs and the iodinated polystyrene can be recovered and recycled.



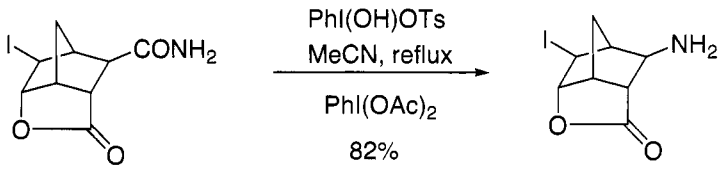
190 58% **191**



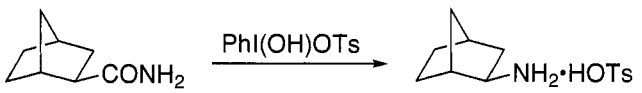
192 85% **193**



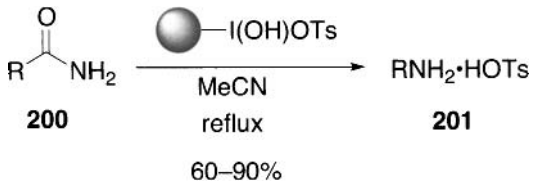
194 90% **195**



196 82% **197**



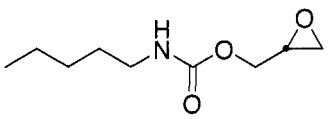
198 80% **199**



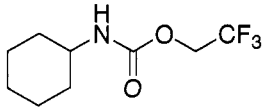
R = Me, Et, *n*-Pr, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-$C_{11}H_{23}$, *n*-$C_{17}H_{35}$, Bn, 1-naphthyl CH_2

Electrochemical

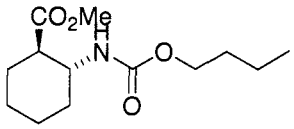
The newest variation of the HR is an electrochemical method; e.g., **46→48**, which does not appear to have been explored beyond its discoverers.[44,178–180] The method is particularly useful for the synthesis of alkyl carbamates from primary alcohols containing sensitive functional groups since this electrochemical HR operates under neutral conditions. Some of the alkyl carbamates prepared using this HR are shown (**202–205**).[178,180] The yields of the same methyl carbamates are uniformly higher with this electrochemical HR than with the classical bromine and sodium methoxide HR. Furthermore, little or no urea products are formed in the electrochemical HR.[180]



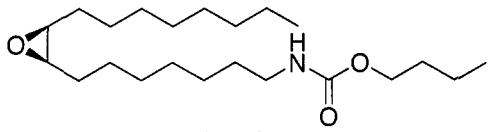
202 (53%)



203 (95%)

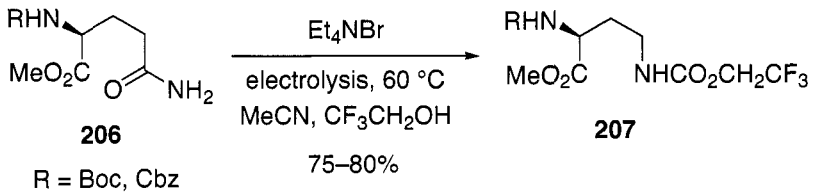


204 (74%)



205 (50%)

The HR of *N*-protected glutamic acid esters **206** proceeds smoothly under electrochemical conditions to afford carbamates **207**.[179] The use of the cosolvent trifluoroethanol prevents formation of the cyclized glutarimide, which is a major byproduct (or only product) with conventional (basic) conditions using bromine and sodium methoxide or by running the electrochemistry in methanol. The several trifluoroethyl carbamates (e.g., **203**) that were prepared in these electrochemical HR studies[178,180] react with primary and secondary amines in the presence of sodium hydride to form unsymmetrical ureas.[181]



In summary, the Hofmann Rearrangement presents the synthetic chemist with a rich selection of possible options depending on the system at hand, something that most name reactions do not offer.

1.1.5.6 Experimental

The reader is referred to the syntheses of β-alanine (Br_2, KOH),[182] 4-aminoveratrole (NaOCl, NaOH),[183] acetyl methylurea (Br_2, NaOH),[184] 3-aminopyridine (Br_2, NaOH),[185] 1-amino-2-methoxymethylpyrrolidine (KOCl, KOH),[186] and cyclobutylamine hydrochloride ($PhI(O_2CCF_3)_2$)[187] published in *Organic Syntheses*, and 3-nitroaniline (NaOCl, NaOH) published as an undergraduate laboratory experiment.[188] The reader is also referred to these syntheses reported in *Organic Reactions*:[1] Neopentylamine (Br_2, NaOH), *n*-pentadecylcarbamate (Br_2, NaOMe), 2-methyl-1,4-diaminobutane (Br_2, NaOH), (*S*)-isoserine (Br_2, $Ba(OH)_2$), γ-truxillamic acid (NaOCl, NaOH), 3-bromoaniline (Br_2, KOH), and phenylacetaldehyde (NaOCl, NaOH) (from cinnanamide).

2-Amino-4-chloropyridine:[189]
To a solution of KOH (17.9 g, 320 mmol) in water (90 mL) at 0–5 °C, bromine (3.3 mL, 63.9 mmol) was added dropwise with stirring, followed by 4-chloropicolinamide (5.0 g, 32.0 mmol) rapidly. Most of the material went into solution; however, 1,4-dioxane (50 mL) was added to ensure a homogeneous solution. The resulting solution was stirred at rt for 30 min, then heated at 55 °C for 60 min. The mixture was cooled and glacial AcOH (10 mL) was added dropwise, when an exothermic reaction took place with CO_2 evolution and a cream coloured precipitate formed. The mixture was heated at 50–55 °C for a further 30 min, causing the precipitate to dissolve and the solution was then allowed to cool. KOH (*ca.* 7 g) was added and the resulting white suspension was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried and concentrated in vacuo to reveal the crude product amine as a pale yellow solid (3.1 g). Recrystallization from Et_2O-hexane (2:1) afforded the title compound as bright white plates (2.1 g, 51%), mp 95–96 °C from Et_2O–hexane (2:1).

1-Benzyloxycarbonyl-2-oxoimidazolidine-5-carboxylic acid:[59]
To a solution of sodium hydroxide (3.3 g) in water (70 mL), bromine (4.4 g) was added dropwise with stirring at 0–5 °C. To the solution, 6.7 g (0.025 mol) of *N*-benzyloxycarbonyl-L-asparagine was added, and stirred at 50 °C for 1 hr. After addition of sodium thiosulfate on cooling, the reaction mixture was washed with ether, and then acidified to pH 2 with 6 N hydrochloric acid to give an oily material which crystallized after allowing to stand in a refrigerator overnight. It was filtered and recrystallized from water to yield 4.3 g (65%) of the title compound; mp 164–168 °C (dec.). Recrystallization from methanol-ether raised the melting point to 190 °C (dec.).

2,6-Diacetoxy-1-*tert*-butoxycarbonylamino-1-cyanocyclohexane (129, **X = CH_2**):[106]
$Pb(OAc)_4$ (20 g) was added to a solution of **128** (X = CH_2) (2.5 g, 9.32 mmol) in *t*-BuOH/DMF (40:10 mL). The mixture was stirred and boiled under reflux for 40 min, and then cooled. Toluene (100 mL) and Et_2O (50 mL) were added and the solution was filtered, washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (Et_2O/hexane, 5:1) to give the title compound (1.9 g, 64%).

N_α-*n*-Boc-L-α,β-diaminopropionic Acid (156):[120a]
A solution of *n*-propanol (81.2 kg), methyl acetate (50.4 kg), and water (10.8 kg) was cooled to 5 °C. To this solution were added N_α-Boc-L-asparagine (**155**) (23.5 kg, 101.2 mol) and $PhI(OAc)_2$ (37.5 kg, 116.4 mol) under agitation. This mixture was warmed to 25 °C over a period of 1 h and stirred at the same temperature for additional 2 h. The reaction mixture was slowly heated to 50 °C over 90 min and then cooled to 3–5 °C. The reaction mixture was held at 3–5 °C for 30 min. The product was isolated by filtration, washed with methyl acetate (2 × 22 kg), and dried under vacuum (50–55 °C) to constant weight (15.5 kg, 75%).

N^2-Benzyloxycarbonyl- L-2,3-diaminopropanoic Acid (170):[132]
To a stirred solution of $PhI(O_2CCF_3)_2$ (645 mg, 1.5 mmol) in dimethylformamide/water (8 mL; 1:1 v/v), N^2-benzyloxycarbonyl- L-asparagine (**169**; 266 mg, 1 mmol) was added at room temperature. After 15 min, pyridine (0.16 mL, 2 mmol) was added, and stirring was continued for 3 h. The solvent was evaporated in vacuo and the residue was dissolved in water (10 mL). The solution was washed extensively with ether and concentrated in vacuo to afford crude product which was crystallized from ethanol/ether to give pure **170** (201 mg, 84%); mp 228–230 °C (dec); $[\alpha]_D^{20}$: −7.8 ° (*c* 0.4, 1 N NaOH).

1-Aminobenzobicyclo[2.2.1]heptene (195):[172]

A mixture of amide **194** (0.318 g, 1.70 mmol) and PhI(OH)OTs (0.800 g, 2.04 mmol) in acetonitrile (25 mL) was refluxed overnight. After removal of the solvent, the residue was dissolved in dilute HCl. The aqueous solution was washed with ether and then basified with concentrated NH_4OH and extracted (CH_2Cl_2). The combined extracts were washed with brine, dried (K_2CO_3), and concentrated to give **195** (0.250 g, 90%).

1.1.5.7 References

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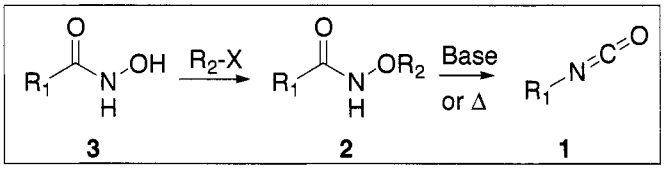
1.1.6 Lossen Rearrangement

Chulho Choi and Jeffrey A. Pfefferkorn

1.1.6.1 Description

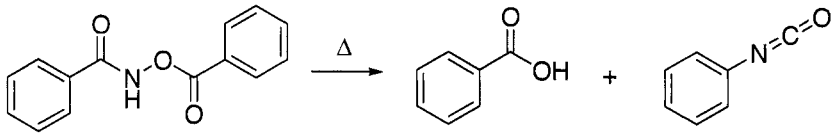
The Lossen rearrangement involves the generation of an isocyanate **1** via thermal or base-mediated rearrangement of an activated hydroxamate **2** which can be generated from the corresponding hydroxamic acid **3**.[1,2] Activation of the hydroxamic acid **2** can be achieved through *O*-acylation,[1–3] *O*-arylation,[4] chlorination,[1,2] or *O*-sulfonylation.[5] Such hydroxamic acids can also be activated using polyphosphoric acid,[6] carbodiimide,[7] Mitsunobu conditions,[8] or silyation.[9] The product of the Lossen rearrangement, an isocyanate can be subsequently converted to an urea or an amine resulting in the net loss of one carbon atom relative to the starting hydroxamic acid **2**.[1,2]



3 **2** **1**

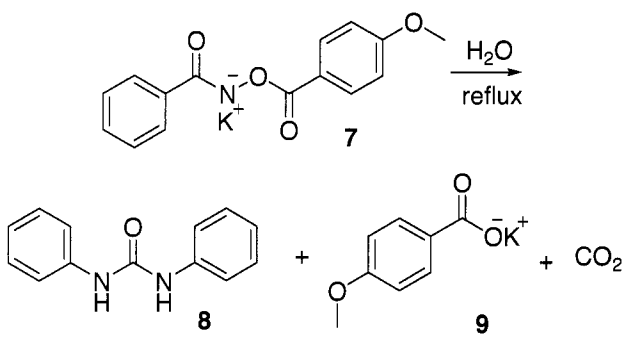
1.1.6.2 Historical Perspective

The observation of isocyanate generation during pyrolysis of mixed anhydride benzoyl benzohydroxamate **4** was first made by Lossen in 1872.[10] This reaction yielding carboxylic acid **5** and urea **6** required the harsh condition of heating at 300–400 °C.



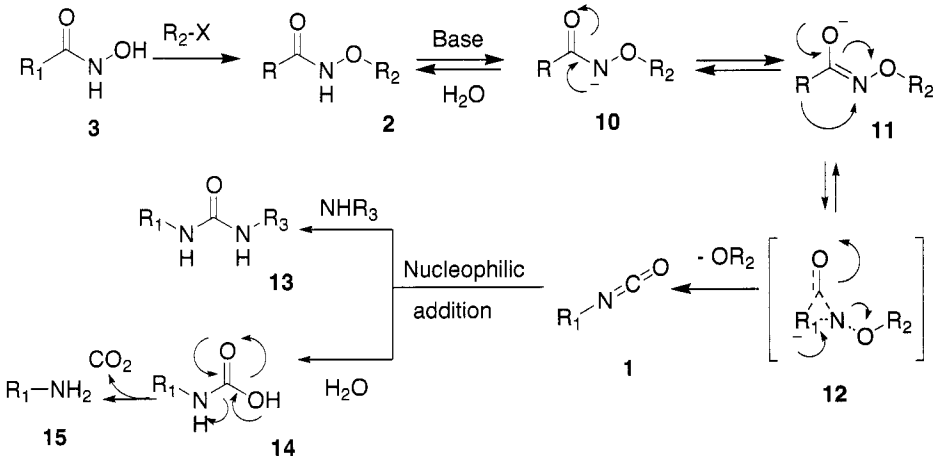
4 **5** **6**

Subsequently, Lossen discovered that potassium salt **7** was readily converted to urea **8**, potassium carboxylate **9** and CO_2 in boiling water.[11] The recognition that base facilitated this rearrangement significantly increased the synthetic utility of the reaction.[1,2]



Early attempts to further facilitate this rearrangement via generation of more highly activated hydroxamates through *O*-phosphorylation or *O*-sulfonylation were not successful as these systems preferentially underwent spontaneous dimerization.[2] In later studies, the problem of spontaneous dimerization could be mitigated through the use of intramolecular nucleophiles to generate *N*-hydroxyimides (see ***1.1.6.4*** for further discussion). *N*-Hydroxyimides were found to yield stable precursors via *O*-phosphorylation and *O*-sulfonyloxylation.[2]

1.1.6.3 Mechanism



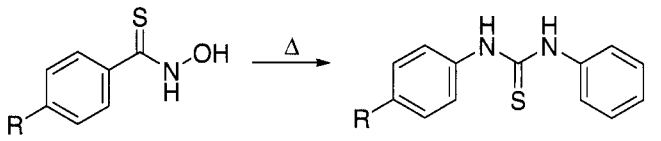
Hydroxamic acid **3** can be converted to activated hydroxamate **2** via reaction with a variety of electrophilic reagents. The Lossen rearrangement is then initiated by exposure of **2** to base or heat resulting in anion **10**. Through a fast subsequent transformation via cyclic intermediate **12**,[12,13] isocyanate **1** is generated. This isocyanate **1** can be further converted to urea **13** or amine **15**.

The Lossen rearrangement is mechanistically related to the Curtius, Hoffman, Schmidt and Tiemann rearrangements as all provide isocyanates from carboxylic derivatives. All of these transformations are categorized as classical carboxyl degradations.[14] The advantage of Lossen rearrangement over these related reactions is that the reaction conditions are milder and safer making this reaction more amenable to scale-up. Several disadvantages of the Lossen rearrangement include: (a) in certain cases the requisite starting hydroxamic acids are unavailable; and (b) some of the activated hydroxamates can undergo uncontrolled dimerization owing to unfavourable reaction kinetics. In light of these disadvantages, the use of the Lossen rearrangement has been largely limited to intramolecular transformations otherwise known as Lossen degradations. Recent improvements have been focused on controlling reaction kinetics and utilizing stable activated hydroxamates to realize the full potential of this transformation as a practical and general synthetic method.

1.1.6.4 Variations and Improvements

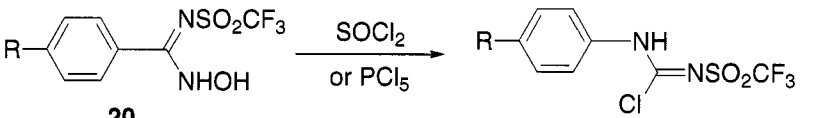
The Lossen Rearrangement of Related Hydroxamic Acids

Related hydroxamic acids such as thiohydroxamic acids can also undergo Lossen rearrangement. Under thermal condition, thiohydroxamic acids **16** can generate thioureas **17**.[15]



16 **17**

A recent report disclosed that trifluoromethane sulfonylimides **18** can undergo an aza-Lossen rearrangement to provide **19**.[16] This reaction proceeds through a 5-membered cyclic transition state formed upon reaction with $SOCl_2$ or PCl_5.

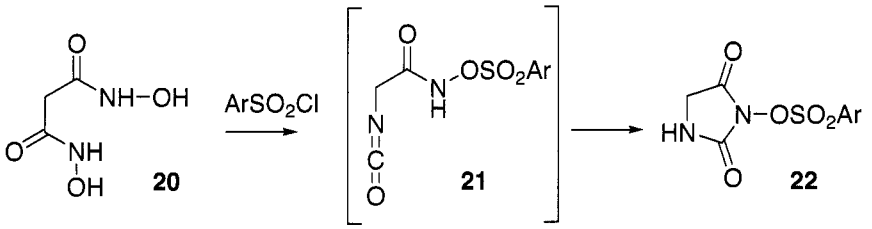


20

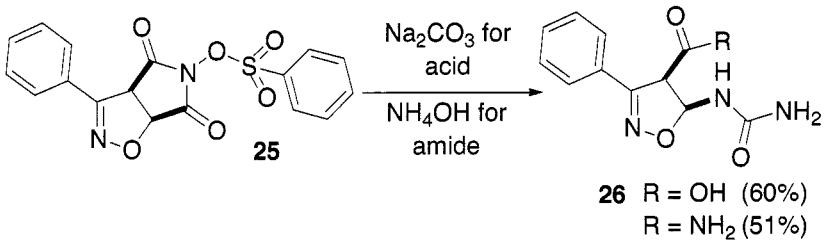
21, R = H, OMe, $OCHF_2$, F, Cl, NO_2, (65–90%)

Lossen Degradation

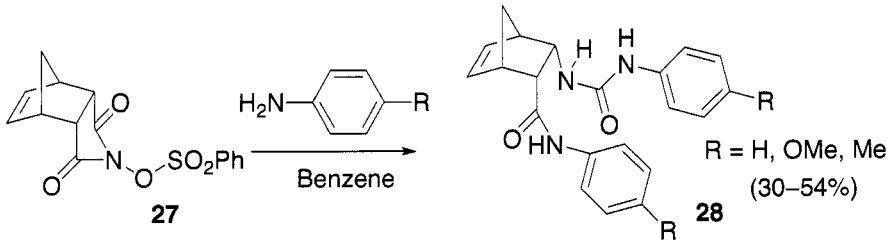
Unlike hydroxamic acids, *N*-hydroxyimides form stable *O*-phosphoryloxy and *O*-sulfonyl derivatives. These hydroxyimides can be prepared from hydroxamic acid and isocyanates. As an example, cyclic *N*-hydroximide **22** was prepared from dihydroxamic acid **20** through Lossen rearrangement and followed by self-condensation of intermediate **21**.



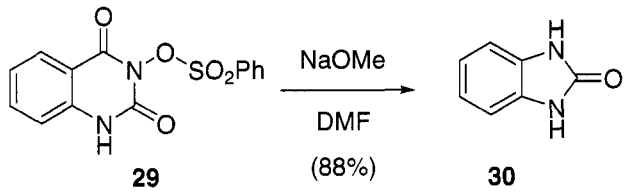
The Lossen rearrangement of cyclic *N*-hydroxyimides provides access to interesting heterocycles.[12,17,18] For example, in the work done by Bauer **23** was formed via a Lossen rearrangement then further converted to dihydroisoxazole **24**.[17]



A few decades later, a similar reaction of the tricyclic substrate, *N*-sulphonyloxy-2,3-norborn-5-enedicarboximide **25** was reported to undergo Lossen rearrangement under basic conditions to yield urea **26**.[19]

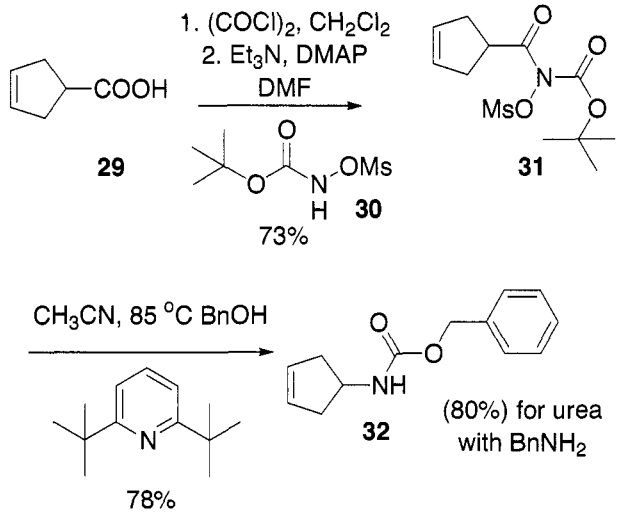


Aromatic *N*-hydroxamate **27** can be transformed to cyclic urea **28** through DMF assisted Lossen rearrangement in excellent yield.[18]

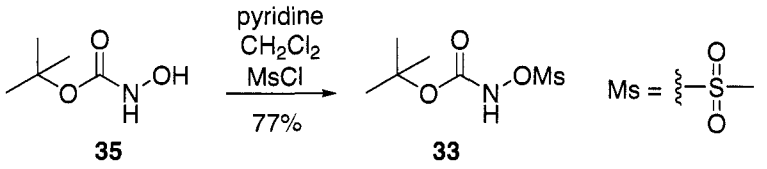


Improved Reagents for Controlled Lossen Rearrangements

Reagents for controlled Lossen rearrangements are designed to mimic hydroxyimide-like structures after reaction with substrates. Due to lack of acidic protons, hydroxyimides can easily undergo activation through *O*-phosphorylation and *O*-sulfonylation without forming dimerization side products. Utilizing reagent **30**, developed by Glaxo Wellcome, starting carboxylic acid **29** was converted to *O*-mesylated hydroximide **31**, which was then transformed to Cbz protected amine **32.**[14(a)]

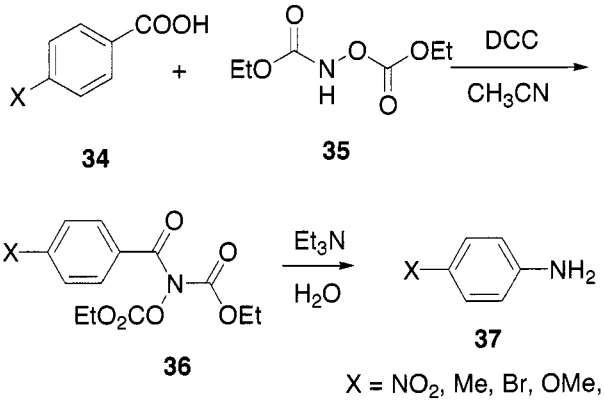


Reagent **31** can be readily prepared from commercially available *tert*-butyl-*N*-hydroxycarbamate **33** in one step.



The authors reported that **31** was designed to facilitate Lossen rearrangements as a safer and miler alternative to Hoffman and Curtius rearrangements for the large scale preparation of the corresponding amine.

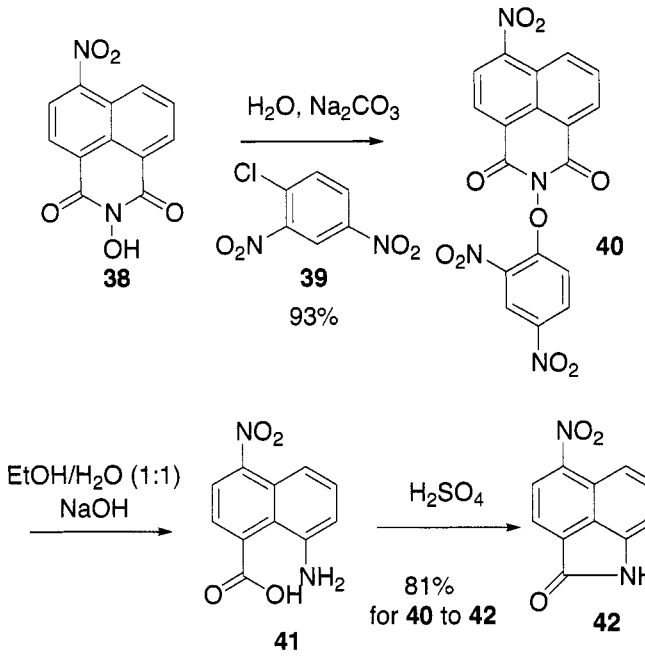
In a similar context, *N*,*O*-bis-(ethoxycarbonyl)hydroxylamine **35** has been utilized in the Lossen rearrangement. As illustrated, aromatic carboxylic acids **34** can be successfully transformed to amines **37** with this reagent under mild conditions proceeding through intermediate **36**.[20] Unfortunately the substrate scopes of the reagent **35** was reported to be limited to only aromatic carboxylic acids.



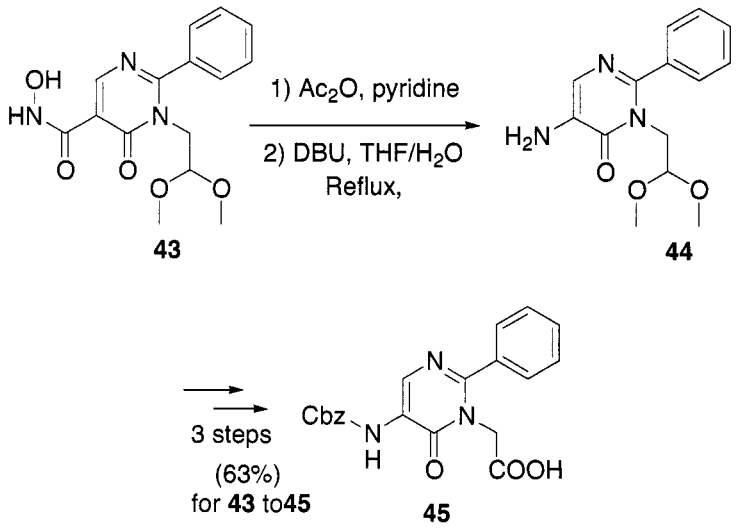
1.1.6.5 Synthetic Utility

A survey of the literature has revealed the synthetic application of the Lossen rearrangement in three main areas: (a) as a scale-up alternative to the Curtius and Hoffman reaction; (b) for stereospecific transformations; (c) in the degradation of studies of peptides and carbohydrates.

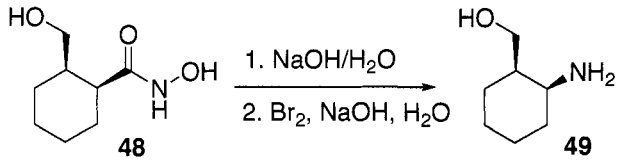
In the scale up effort of 5,6-disubstituted benz[*cd*]indolones **42**, a precursor for inhibitors of thymidylate synthase, the Lossen rearrangement was utilized as the key step. *N*-hydroxylnaphthalimide **38** was converted to activated hydroxamate **40** through aromatic nucleophilic substitution reaction with **39**. The Lossen precursor **40** then underwent conversion to amino acid intermediate **41**, which was subsequently transformed to lactam **42** under acidic conditions.[21]



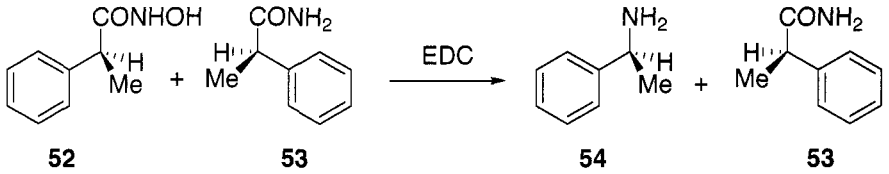
In a second example, the Lossen rearrangement was utilized in the scale-up synthesis of neutrophil elastase inhibitor, ONO-6868, circumventing the need for a potentially explosive Curtius rearrangement reaction. Lossen transformation of **43** using *O*-acetylated hydroxamate took place in refluxing THF/H_2O condition. The yield for the rearrangement itself was not provided, however, the overall yield for conversion of **43** to **45** was reported to be 63%.[22]



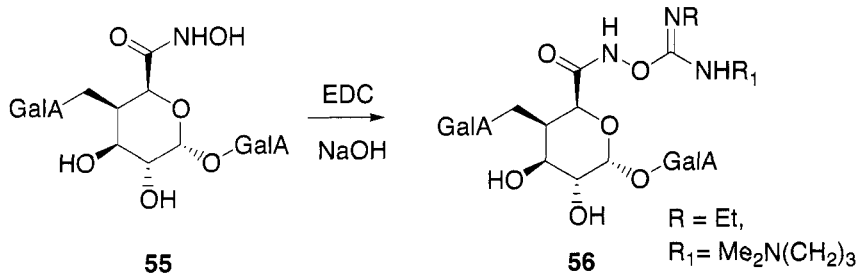
Several examples of stereospecific Lossen rearrangement have also been published.[23,24]

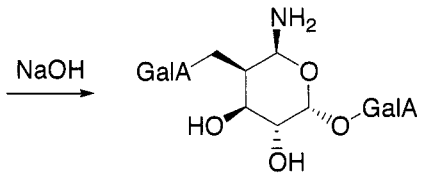


(*S*)-2-Phenylpropionylhydroxamic acid **50**, which was prepared by enzymatic kinetic resolution of racemic 2-phenylpropanamide, was transformed to (–)-(*S*)-phenylethanamine **52** using the Lossen transformation to generate the products without eroding stereochemistry.[24,25]



Lossen rearrangements have also been utilized in the field of peptide[26] and carbohydrate chemistry.[27] The structure determination of pectins, important polisacchrides for the cell wall assembly, has been done through degradation by enzymes or chemicals. The degradation via Lossen rearrangement of methyl esterified galacturonic acid residues is an important tool for their studies. The hydroxamic acid **53** was reacted with EDC to be isourea derivative **54**, which underwent Lossen rearrangement to generate 5-aminoarabino pyranose **55**.[27]





57

1.1.6.6 Experimental

1*H*-benzo[*d*]imidazol-2(3*H*)-one (28):[18]
To a solution of **27** (3.18 gram, 0.01mol) in 100 mL of DMF was added 0.48 gram of NaH in mineral oil (50%). It was then heated at 100 °C for 1 h. Solvent was removed *in vacuo*, and the residue was triturated with 25 mL of water and 25 mL of petroleum ether to provide desired product.

Benzyl cyclopent-3-enylcarbamate (32):[13(a)]
To a solution of **31** (305 mg, 1.0 mmol) in CH_3CN (5 mL) were added benzyl alcohol (1.1 mmol) and 2,6-di-*tert*-butylpyridine (1.0 mmol). The mixture was heated with stirring to 85 °C for 22 h and then cooled to room temperature. It was then diluted with EtOAc (50 mL) and washed with water (50 mL), 1 M H_3PO_4 (50 mL) and brine (50 mL). The combined aqueous layers were back-extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (4:1 hexane/ethyl acetate) afforded **32** as a colorless solid (168 mg, 78%).

4-Nitrobenzenamine (37):[20]
34 (1 mmol), **35** (1 mmol) and DCC (1 mmol) in CH_3CN (5 mL) were stirred at 25 °C for 5 h. The resulting **36** was treated with Et_3N (1 mmol) and a drop of water. The combining reaction mixture was refluxed for 8 h, cooled, and H_2O and EtOH were added. The reaction mixture was concentrated and crude product was purified by chromatography to give 56 % yield.

5-Nitrobenzo[*cd*]indol-2(1*H*)-one (42):[21]
To a clean, dry, three-necked, 22-L flask were added 4650 mL of deionised water and 10,750 mL of absolute ethanol. To this solution was added sodium hydroxide (236 g, 5.90 mol, 4.04 equiv). The resulting solution was cooled to 10 °C, and *N*-(2,4-dinitrophenoxy)-4-nitronaphthalimide (**40**) (620 g, 1.46 mol, 10.0 equiv) was added. The mixture was stirred for 44 h at ambient temperature until complete by TLC (95/5:$CHCl_3$/MeOH). The pH was adjusted to 3 with 175 mL of concentrated sulphuric acid, and the mixture

was cooled to < 10 °C and filtered. The web filter cake was re-slurred in 3 L of deionised water and the pH adjusted to 7–8 by the addition of saturated aqueous sodium bicarbonate solution. The mixture was filtered, washed with water and 95% ethanol, and dried under vacuum to yield 254 g (81% theoretical yield) of **42**.

1.1.6.7 References

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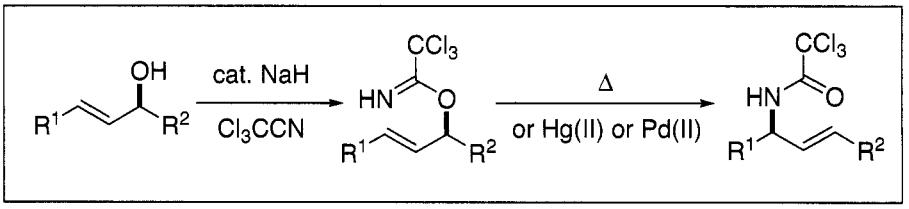
1.1.7 Overman Rearrangement

Yong-Jin Wu

1.1.7.1 Description

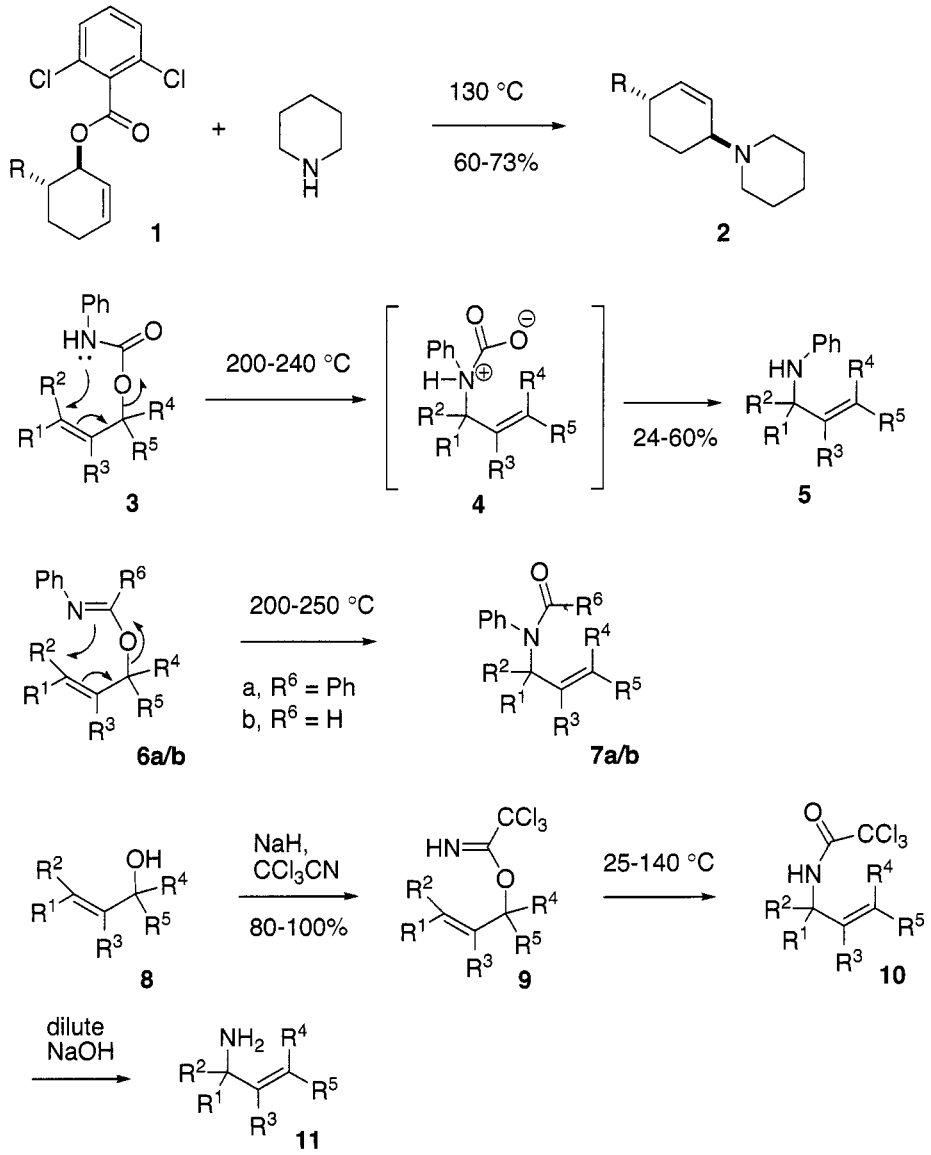
The Overman Rearrangement describes the [3,3]-aza-oxa-Cope sigmatropic rearrangement of *N*-allyltrichloroacetimidates to *N*-allyltrichloroacetamides. This rearrangement has become the preferred method for converting allylic alcohols to transposed allylic amines and their derivatives.



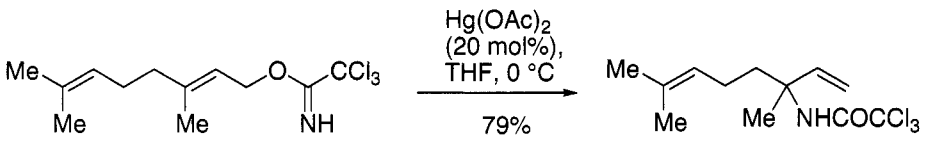
1.1.7.2 Historical Perspective

Prior to 1974, a generally useful synthetic method for the 1,3-conversion of allylic alcohols to allylic amines was not available. Such a method would be useful in synthesis as it is typically easier to introduce oxygen than nitrogen functionality into complex molecules. Previously existing methods for achieving this transformation include S_N2' reaction of allylic alcohol derivatives with amines as exemplified by the formation of piperidine **2** from allylic carbonate **1**,[1] but this approach is restricted to cases where direct displacement is precluded by steric or other factors. The base-catalyzed thermal rearrangement of allylic phenyl urethanes **3** affords the allylically transposed amines **5** in moderate yields.[2–4] However, reactions of this type proceed with some ionization (S_Ni) component, and even in the most favourable cases, significant amounts of the unrearranged allylic isomer are recovered. Allylic *N*-phenylbenzimides **6a** and *N*-phenylformimidates **6b** also undergo rearrangement at 200–250 °C to give the corresponding amides **7a** and **7b**, respectively, in good yields.[5–7] Unfortunately, these rearrangements suffer from three major drawbacks: the moderate yields in preparing the imidate derivatives (< 50% yields based on the allylic alcohols), the high pyrolysis temperatures which may bring about further transformations of the resulting products,[8] and the lack of flexibility in nitrogen substitution. These issues are obviated when trichloroacetimidic esters are utilized as the intermediates for this transformation as originally

developed by Overman in 1974.[9–14] Trichloroacetimidates **9** are readily prepared in good yields from primary, secondary, and tertiary alcohols **8** by base-catalysed condensation with trichloroacetonitrile at 0 °C. Allylic trichloroacetimidic esters **9** undergo smooth [3,3]-sigmatropic rearrangement to give the allylically transposed trichloroacetamides **10** when heated at temperatures between 25 and 140 °C. The trichloroacetyl group can be easily removed from the product amide to give amine **11** upon treatment with aqueous base at room temperature, thus completing the allylic alcohol to allylic primary amine conversion.



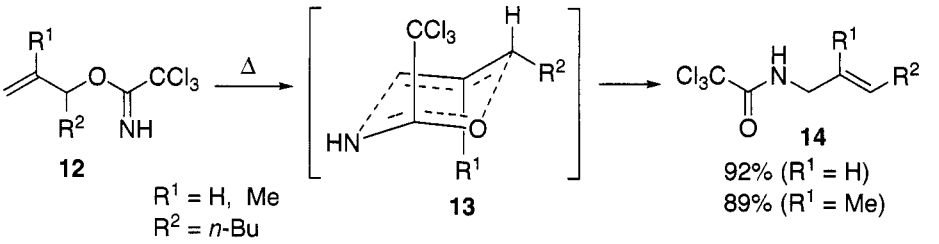
In some cases, the mercury(II)- and palladium(II)-catalysed allylic Overman rearrangement of trichloroacetimidates can be accomplished under mild conditions at room temperature or even much lower temperature.[10] For example, the trichloroacetimidic ester of geraniol **12** is converted to linalyl trichloroacetamide **13** when treated with 0.2 equiv of mercuric trifluoroacetate at room temperature for 10 min. This catalytic transformation also occurs readily at –60 °C.



12 **13**

1.1.7.3 Mechanism

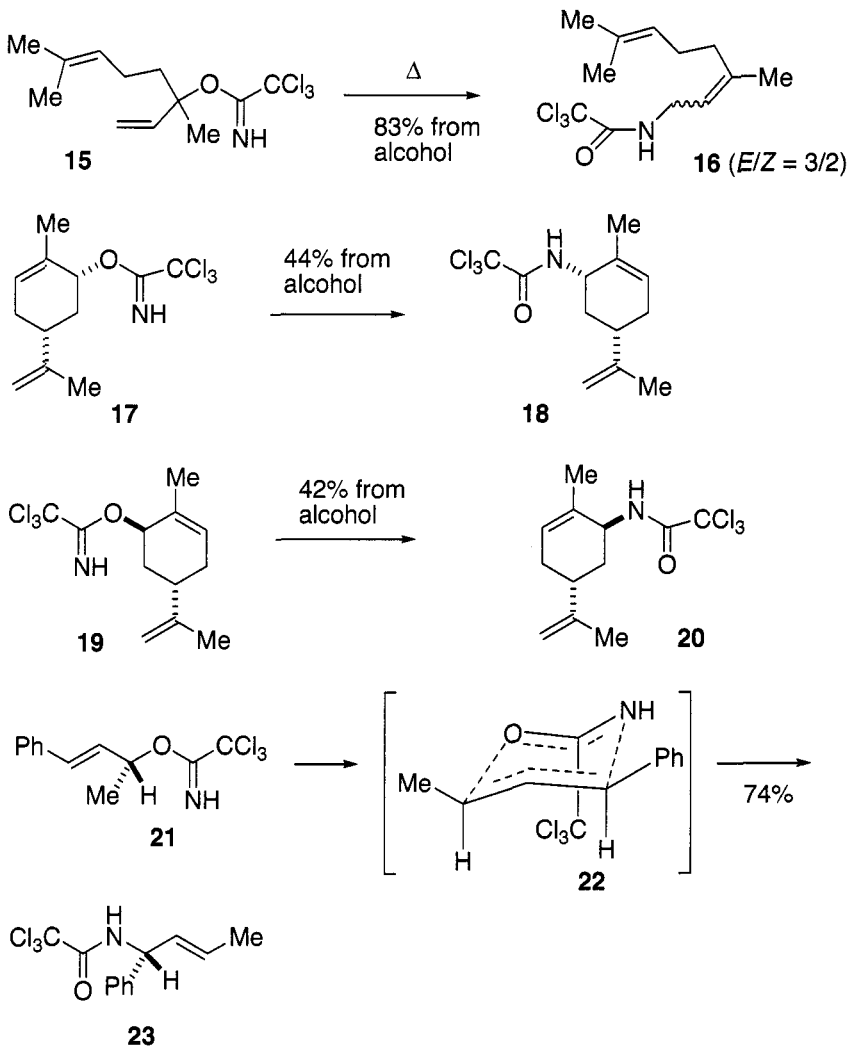
The Overman rearrangement of allylic trichloroacetimidates under thermal conditions is irreversible due to the large enthalpic driving force associated with the conversion of the imidate to the amide functionality. The mechanism is generally considered as concerted pericyclic process. The stereoselectivity observed in the formation of substituted alkenes is similar to that observed with other [3,3]-sigmatropic rearrangements. The thermal rearrangement of trichloroacetimidic esters **12**, derived from secondary alcohols, gives exclusively (*E*)-trichloroacetamides **14**, which is expected from the large steric bulk of the trichloromethyl substituent and the usual chair model for the cyclic six-membered transition state **13**. The lack of stereoselectivity observed in the formation of **16** is also consistent with this model, and similar product ratios are also seen in the rearrangement of other linalool derivatives. The trichloroacetimidates **17** and **19**, derived from the terpene alcohols, *cis*- and *trans*-carveol, respectively, undergo smooth suprafacial rearrangement.[15] The rearrangement of (*R*)-3-phenyl-2(*E*)-buten-1-yl trichloroacetimidate **21** proceeds suprafacially with complete (> 97%) transfer of chirality.[15]



12 **13** **14**

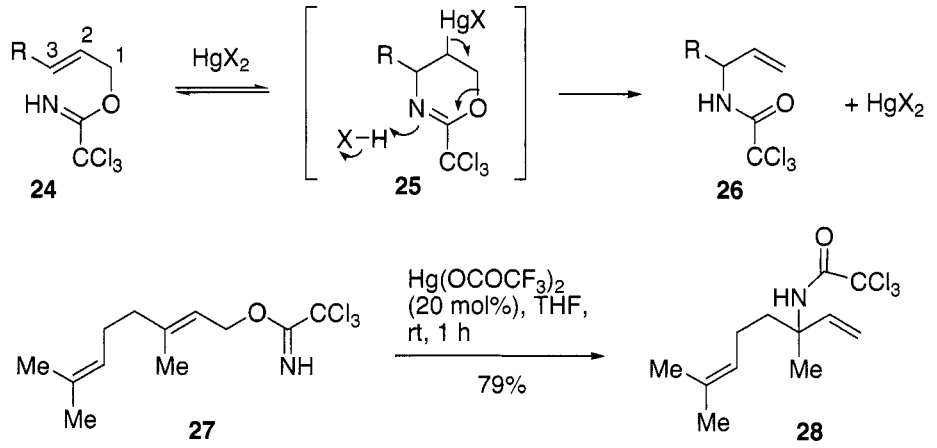
R^1 = H, Me
R^2 = *n*-Bu

92% (R^1 = H)
89% (R^1 = Me)



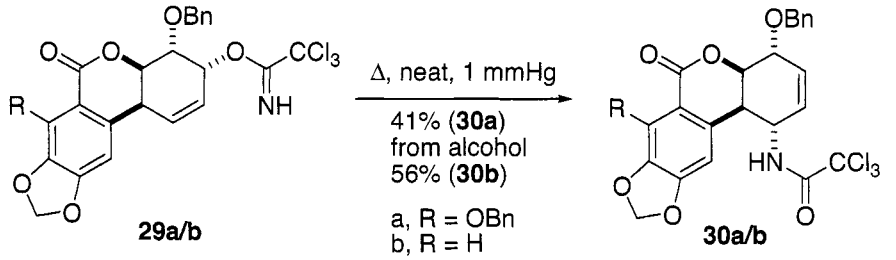
A two-step mechanism involving iminomercuration-deoxymercuration has been proposed for the mercury(II)-catalyzed reaction.[10] In the first step, the mercuric electrophile adds to the double bond to form a mercurinium ion (or its equivalent) which is then captured intramolecularly at C-3 by the nucleophilic imino nitrogen to afford dihydrooxazine **25**. This intermediate can then undergo cleavage of the carbon–nitrogen bond to regenerate the starting material or the carbon–oxygen bond to furnish the rearranged amide. The latter process is expected to be favourable due to the thermodynamic driving force. The supporting evidence for the proposed mechanism derives mainly from the observed dependence of the catalyzed reaction on trichloroacetimidate structure. Thus, the catalyzed reaction is successful for

the imidates with R groups which promote nucleophilic addition to C-3 and fails in cases such as allyl, 1-hepten-3-yl, and 2-cyclohexen-1-yl where nucleophilic addition at C-2 is preferred. Also consistent with this mechanism is the failure of the mercury(II)-catalyzed rearrangement of **27** in protic solvents such as methanol, and the failure of using stronger Lewis acids such as aluminum chloride etherate, silver fluoroborate, or boron trifluoride etherate to promote this rearrangement. Other transition-metal-catalyzed Overman rearrangements presumably proceed via a similar mechanism.

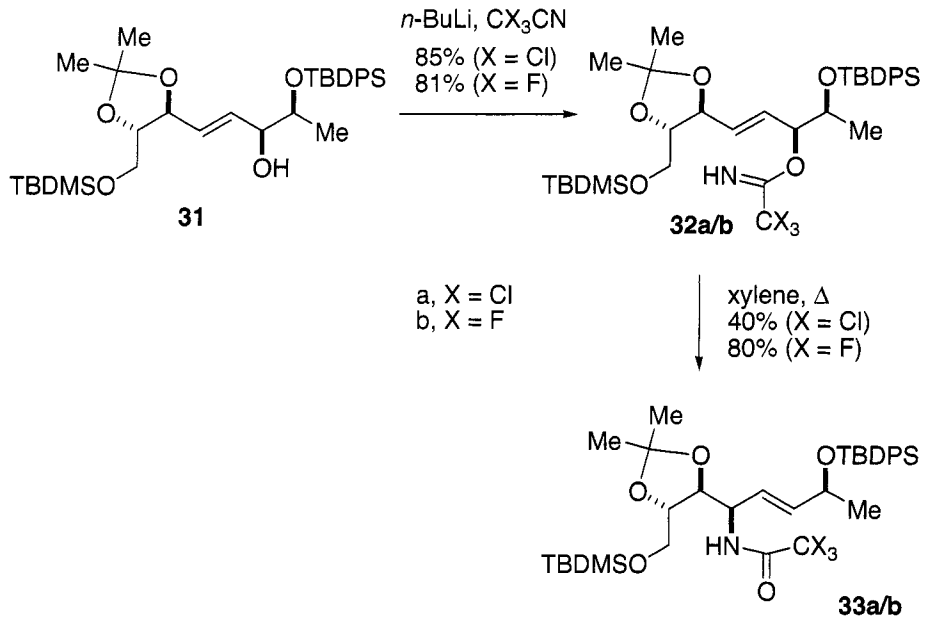


1.1.7.4 Variations and Improvements

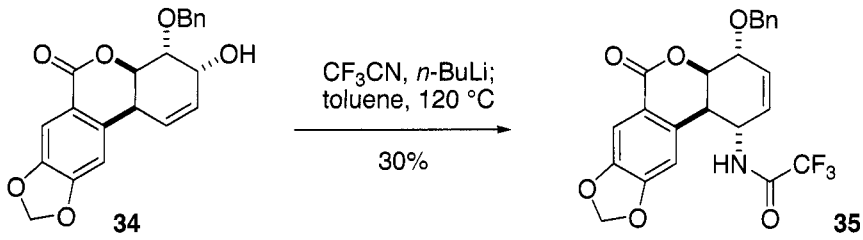
An overwhelming majority of Overman rearrangements are conducted under thermal conditions such as refluxing xylene, as originally reported by Overman. Other conditions include pyrolysis under high vacuum. For example, the optimal results are obtained when imidate **29a** is heated in neat form at 100–105 °C under reduced pressure (0.05–1 mmHg), and the rearrangement product **30a** is obtained in 56% yield.[16] Application of pyrolysis conditions to **29b** gives trichloroacetamide **30b** in 41% yield from the allylic alcohol.[17]



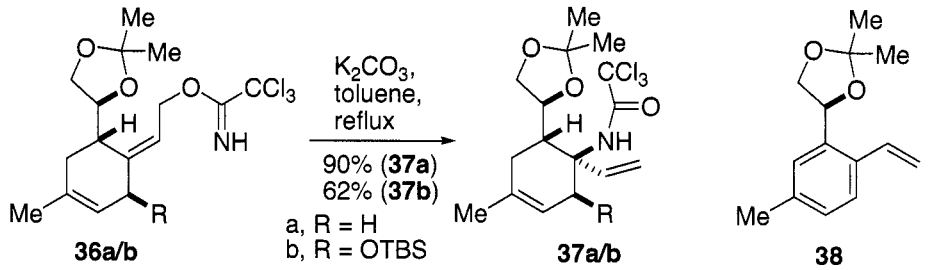
The Overman rearrangements generally involve allylic trichloroacetimidates, but in several instances, better yields are obtained with allylic trifluoroacetimidates.[18] For example, the arrangement of the trichloroacetimidate **32a** requires heating in refluxing xylene for 48 h, and the trichloroacetamide **33a** is obtained in only 40% yield due to competing decomposition under the prolonged reaction conditions. In contrast, the trifluoroacetimidate **32b** is converted to the trifluoroacetamide **33b** in 85% yield under thermal conditions (refluxing xylene, 24 h). This reaction appears to be faster than that of the corresponding trichloroacetimidate, and this increase in reactivity results in improved yields.

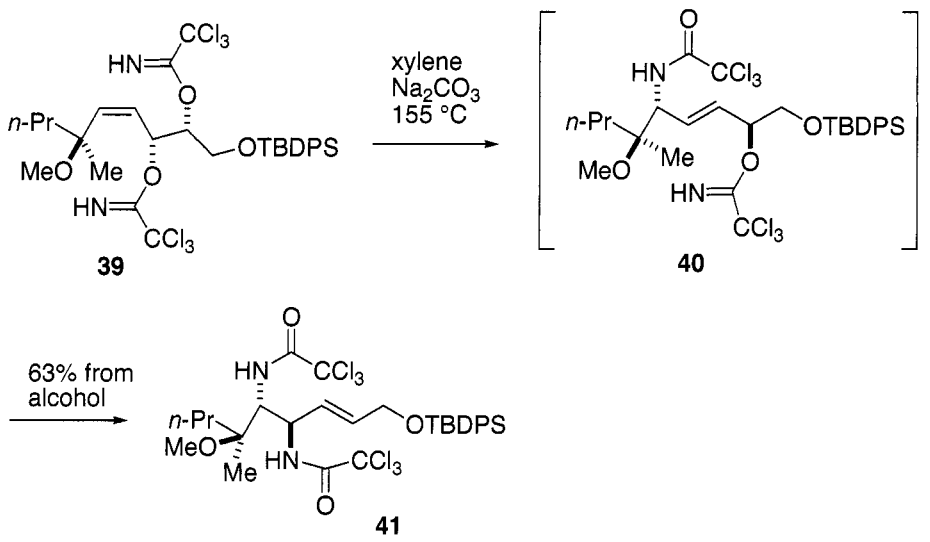


The improvement with allylic trifluoroacetimidates depends on substrates as shown in the case of allylic alcohol **34**.[17] Exposure of **34** with *n*-BuLi and trifluoroacetonitrile gave the corresponding trifluoroacetimidate, which is heated in refluxing toluene to afford trifluoroacetamide **35** in 30% yield, which is even lower than that obtained with the corresponding trichloroacetamide (**29b** to **30b**, *vide supra*).[17] As the preparation of trifluoroacetimidates requires trifluoroacetonitrile, which is a highly toxic gas, application of trifluoroacetimidates to Overman rearrangements is limited.

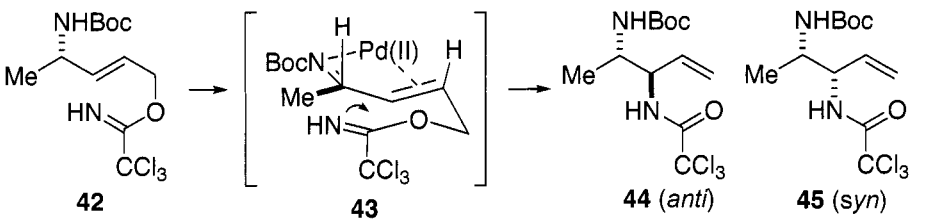


The commonly used thermal conditions can generate some acids, which may cause decomposition of the starting imidates. As a result, some thermal reactions are carried out in either low or irreproducible yields. For example, on a small scale, imidate **36a** undergoes rearrangement in refluxing xylene in a highly stereoselective manner to afford the allyl trichloroacetamide **37a** as a single isomer in 74% yield (two steps). However, only 50% yield is obtained on a relatively large scale. Both the yield and reproducibility are improved by addition of potassium carbonate to trap any acids released under thermal conditions. The optimized conditions include refluxing xylene in the presence of potassium carbonate (2 mg/mL).[19] Under these conditions, **37a** is obtained in 90% yield even with 10 g scale. A similar improvement is observed with trichloroacetamide **36b**. In the absence of potassium carbonate, rearrangement of **36b** in refluxing xylene gives a mixture of the desired product **37b** and the aromatized by-product **38** in 37% and 32% yields, respectively. Addition of potassium carbonate increases the yield to 62% (with 10% starting material recovered), and no aromatic by-product is observed. In addition to potassium carbonate, other bases such as pyridine, DBU and *n*-Bu_3N have also been evaluated, and they provide little improvement. The choice of base also depends on substrates. Thus, in the cascade rearrangement of **39**, sodium carbonate produces higher yields than potassium carbonate.[20] One drawback with potassium carbonate is that it can bring about decomposition of base sensitive substrates under thermal conditions as shown in the case of **29b**.[17] Treatment of imidate **29b** (*vide supra*) with potassium carbonate in refluxing toluene results in only decomposition of the starting imidate.

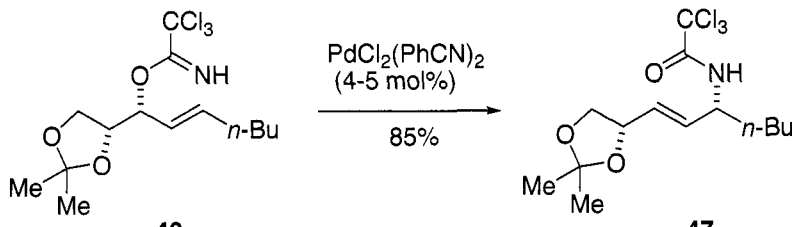




The palladium-catalyzed Overman rearrangements can deliver much higher diastereoselectivity than the corresponding thermal ones.[21–23] Thus, treatment of allylic trichloroacetimidate **42** with a catalytic amount of $PdCl_2$•$(MeCN)_2$ at room temperature provides the *anti*-product **44** in 48% yield (the *syn*-product is not detected).[21] In contrast, the thermal reaction proceeds in much higher yield but much lower diastereoselectivity (*anti*/*syn* = 62/38). The *anti* product presumably results from the transition state **43** where a minimal 1,3-diaxial interaction is expected. Intramolecular attack by the lone pair of the trichloroacetimidate nitrogen follows the β-face trajectory towards the palladium-bound olefin, thus delivering the *anti*-product **44**.[21] The Overman rearrangement of **46** catalyzed by $PdCl_2$•$(PhCN)_2$ also proceeds in high diastereoselectivity to furnish **47** in good yield.[22] In addition to Pd(II) and Hg(II) salts, $PtCl_2$, $PtCl_4$, AuCl and $AuCl_3$ are also identified as efficient catalysts for the Overman rearrangements.[24]

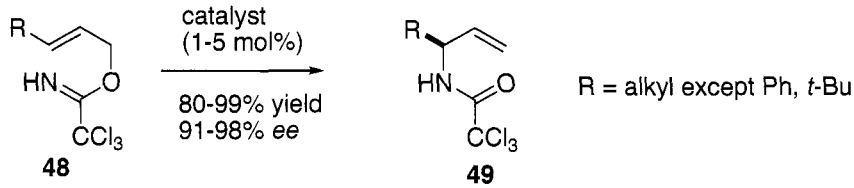


a: *o*-xylene, 140 °C, 24 h, 85% yield, *anti*/*syn* = 62/38
b: $PdCl_2(MeCN)_2$ (6-8 mol%), rt, 3 h, 48% yield, *anti*/*syn* > 99/1

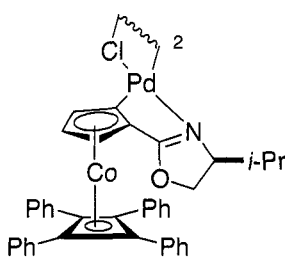


46 **47**

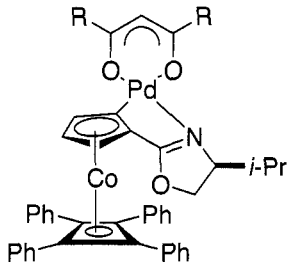
More recently, Overman and co-workers have developed a catalytic asymmetric rearrangement of allylic trichloroacetimidates.[25,26] Thus, the chloride-bridged dimer COP-Cl catalyzes the rearrangement of (*E*)-allylic trichloroacetimidates **48** to furnish the transposed allylic trichloroacetamides **49** in high yield and 92–98% *ee*, thus providing a practical method for transforming prochiral allylic alcohols to enantioenriched amines and their derivatives.[25] However, this methodology does not work for substrates where R is *t*-butyl or Phenyl. As COP-Cl has limited solubility in solvents other than dichloromethane, more soluble monomeric palladacycles **50** and **51** are developed.[26] Both catalysts are soluble in a variety of solvents, and they are effective in the asymmetric Overman rearrangements. When the reactions are carried out in dichloromethane, yields and enantioselectivities are slightly inferior to those realized with COP-Cl. Nevertheless, the enhanced solubility allows reactions to be carried out at high substrate concentrations (e.g. 2.6 M) with practical catalytic rates being achieved in acetonitrile using as little as 1 mol% of COP-hfacac.



48 **49**



COP-Cl

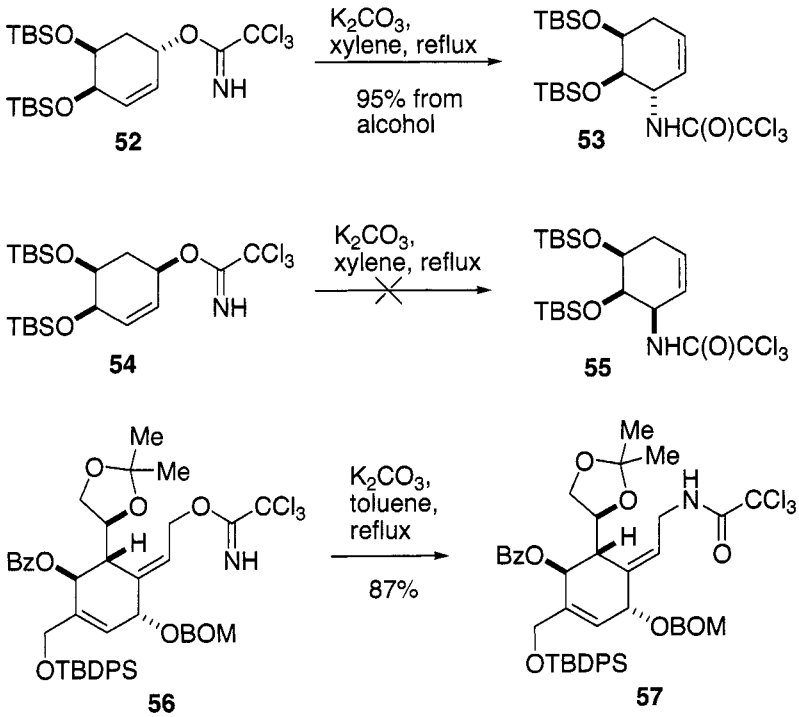


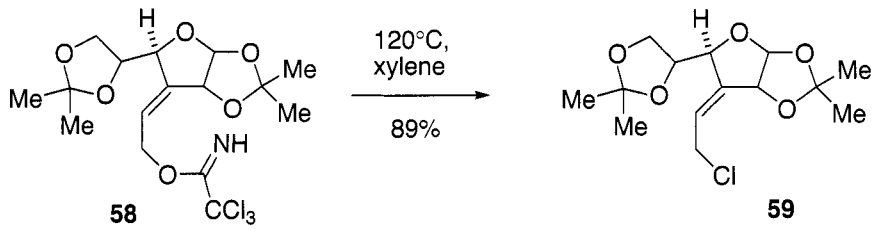
50, COP-hfacac (R = CF_3)
51, COP-acac (R = Me)

1.1.7.5 Scope and Limitation

Like other [3,3]-sigmatropic rearrangements, the Overmann rearrangement is sensitive to steric effects. For example, trichloroacetimidate **52** is converted to the rearranged allylic amine **53** in excellent yield using potassium carbonate in refluxing xylene. However, no desired product is obtained from the corresponding *cis*-isomer **54** under the same conditions. Apparently, the siloxy groups present too much steric bulk to allow the trichloroacetimidate to rearrange towards them in the *cis*-isomer **54** where all of the substituents are on the same face.[27]

As described previously, simple *exo*-allylic trichloroacetimidates **36a/b** undergo smooth Overmann rearrangement to give **37a/b** in good yields.[19] However, the fully functionalized trichloroacetimidate **56** fails to deliver any desired rearranged product, and instead, the 1,3-shift product **57** is obtained.[28] Presumably, the C-5 benzoyloxy substituent occupies the axial position, which causes steric hindrance against incoming nitrogen during rearrangement. The thermal reaction of trichloroacetimidate **58** provides the allylic chloride **59** instead of the rearranged product presumably due to steric effects.[29]

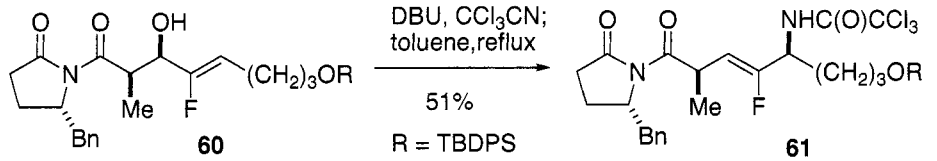




58 59

1.1.7.6 Synthetic Utility

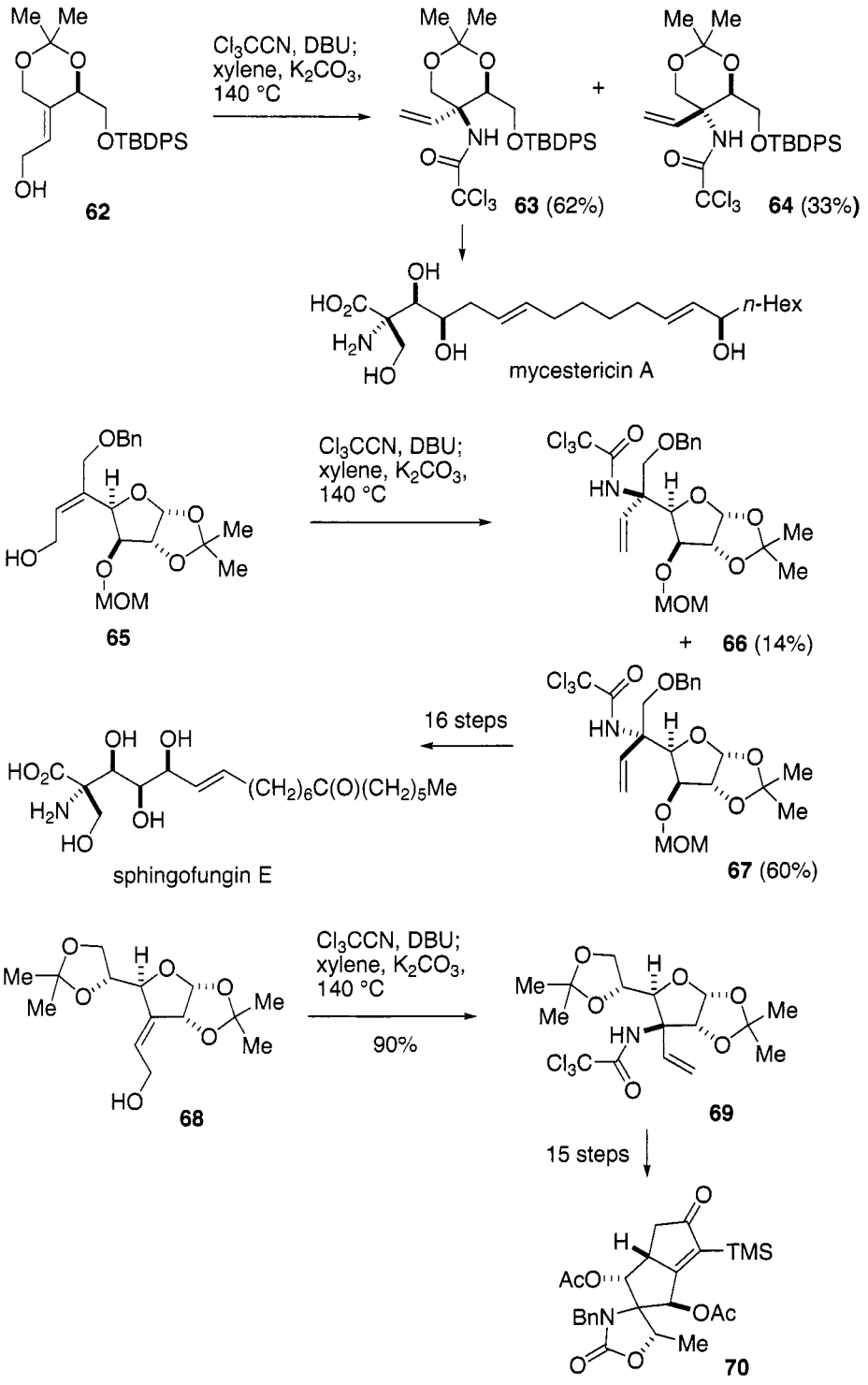
Since its discovery in 1974, more than 180 papers have been published on the use of the Overmann rearrangement to prepare allylic amines and their analogs from their allylic alcohols.[25] For example, a recent synthesis of the fluoroalkene peptidomimetic precursor of *N*-acetyl-*L*-glutamyl-*L*-alanine involves the Overman rearrangement of the imidate derived from the allylic alcohol **60**.[30] This alcohol is readily prepared through Evans asymmetric aldol reaction of oxozolidinone with an aldehyde.



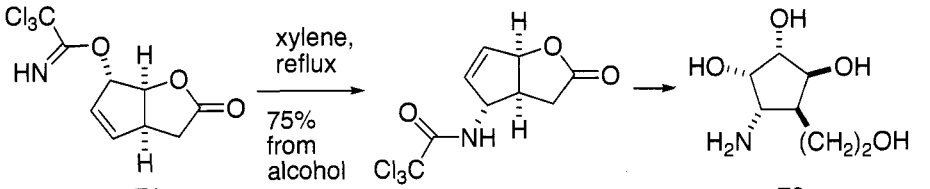
60 61

The Overmann rearrangement of the trisubstituted allylic trichloroacetimidates is a powerful tool in the synthesis of natural products with a tetra-substituted carbon bearing a nitrogen substituent as demonstrated in the first total synthesis of mycestericin A.[31] Reaction of the allylic alcohol **62** with trichloroacetonitrile and DBU afforded the corresponding trichloroacetimidate, which, without isolation, is heated in xylene in the presence of potassium carbonate to give a mixture of two diastereomers **63** and **64**, with the desired isomer **63** predominating. Compound **63** has been converted into mycestericin A in a number of steps. A similar strategy has been applied to the construction of the core of sphingofungin E.[32]

The synthesis of a fully functionalized cyclopentane core structure of pactamycin, a potent antitumor antibiotic, involves Overman rearrangement as a key reaction.[33] Heating a mixture of potassium carbonate and the imidate derived from allylic alcohol **68** in *p*-xylene yields the desired trichloroacetamide **69** as a single isomer in 90% yield from **68**. In this reaction, potassium carbonate is a crucial additive as no desired product is obtained when the same reaction is carried out without potassium carbonate. Trichloroacetimidate **69** has been elaborated into the tricyclic compound **70** which contains all the carbon atoms for the core cyclopentane of pactamycin.

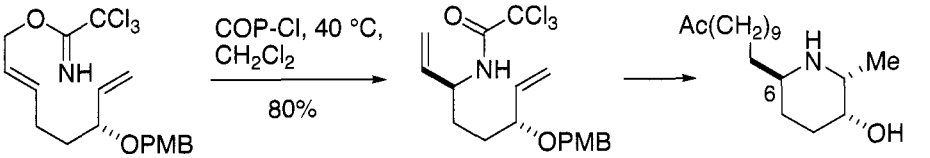

Me Me
OTBDPS
OH
62
Cl3CCN, DBU;
xylene, K2CO3,
140 °C
NH OTBDPS
O
CCl3
63 (62%)
+
64 (33%)
OH
HO2C
H2N
HO
n-Hex
mycestericin A
OBn
HO
Me
MOM
65
Cl3C
HN
66 (14%)
16 steps
(CH2)6C(O)(CH2)5Me
sphingofungin E
67 (60%)
68
90%
69
15 steps
TMS
AcO
OAc
BnN
70

The Overman rearrangement of the disubstituted allylic trichloroacetimidates has also been used in the construction of trisubstituted carbons bearing a nitrogen substituent. For instance, heating a solution of the imidate **71** in refluxing xylene furnishes the allylic trichloroacetamide **72** in good yield. Compound **72** is a precursor to aminocyclopentanol **73**.[34]



71 **72** **73**

A recent synthesis of (+)-*iso*-6-cassine makes use of enantioselective Overman rearrangement of imidate **74**. Treatment of **74** with chiral cobalt oxazoline palladacycle (*S*)-COP-Cl (*vide supra*) in dichloromethane gives rise to the *N*-trichloroacetyl derivative **75** in good yield. This asymmetric reaction installs the absolute stereochemistry of C-6 in (+)-*iso*-6-cassine.[35]



74 **75** (+)-*iso*-6-cassine

1.1.7.7 Experimental

(*E*)-2,2,2-Trichloro-*N*-(hept-2-enyl)acetamide (14, **R^1 = H**)[10]

A solution of the distilled imidate **12** (R^1 = H) (432 mg, 1.67 mmol) in xylene (20 mL) was heated at reflux for 2.5 h. The solvent was removed, and the residue was purified by silica gel chromatography eluting with 10% ethyl acetate/90% hexanes to give the title compound (399 mg, 92% yield).

2,2,2-Trichloro-N-(3,7-dimethylocta-1,6-dien-3-yl)acetamide (28)[10]

Method A (pyridine quenched).

A solution of the distilled imidate **27** (7.47 g, 25 mmol) in anhydrous THF (125 mL) was cooled to –78 °C. A solution of mercuric trifluoroacetate (25 mL of 0.2 M THF solution) was added dropwise over 15 min using a glass addition funnel. The resulting solution was allowed to warm to room temperature during 1 h, and pyridine (8 mL) was added to complex free mercuric ion. THF and excess pyridine were removed *in vacuo*, ether was

added, and the ether solution was washed with water until the aqueous extracts gave a negative test for ionic mercury ($NaBH_4$-NaOH). Drying over anhydrous magnesium sulphate and distillation through a short Vigreux column afforded the title compound (5.93 g, 79%).

Method B (triphenylphosphine quenched).

A solution of the distilled imidate **27** (595 mg, 1.99 mmol) in anhydrous THF (10 mL) at room temperature was treated with mercuric trifluoroacetate (181 mg, 0.424 mmol). After 4 h, the reaction was quenched with triphenylphosphine (230 mg, 0.88 mmol). The resulting solution was stirred for 5 min, a few crystals of bis(triphenylphosphine)bis(trifluoroacetato)-mercury(II) were added, followed by 15 mL hexanes. A light-gray precipitate began to form, and the mixture was stirred overnight. The reaction mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was purified by dry column chromatography eluting with 20% ethyl acetate/80% hexanes to give the title compound (421 mg, 70%).

2,2,2-Trichloro-*N*-((1*R*,6*S*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-1-vinylcyclohex-3-enyl)acetamide (37a)[19]

To a solution of (*Z*)-2-((S)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-cyclohex-3-enylidene)ethanol (701 mg, 2.94 mmol) in dry dichloromethane (20 mL) was added DBU (0.53 mL, 3.52 mmol), and the solution was cooled to 0°C. To this solution was added CCl_3CN (0.44 mL, 4.41 mmol) over 15 min. The resulting reaction mixture was stirred at 0 °C for 1 h and then quenched with sat. NH_4Cl solution. The organic layer was washed with sat. NH_4Cl and then passed through a column packed with anhydrous sodium sulphate and silica gel (to remove polymeric products). The filtrate was evaporated *in vacuo*, and the crude imidate **36a** was used directly for the next step.

To a solution of the crude imidate **36a** obtained as above in *p*-xylene (50 mL) was added potassium carbonate (100 mg), and the reaction mixture was heated at reflux for 13 h. After cooling to room temperature, the mixture was filtered through a pad of Super-Cel, and the precipitate was washed with toluene. The combined filtrate was evaporated *in vacuo*, and the residue was purified by silica gel chromatography eluting with ether/hexane from 1:10 to 1:5 to give the title compound **37a** (1.02 g, 91%).

***tert*-Butyl (2*S*,3*R*)-3-(2,2,2-trichloroacetamido)pent-4-en-2-ylcarbamate** (44)[21]

To a solution of crude (*S*,*E*)-4-(tert-butoxycarbonylamino)pent-2-enyl 2,2,2-trichloroacetimidate (**42**) (prepared from the corresponding allylic alcohol

(4.25 g, 21 mmol)) in THF was added $PdCl_2$•$(MeCN)_2$ (552 mg, 2.13 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 3 h, the solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography eluting with 20% ethyl acetate/80% toluene to give the title compound (3.48 g, 48%).

(*S*)-2,2,2-Trichloro-*N*-(1-iso-butylallyl)acetamide (49, **R = *i*-Bu**)[25]
A solution of COP-Cl (0.13 mL, 0.12 M in dichloromethane, 0.016 mmol) was added to (*E*)-5-methylhex-2-enyl 2,2,2-trichloroacetimidate (**48,** R = *i*-Bu) (41 mg, 0.16 mmol). The reaction flask was then sealed, protected from light and maintained at 38 °C. After 18 h, the reaction was cooled to room temperature. Purification of the residue directly by chromatography (Davisil grade SiO_2, 99.5 : 0.5 hexanes/ethyl acetate) afforded the title compound as a colorless solid (38 mg, 92%). Chiral HPLC (Chiracel OD-H, 99.5 : 0.5 n-hexane/IPA, 0.8 mL/min, 230 nM) showed that compound **49** (R = *i*-Bu) had been formed in 98% *ee*.

(*S*)-2,2,2-Trichloro-*N*-(hex-1-en-3-yl)acetamide (49, **R = *n*-Pr**)[26]

Method A.

COP-hfacac **50** (5.8 mg, 0.0065 mmol, 5 mol%) was added to a solution of (*E*)-hex-2-enyl 2,2,2-trichloroacetimidate (**48**, R = *n*-Pr) (40 mg, 0.13 mmol) in THF (0.05 mL), and the reaction vial was sealed, protected from light, and maintained at 50 °C. After 6 h, the orange solution was concentrated under reduced pressure. Purification of the residue by silica gel chromatography eluting with 10% ethyl acetate/90% hexanes to give the allylic trichloroacetamide **49** as a colorless solid (37 mg, 0.12 mmol, 93%). Chiral GC (Chiraldex γ cyclodextrin trifluoroacetyl, 20 m × 0.25 m; initial temperature 50 °C (1 min), final temperature 150 °C, 5 °C/min) showed that compound 48 had been formed in 96% *ee*.

Method B.

COP-hfacac **50** (1.2 mg, 0.0013 mmol, 1 mol%) was added to a solution of (*E*)-hex-2-enyl 2,2,2-trichloroacetimidate (**48**, R = *n*-Pr) (40 mg, 0.13 mmol) in MeCN (0.05 mL), and the reaction vial was sealed, protected from light, and maintained at 50 °C. After 6 h, the solution was concentrated under reduced pressure. Purification of the residue by silica gel chromatography eluting with 10% ethyl acetate/90% hexanes to give the allylic trichloroacetamide **49** as a colorless solid (36 mg, 0.12 mmol, 90%). Chiral GC (Chiraldex γ cyclodextrin trifluoroacetyl, 20 m × 0.25 m; initial

temperature 50 °C (1 min), final temperature 150 °C, 5 °C/min) showed that compound 48 had been formed in 95% *ee*.

1.1.7.8 References

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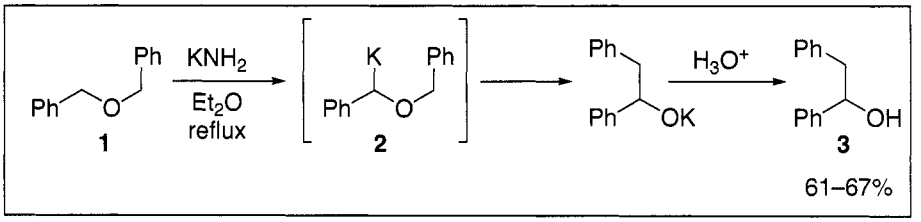
1.1.8 [1,2]-Wittig Rearrangement

John P. Wolfe and Nicolette J. Guthrie

1.1.8.1 Description

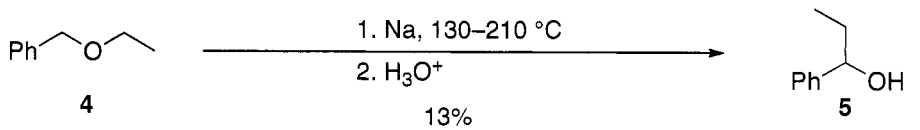
The [1,2]-Wittig rearrangement[1] is the conversion of a dialkyl ether to a secondary alcohol via deprotonation followed by *O*-to-*C* 1,2-alkyl migration from the resulting carbanion.[2–5] For example, treatment of dibenzyl ether (**1**) with two equiv of KNH_2 in refluxing ether effects deprotonation to generate alkylpotassium intermediate **2**, which undergoes [1,2]-Wittig rearrangement to afford benzylphenyl carbinol (**3**) in 61–67% yield after workup.[6]



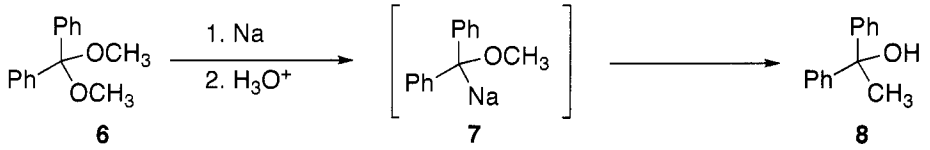
The reactive carbanion that undergoes [1,2]-rearrangement is most commonly generated through deprotonation (as above), or through transmetallation of an organostannane with *n*-BuLi.[2–5] However, ethers bearing α-silyl groups have also been employed as carbanion precursors, and can be converted to the reactive species via treatment with CsF or MeLi.[7] In addition, α-chloro ethers can serve as precursors to organolithium intermediates in [1,2]-Wittig rearrangements, and are activated via metal halogen exchange using lithium powder.[8]

1.1.8.2 Historical Perspective

The first example of a [1,2]-Wittig-type rearrangement was reported in 1924 by Schorigin, and was discovered during studies on the reactivity of benzyl ethers towards alkali metals.[9] Schorigin found that heating a mixture of benzyl ethyl ether (**4**) with metallic sodium to 130–210 °C generated a small amount (13%) of phenyl ethyl carbinol (**5**).

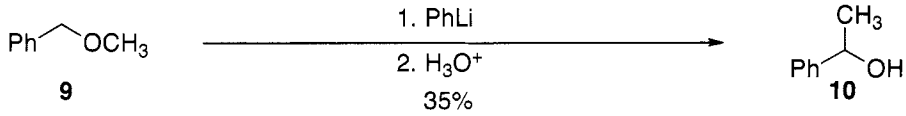


A related [1,2]-rearrangement was described by Schlenk and Bergman in 1928. As shown below, reduction of benzophenone dimethyl acetal (**6**) with metallic sodium led to the formation of diphenyl methyl carbinol (**8**), presumably via intermediate organosodium species **7**.[10]



6 **7** **8**

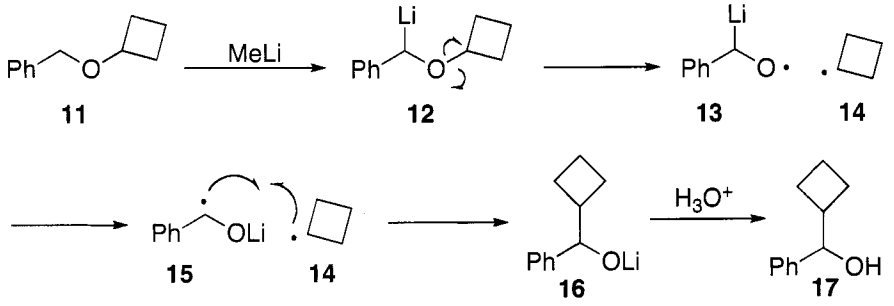
Subsequent studies by Wittig demonstrated that deprotonation of benzyl alkyl ether derivatives with phenyllithium could provide the requisite carbanion and induce [1,2]-Wittig rearrangement.[1] For example, treatment of benzyl methyl ether (**9**) with phenyllithium provided α-methyl benzyl alcohol (**10**) in 35% yield upon workup.



9 **10**

1.1.8.3 Mechanism

The [1,2]-Wittig rearrangement is believed to proceed via a radical mechanism,[2,3] which is illustrated in the example shown below. The reaction of **11** with MeLi provides organolithium intermediate **12**, which undergoes C–O bond homolysis to form radicals **13** and **14**. Radical **13** is converted to **15** via 1,2-lithium migration, and a subsequent intermolecular radical coupling of **15** with **14** yields alkoxide **16**. The alcohol product **17** is obtained after an aqueous workup. The homolysis/recombination events are believed to occur inside a solvent cage.



11 **12** **13** **14**

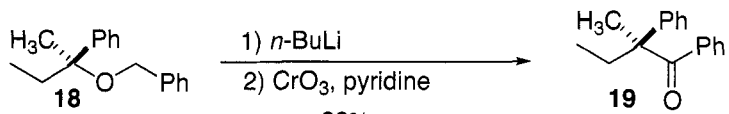
15 **14** **16** **17**

The homolysis/radical recombination mechanism is supported by several important pieces of data.[4,11,12] For example, partial loss of stereochemistry is observed in reactions of substrates bearing a stereocenter at the migrating carbon atom. In addition, migratory aptitudes of R-groups mirror the stability of the corresponding radicals (R•). Although both of these observations could also be attributed to a mechanism involving carbocation intermediates, products resulting from carbocation rearrangement processes are not observed. Moreover, the rearrangement of benzhydryl(5-hexenyl)ether provides small amounts of products bearing a cyclopentylmethyl group, which results from 5-endocyclization of an intermediate 5-hexenyl radical.[12]

Although a considerable body of evidence suggests that solution-phase [1,2]-Wittig rearrangements of lithiated ethers usually proceed via the homolysis/recombination pathway described above, recent theoretical studies suggest that gas-phase [1,2]-Wittig rearrangements[13] may involve heterolytic mechanisms.[14] In addition, it appears likely that rearrangements of aryl allyl ethers proceed via an aromatic addition/elimination mechanism.[15]

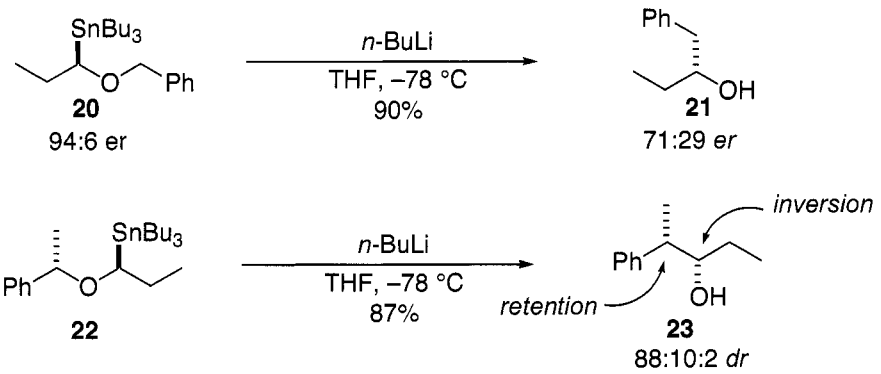
1.1.8.4 Stereochemistry

In most cases the 1,2-Wittig rearrangement proceeds with retention of configuration at the migrating (non-metallated) carbon center and inversion of configuration at the metallated carbon center. The stereochemical course of the [1,2]-Wittig rearrangement with respect to the migrating carbon center was elucidated by Schöllkopf in the early 1960's.[16] As shown below, treatment of enantiomerically enriched ether **18** with *n*-BuLi followed by oxidation of the resulting alcohol afforded **19** with predominant retention of configuration at the tertiary benzylic stereocenter (slight loss of enantiomeric purity was observed).[16a] This preference for retention of configuration at the migrating carbon center appears to be quite general,[17,18] although exceptions can arise in sterically hindered systems.[19]

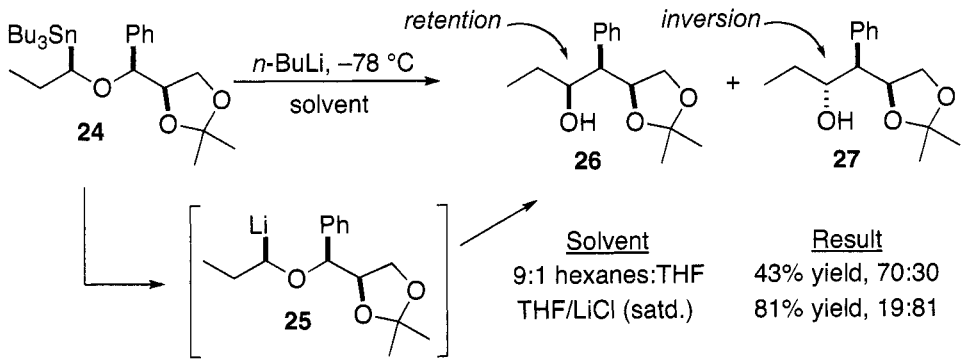


Several groups have examined [1,2]-Wittig rearrangements of configurationally stable organolithium reagents in order to elucidate the stereochemical course of reaction at the metallated center.[20] For example, Nakai has demonstrated that treatment of enantiomerically enriched α-stannyl ether **20** (94:6 er) with *n*-BuLi generates alcohol **21** in 90% yield and 71:29 *er* (76% inversion of configuration).[20c,d] Nakai has also conducted

[1,2]-Wittig rearrangements of substrates bearing chiral centers at both the migrating and metallated positions. As shown below, the conversion of **22** to **23** further illustrates the preference for retention of stereochemistry at the migrating center and inversion at the metallated center.



In some transformations the product stereochemistry can be greatly influenced by reaction conditions. For example, Maleczka has shown that [1,2]-Wittig rearrangements of substrates bearing chelating groups can be induced to proceed with either inversion or retention of configuration at the metallated center.[21] As illustrated below, treatment of **24** with *n*-BuLi using a solvent system composed of 9:1 hexanes:THF provided a 70:30 mixture of **26** and **27**. These conditions promote chelation between the oxygen of the dioxolane moiety and the lithium atom of the metallated intermediate (**25**), which leads to retention of configuration at the lithiated center. In contrast, chelation was disrupted when THF saturated with LiCl was used as the reaction medium, and a 19:81 mixture of **26** and **27** was obtained.



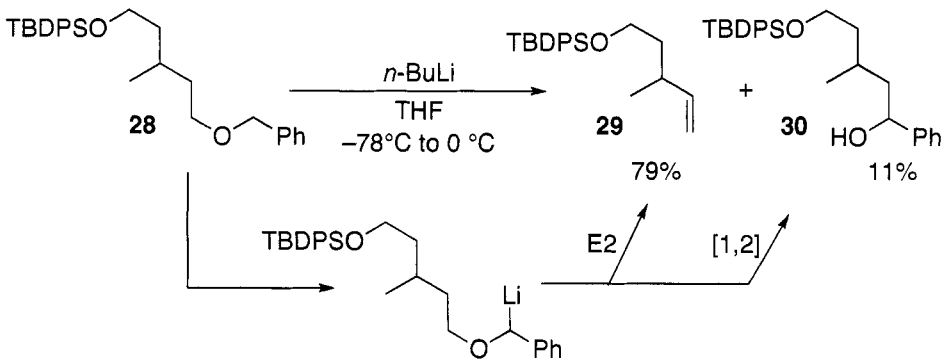
In addition to the trends noted above, scrambling of stereochemistry at the metallated carbon is observed in transformations that involve alkenyl migrating groups.[22] This observation provides additional evidence for the intermediacy of radical species in these reactions.

1.1.8.5 Scope and Limitations

The [1,2]-Wittig rearrangement suffers from several problems that limit synthetic utility. The strongly basic conditions typically employed in these reactions are not tolerant of many common functional groups, and low yields are frequently obtained even with unfunctionalized substrates due to other competing pathways. In addition, a relatively limited range of substrates are sufficiently reactive to undergo the [1,2]-rearrangement.

In general, the ease of [1,2]-Wittig rearrangement is directly correlated with the radical stability of both the migrating radical (from the non-metallated center) and the accepting radical formed from the metallated carbon center.[2,20d] The best yields are obtained when relatively stable radicals derived from both the migrating group and the accepting group are formed upon homolysis of the intermediate carbanion. Conversely, substrates that do not contain a good radical stabilizing group at either the migrating center or the accepting center are not efficiently transformed. The observed migratory aptitude and/or acceptor ability of alkyl groups typically follows the order: benzyl, allyl > tertiary > secondary > primary. Alkenyl groups and aryl groups can also undergo 1,2-migration in Wittig rearrangements, although with less facility than benzyl or allyl groups.[15,22]

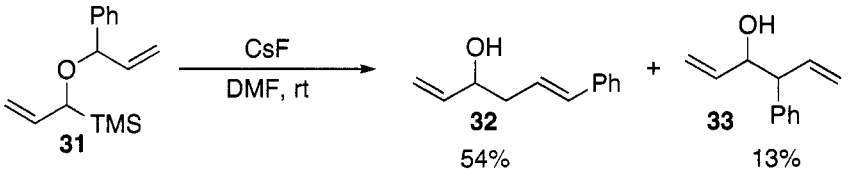
The most common side reaction observed in the [1,2]-Wittig rearrangement is intramolecular E_2 elimination of the metallated substrate to generate an alkene. This is particularly problematic when the radical intermediate derived from the migrating group is relatively unstable, such as with substrates bearing primary alkyl groups. For example, treatment of **28** with *n*-BuLi under standard conditions provided alkene product **29** in 79% yield, whereas the [1,2]-rearrangement product **30** was obtained in only 11% yield.[23]



In cases where the intermediate organolithium species is generated via transmetallation from an α-stannyl ether, competing proteodestannylation is

commonly observed.[2,20d] As above, the degree of this problem increases when substrates contain groups with poor migratory aptitude.

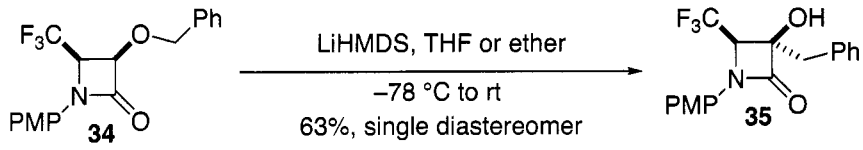
In addition to problems associated with migratory aptitude, competing [2,3]- and/or [1,4]-rearrangement of allyl ether derivatives can also lead to mixtures of products.[2,7,24] For example, treatment of **31** with CsF provided a 4:1 mixture of **32** (from [2,3]-rearrangement) and **33** (from [1,2]-rearrangement).[7a]



1.1.8.6 Variations and Improvements

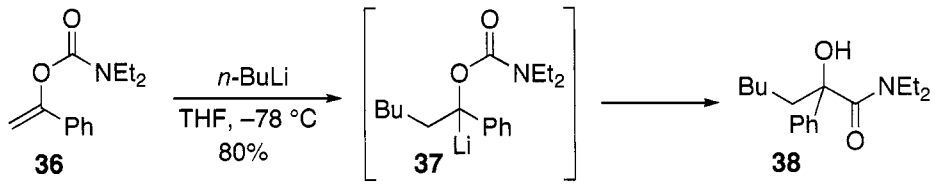
[1,2]-Wittig Rearrangements of Enolates

Most examples of [1,2]-Wittig rearrangements involve relatively basic carbanions. However, a few reports have demonstrated that enolates derived from α-alkoxy carbonyl compounds can also participate in [1,2]-Wittig rearrangements.[25] For example, α-benzyloxy lactam **34** was converted to **35** in 63% yield upon treatment with LiHMDS. Related enolate Wittig rearrangements have also been used in tandem processes as described below.

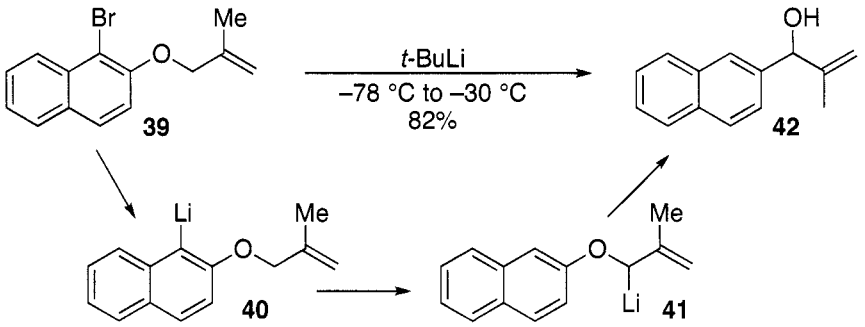


[1,2]-Wittig Rearrangements in Tandem Reactions

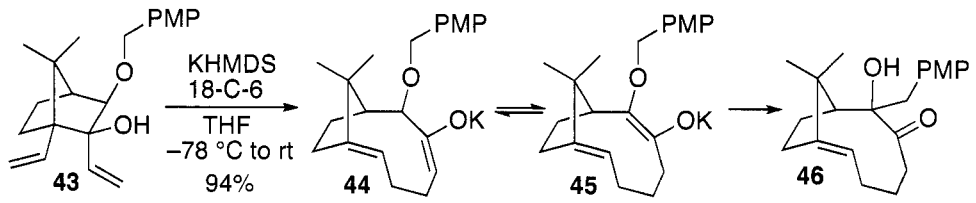
The [1,2]-Wittig rearrangement has occasionally found application in transformations that involve tandem or sequential reactions. An interesting sequential process was developed by Snieckus, and is initiated by carbolithiation of α-aryl-*O*-vinyl carbamate **36** with *n*-BuLi to provide organolithium intermediate **37**. Subsequent [1,2]-Wittig rearrangement with migration of the carbamate group affords alcohol **38** in 80% yield.[26]



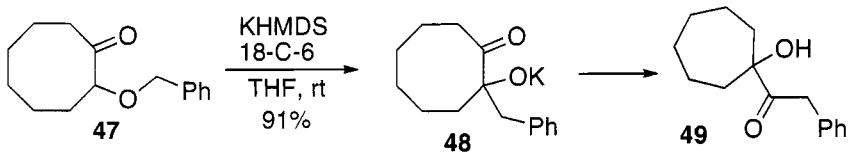
Barluenga has observed that *o*-bromoaryl ethers undergo tandem anion translocation/[1,2]-Wittig rearrangement reactions when treated with *t*-BuLi and warmed to –30 °C.[27] For example, 1-bromonaphthalene derivative **39** was converted to **42** in 82% yield under these conditions. This reaction proceeds via initial metal-halogen exchange to afford **40**, which undergoes anion translocation to generate **41**. The product **42** is then obtained following [1,2]-Wittig rearrangement of **41**.



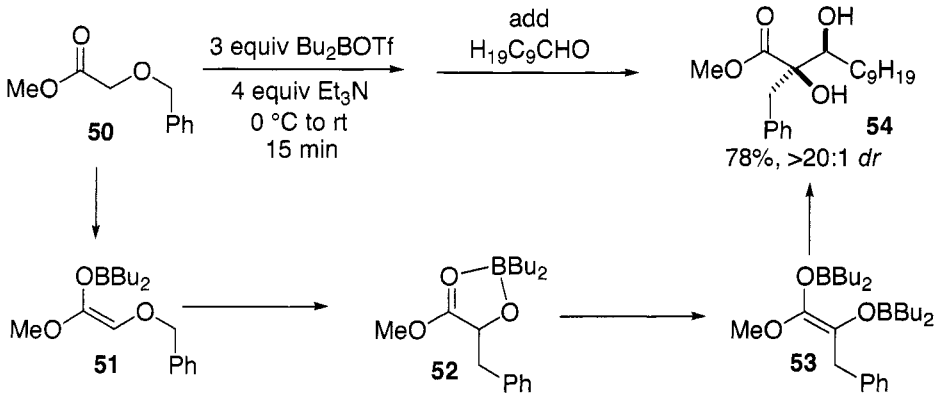
A tandem oxy-Cope rearrangement/enolate [1,2]-Wittig rearrangement has been used for the conversion of alcohol **43** to ketone **46**.[28] As shown below, treatment of **43** with KHMDS/18-crown-6 effects [3,3]-sigmatropic rearrangement to provide intermediate **44**, which undergoes equilibration to enolate **45**. Subsequent [1,2]-Wittig rearrangement of the enolate affords **46** in 94% yield.



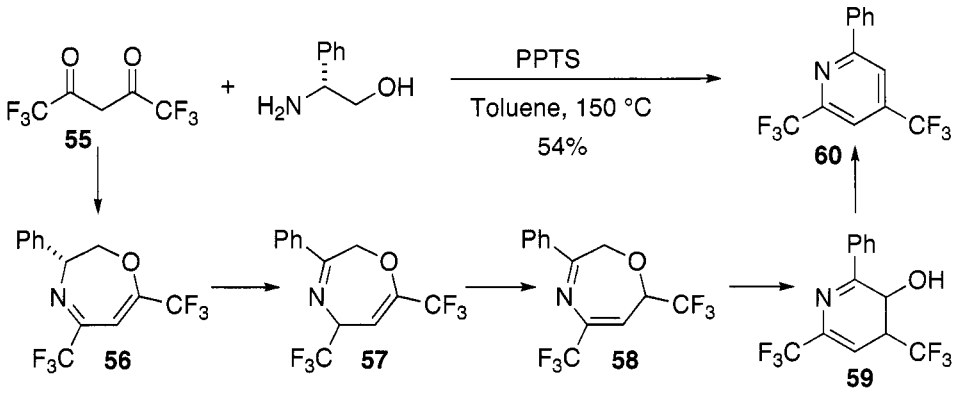
Similar conditions have been employed for the conversion of **47** to **49**. This transformation proceeds via enolate [1,2]-Wittig rearrangement to yield **48**, which undergoes α-ketol rearrangement to produce **49** in 91% yield.[29]



A tandem enolate [1,2]-Wittig rearrangement/aldol reaction of glycolate ester derivatives has recently been described.[30] This transformation provides 1,2-diol products in good yield and excellent diastereoselectivity, and effects formation of two C–C bonds and two stereocenters in a one-flask procedure. For example, treatment of methyl *O*-benzyl glycolate (**50**) with Bu_2BOTf/Et_3N followed by warming to rt and introduction of decanal affords **54** in 78% yield with > 20:1 *dr*. This transformation is believed to proceed by initial Wittig rearrangement of enolate **51** to boron alkoxide **52**, followed by a second deprotonation to give doubly borylated enolate **53**. The final product **54** is then generated through a highly stereoselective aldol reaction.

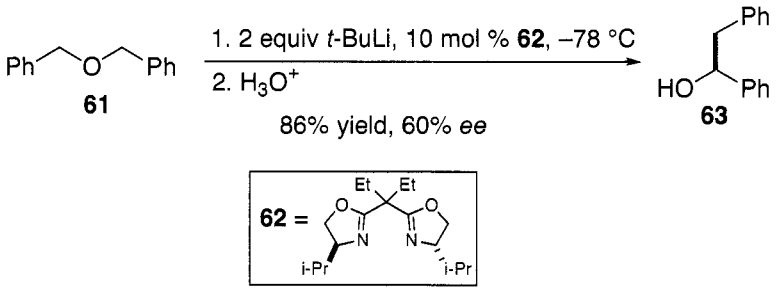


The synthesis of 2,4-bis(trifluoromethyl)-6-phenyl pyridine (**60**) from diketone **55** was achieved via an unusual sequence of 1,3-proton shifts followed by [1,2]-Wittig rearrangement.[31] As shown below, treatment of **55** with phenylglycinol and PPTS in refluxing toluene leads to initial formation of **56**, which undergoes two 1,3-proton shifts to provide **58**. Intermediate **58** is presumably converted to **59** via [1,2]-Wittig rearrangement (under very mild conditions), and subsequent dehydration affords the pyridine derivative **60**. Although this transformation is reasonably efficient, the scope appears to be limited, as the analogous reaction of **55** with phenylalaninol failed to generate a pyridine derivative.

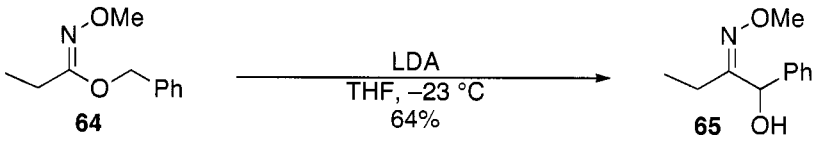


Enantioselective [1,2]-Wittig Rearrangement

A single report on enantioselective [1,2]-Wittig rearrangements was published by Tomooka and Nakai in 1999.[32] A chiral bis-oxazoline ligand was employed to facilitate asymmetric lithiation/rearrangement of dibenzyl ether and benzyl(propargyl) ether derivatives with enantioselectivities ranging from 40–65% *ee*. In a representative transformation, treatment of **61** with *t*-BuLi and bis-oxazoline **62** led to the formation of **63** in 86% yield and 60% *ee*.



The Imino [1,2]-Wittig Rearrangement

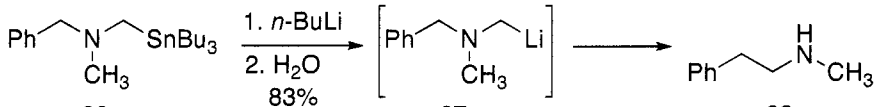


The imino [1,2]-Wittig rearrangement was originally reported by Katritzky in 1981,[33] and has been subsequently explored by Uneyama[34] and Naito.[35] These transformations involve rearrangements of benzyl or allyl hydroximates to α-hydroxy oximes. An illustrative example involves the

conversion of **64** to **65** in 64% yield by treatment with excess LDA at –23 °C.[35] The products of these reactions can be converted to synthetically useful α-hydroxy ketones or 1,2-amino alcohols through subsequent manipulation.

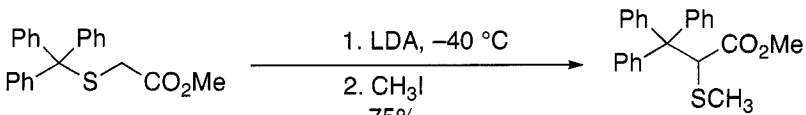
[1,2]-Wittig-type Rearrangements of Amines and Sulfides

A few examples of [1,2]-Wittig rearrangements of amines and sulfides have been observed, although these transformations are much less common than the analogous reactions of ethers described above. The [1,2]-aza-Wittig rearrangements usually involve migrations of allyl groups, which may occur via a concerted [2,3]-rearrangement pathway under certain conditions.[36] However, benzyl and trityl migration has also been observed in a few [1,2]-aza-Wittig rearrangements.[37] For example, organolithium reagent **67**, prepared by treatment of the corresponding α-aminostannane **66** with *n*-BuLi, rearranged to provide **68** in 83% yield after aqueous workup.[37a]



66 **67** **68**

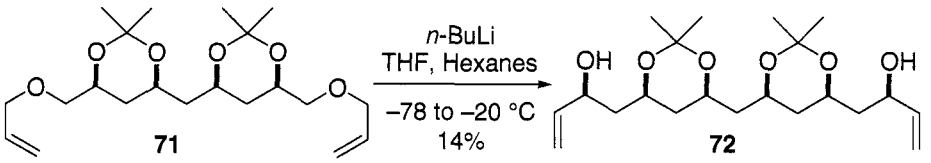
The [1,2]-thio-Wittig rearrangement has been examined by several groups, and is known for both simple thioethers and α-thiocarbonyl derivatives.[38] In a representative transformation, deprotonation of ester **69** followed by warming to –40 °C led to [1,2]-thio-Wittig rearrangement. A 75% yield of **70** was obtained after a CH_3I quench.[38d]



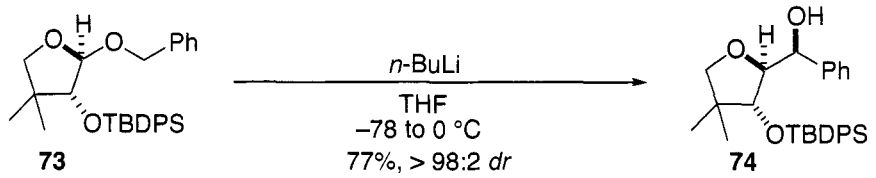
69 **70**

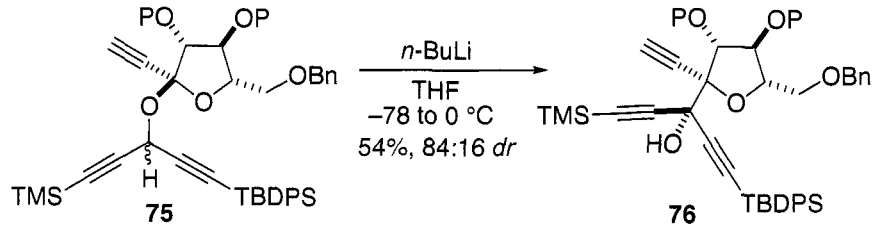
1.1.8.7 Synthetic Utility

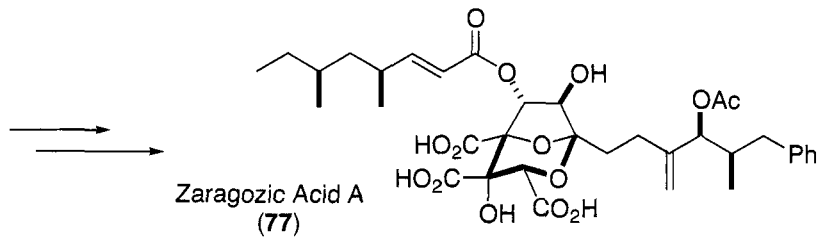
Despite the limitations of the [1,2]-Wittig rearrangement, this transformation has been used in a few interesting and creative syntheses of complex molecules. One of the earliest applications of this reaction was reported by Schreiber in 1987.[39] As shown below, a synthesis of skipped *syn*-poylol chains was accomplished using a stereoselective [1,2]-Wittig rearrangement to effect the conversion of **71** to **72**. The product was formed as a single stereoisomer, albeit in only 14% yield.



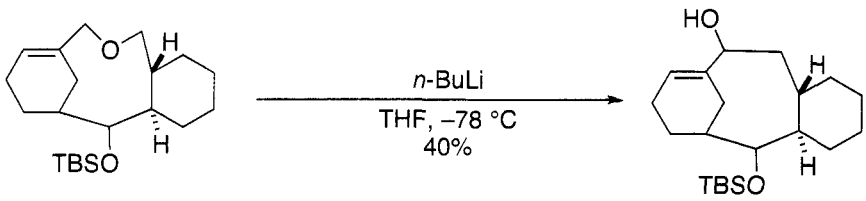
The [1,2]-Wittig rearrangement has found several applications in the stereocontrolled conversion of *O*-glycosides to *C*-glycosides.[18,40,41] In a representative case, treatment of **73** with *n*-BuLi provided **74** in 77% yield with > 98:2 *dr*.[40] The products of these reactions are potentially of biological significance, and are also synthetically useful intermediates. For example, this strategy has been employed as a key step in the synthesis of zaragozic acid A.[42] As shown below, the conversion of *O*-glycoside **75** to *C*-glycoside **76** proceeded in 54% yield and 84:16 diastereoselectivity. This intermediate was subsequently transformed to the natural product (**77**) after a number of steps.





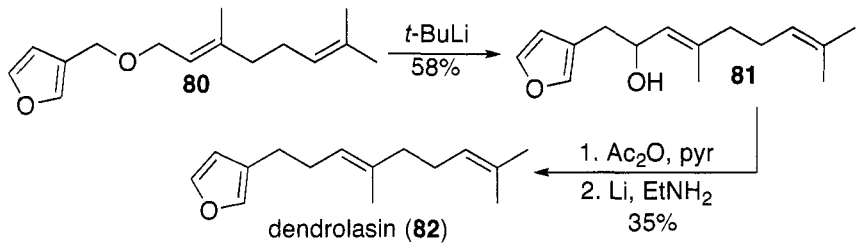


The [1,2]-Wittig rearrangement has been used to access a functionalized taxane skeleton. As shown below, treatment of **78** with *n*-BuLi generated **79** in 40% yield.[43] Unfortunately the stereoselectivity of this transformation was not reported.

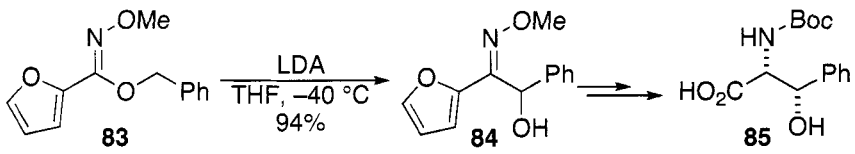


78 **79**

The furan-containing natural product dendrolasin was synthesized using a [1,2]-Wittig rearrangement of geranyl 3-furylmethyl ether **80**.[44] This reaction provided alcohol **81**, which results from metallation at the allylic position and migration of the furylmethyl group, in 58% yield when deprotonation was effected using *t*-BuLi. Deoxygenation of intermediate **81** then afforded the natural product (**82**).

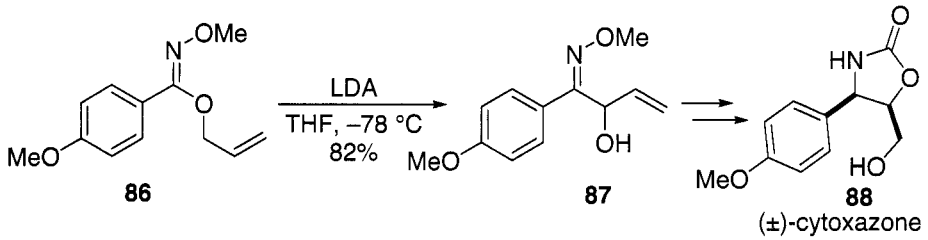


The synthesis of β-hydroxyphenylalanine derivatives has been accomplished using a multi-step sequence that features a key imino [1,2]-Wittig rearrangement.[45] Hydroximate **83** was prepared in two steps from 2-furoyl chloride, and transformed to **84** in 94% yield by treatment with LDA. The α-hydroxy oxime **84** was subsequently converted to the boc-protected amino acid **85** in five steps. Use of an appropriate reagent for reduction of the C–N double bond allows for the stereoselective generation of either the *syn*- or *anti*-amino alcohol stereoisomer. A related rearrangement of imino ethers has been employed for the generation of β-trifluoromethyl-substituted isoserine.[34]

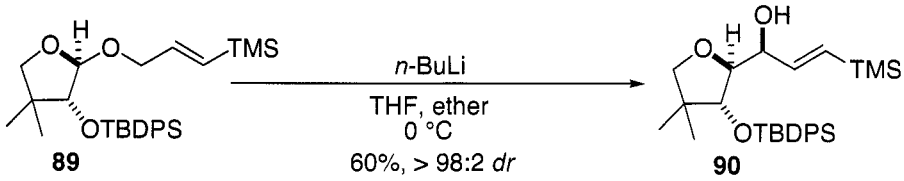


The imino [1,2]-Wittig rearrangement of hydroximates has also been employed in the construction of natural products. For example, (±)-cytoxazone (**88**) was prepared from intermediate **87**, which was generated via [1,2]-Wittig rearrangement of **86**.[46] An asymmetric synthesis of (+)-

cytoxazone has been achieved using a similar route with an oxime ether bearing a chiral auxiliary,[47] and the furopyran core of dysiherbaine has also been prepared using imino [1,2]-Wittig rearrangement as a key step.[48]



1.1.8.8 Experimental



(*E*)-(1*S*,2*S*,3*R*)-1-[3-(*tert*-butyldiphenylsiloxy)-4,4-dimethyltetrahydrofuran-2-yl]-3-(trimethylsilyl)prop-2-en-1-ol (90).[18]

An oven-dried flask was cooled under a stream of argon and charged with **89** (145 mg, 0.30 mmol), THF (13 mL) and ether (13 mL). The solution was cooled to 0 °C and a solution of *n*-BuLi in hexanes (0.33 mL, 1.36 M, 0.45 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min, then warmed to rt and stirred for 2 h. Water and acetic acid were added to quench the reaction, and the mixture was transferred to a separatory funnel. The layers were separated and the organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 87 mg (60%) of the title compound as a colorless oil. This material was judged to contain a > 98 : 2 mixture of stereoisomers by ^{1}H NMR analysis.

3.1.8.9 References

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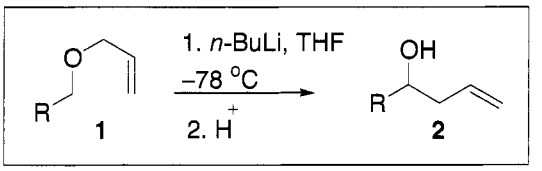
1.1.9 [2,3]-Wittig Rearrangement

Nadia M. Ahmad

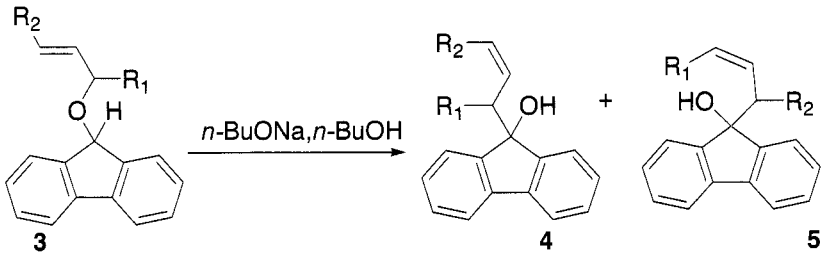
1.1.9.1 Description

The [2,3]-Wittig rearrangement is a sigmatropic reaction which results in the construction of homoallylic alcohols **2** from allyl ethers **1** upon treatment with base at low temperatures.



1.1.9.2 Historical Perspective

The history of the [2,3]-Wittig rearrangement is a relatively recent one and arose through observations during mechanistic studies on the classic [1,2]-Wittig rearrangement. Stevens and Holmes observed the rearrangement of the allyl fluorenyl ether **3** and realised that it formally represented a [2,3]-sigmatropic version of the well-known 1,2-alkyl shift of oxycarbanions.[1–4]

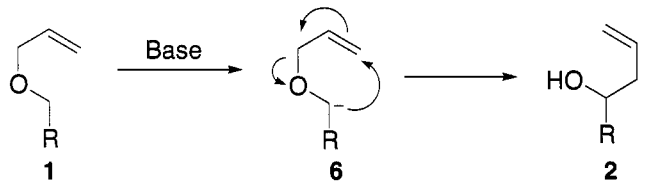


Since then, the [2,3]-Wittig rearrangement has been utilized in numerous synthetic applications. Highly stereoselective variants, and hetero [2,3]-Wittig rearrangements have also been discovered, and several excellent reviews have been published.[5–8]

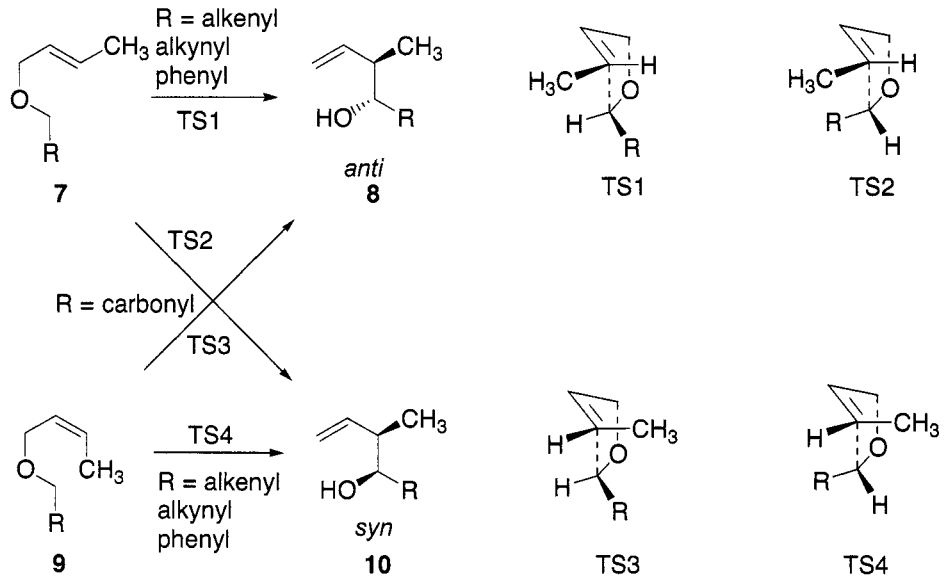
1.1.9.3 Mechanism

The mechanism of the [2,3]-Wittig rearrangement is a concerted, thermally allowed sigmatropic reaction which follows the Woodward–Hoffman rules

and proceeds through a six-electron, five-membered transition state in a suprafacial fashion.



The formation of a carbanion **6** results *via* treatment of an allylic ether **1** with base. The reactions are usually are carried out at low temperatures in order to prevent the competing Wittig [1,2]-rearrangement. The rate of reaction depends upon the energy gap between the HOMO (carbanion) and the LUMO (allyl π* orbital) such that the less stable the carbanion, the faster the rearrangement.

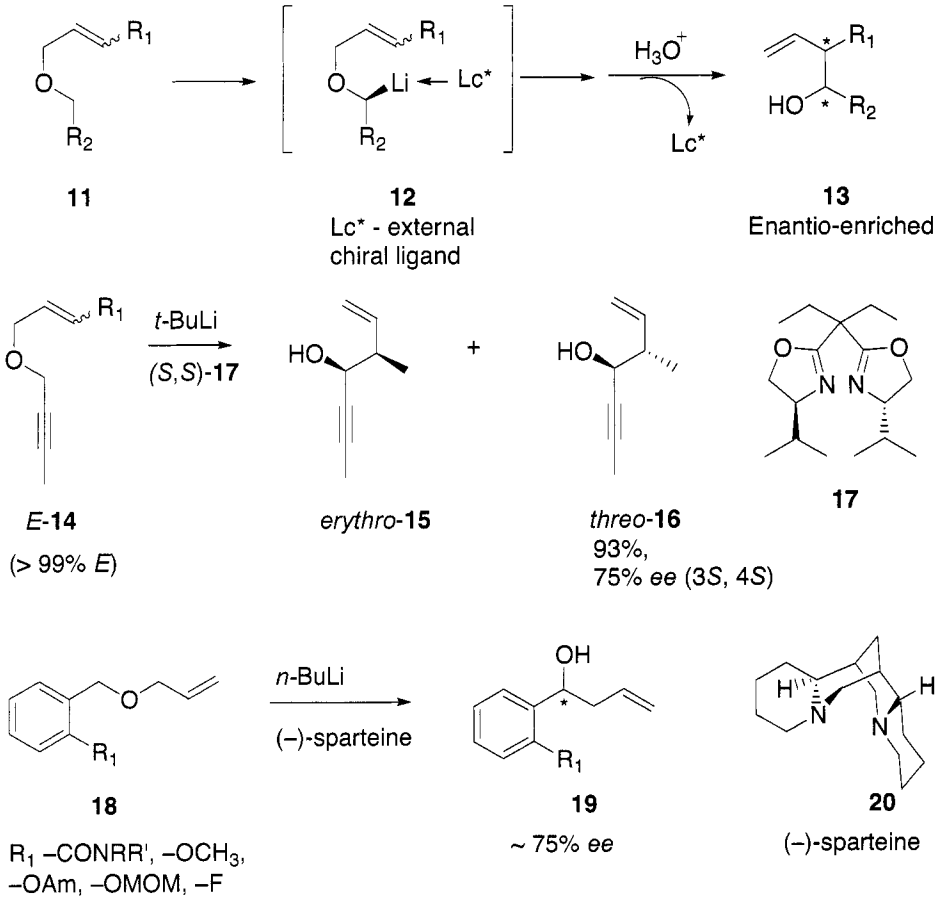


The high stereoselectivity of the reaction can usually be explained in terms of electronic interactions and steric effects. This can be clarifyed by Houk's calculated transition state structure.[9,10] Using *ab initio* molecular orbital calculations, a new hypothesis was provided to explain the stereoselectivities observed. The summary of these observations is as follows: (i) *E*-homoallyl alcohols are usually the major products, but especially when R is an alkenyl, alkynyl, or phenyl group,[11,12] (ii) the diastereoselectivity at the termini of the new C–C bond can be attributed to the starting material – a *Z* substrate (**9**) usually leads to *syn* selectivity whilst

an *E* substrate (**7**) gives *anti* selectivity.[7,13,14] The selectivity is reversed when R is a carbonyl group.[12,15]

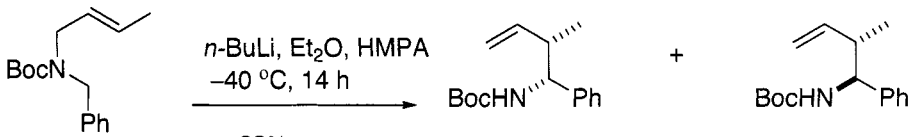
1.1.9.4 Variations, Improvements or Modifications

A number of bases can be utilized in the [2,3]-Wittig reaction. These include *t*-butyllithium, which in conjunction with a chiral bisoxazoline system **17**, has been used to effect an enantioselective [2,3]-Wittig rearrangement of allyl ether **14** *via* an asymmetric lithiation.[16]



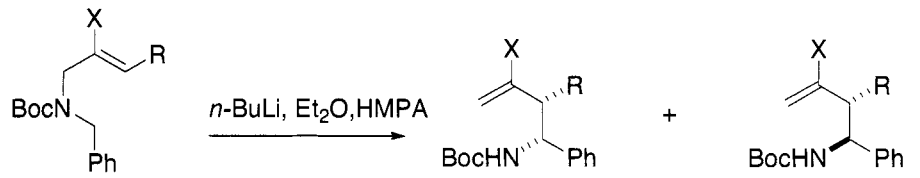
Another protocol to achieve an enantioselective [2,3]-Wittig rearrangement is by the use of *n*-BuLi with sparteine **20** as the chiral ligand. This has been demonstrated by Kimachi and Kawasaki with allyl ortho-substituted benzyl ethers **18** and *ortho*-substituted benzyl prenyl ethers as substrates.[17]

Anderson and coworkers reported the first example of an acyclic aza-[2,3]-Wittig sigmatropic rearrangement.[18] Prior to their publication, only three examples of this reaction had been published.[19–21] However, these all involved cyclic substrates, azetidinones and vinyl aziridines respectively, and thus the ease of the reaction can be partially attributed to the relief of the ring strain during the course of the rearrangement.



21 **22** 3:2 **23**

The reaction of amine **21** with *n*-BuLi preceeded with a diastereoselectivity ratio of 3:2 which, by analogy to the Houk calculated transition state structure for the oxy-[3,2]-Wittig rearrangement, can be attributed to a presumably small difference in the transition state energies leading to each diastereoisomer.[9,21]



24a–f **25a–f** **26a–f**

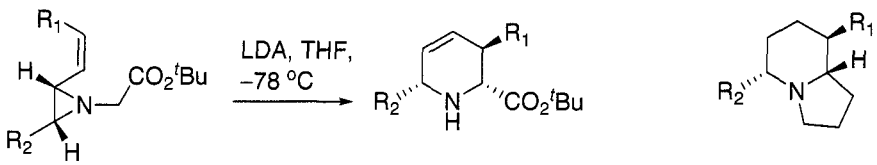
	X	R	Conditions	Yield[b] %	Diastereo-selectivity[c] 25:26
24a	H	*i*-Pr	–40 °C, 14 h	54	4:3
24b[a]	$SiMe_3$	Me	–78 °C, 20 h	88	<1:20
24e	$SiMe_3$	Et	–78 °C, 30 min	92	1:18
24d	$SiMe_3$	*i*-Pr	–78 °C, 30 min	94	1:11

[a]HMPA not added. [b]Isolated yields of **25** and **26** together. [c]Ratios of unpurified products determined by 250 MHz NMR.

To overcome the lack of diastereoselectivity, Anderson *et al.* used the Houk transition state model to rationalise that increased steric bulk would afford better selectivity.[23,24] To this end, several substrates **24a–f** were synthesised and then subjected to the rearrangement conditions.[23]

It was determined that increasing the steric bulk of the groups did not increase the diastereselectivity of the rearrangements and in fact, the use of a *t*-butyl prevented the rearrangement from taking place altogether. Using Houk's transition state structure, however, it was hypothesized that that there should be a small build up of negative charge at the central vinyl carbon atom during the rearrangement and, if this is indeed the case, then an anion stabilising group should aid the transformation. Thus a trimethylsilyl stabilizing group was selected as silicon is known to stabilize an adjacent negative charge.[25] The tabulated results thus illustrate that the use of the trimethylsiyl group does indeed enhance the diastereoselectivity of the rearrangement and also increases the rate of reaction, resulting in significantly shorter reaction times. The Anderson group have also investigated sulphur-containing groups as anion-stabilizing groups and the tributyltin group as a synthetic handle in the aza-[2,3]-Wittig rearrangement.[26,27]

The aza-[2,3]-Wittig rearrangement has been employed in the total synthesis of (–)-indolizidines 209B and 209D which have shown to function as non-competitive blockers of neuromuscular transmission. Vinylaziridines **27a** and **27b** underwent the rearrangement when reacted with LDA to afford tetrahydropyridines **28a** and **28b** respectively as single diastereoisomers in excellent yields. The rearrangement of **27b** installs all three stereogenic stereocentres present in 209D in one step.[28-31]

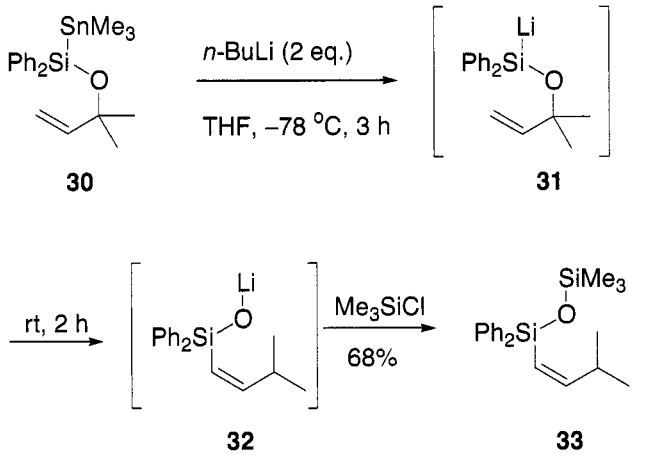


27a
27b

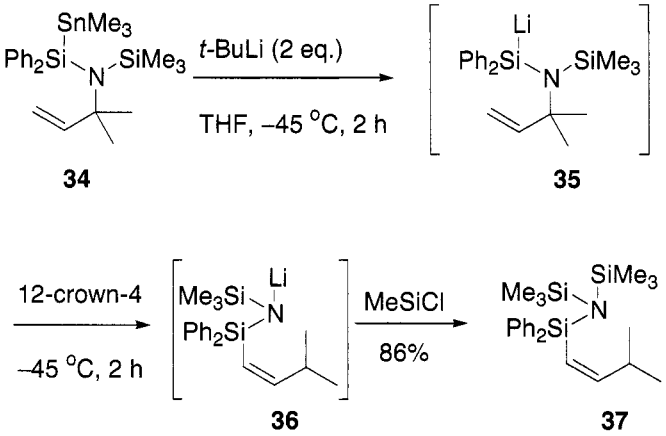
28a $R_1 = C_6H_{13}$, $R_2 = H$, 98%
28b $R_1 = C_5H_{11}$, $R_2 = CH_3$, 97%

29
The indolizidine core

Tamao and coworkers have reported the first examples of the the silicon variant of the [2,3]-Wittig rearrangement, namely [2,3]-sila-Wittig and aza-sila-Wittig rearrangements in which the allyl group migrates from an oxygen or nitrogen to silicon, shown by the transformation of **30** to **33**.[32]

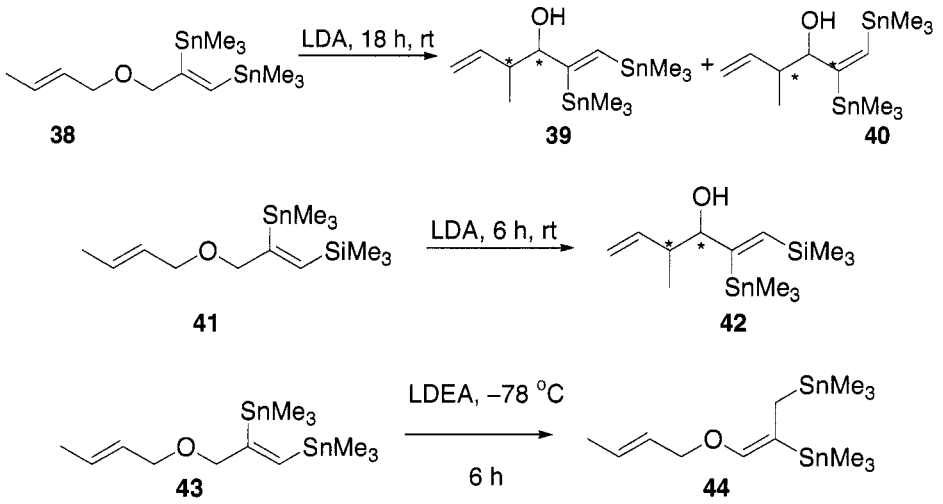


In a similar fashion, the sila-aza precursor **34** resulted in the corresponding allylsilane **37**. In both examples, the transmetalation reactions were found to be complete by trapping the silyllithiums **32** and **36** with Me_3SiCl to give the corresponding disilanes in good yields (68% and 86% respectively).



1.1.9.5 Synthetic Utility

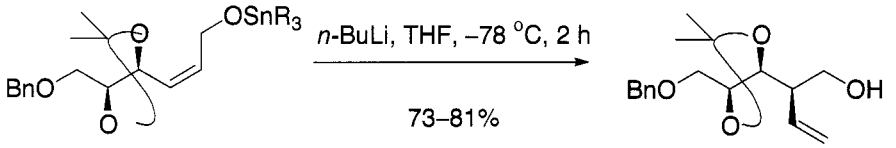
The importance of the base used in the [2,3]-Wittig reaction is made clear by the work of Mitchell and coworkers who have reported the rearrangements of silyl- and stannyl-substituted diallyl ethers. They found that the use of LDA on such substrates (**38**, **41**, **43**) leads to [2,3]-Wittig reaction while employing lithium diethylamide can result in an allyl-vinyl ether rearrangement instead.



Although the distannyl substituted diallyl ether **38** underwent the [2,3]-Wittig reaction a mixture of diastereoisomers was produced as well as *Z*/*E* isomerization, thus affording four products. The authors were able to overcome this by utilizing the corresponding silylstannylsubstituted ether **41** which gratifyingly did not undergo *Z*/*E* isomerization. However, a diastereomeric mixture was still obtained thus lessening the synthetic potential of the reaction.[33]

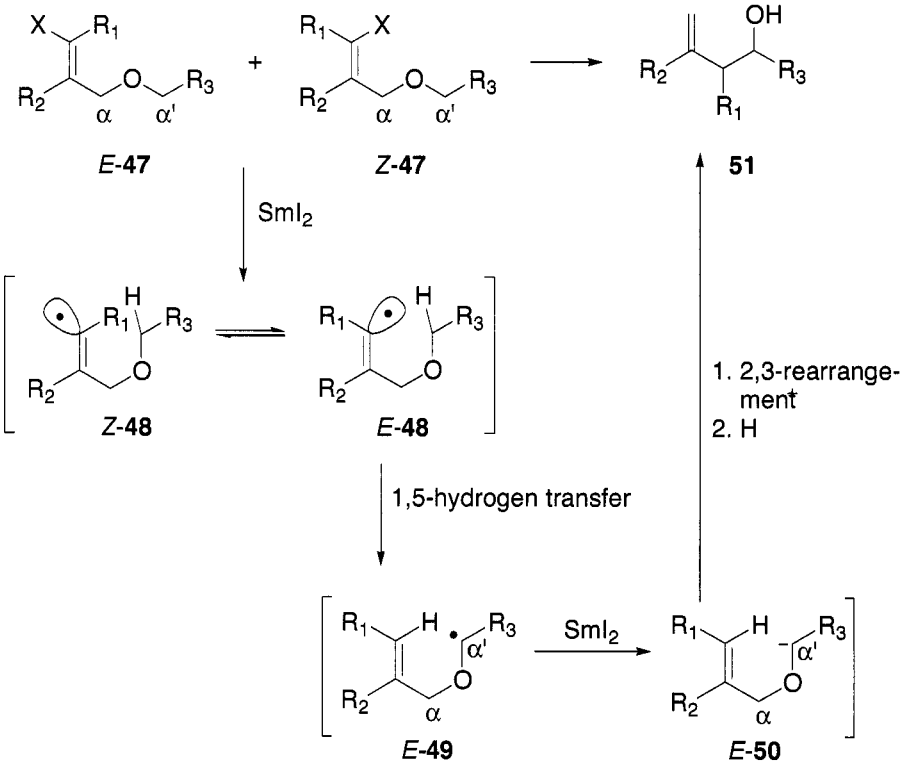
The synthetic utility of the rearrangement is limited by procedures available for generating anions at the low temperatures required to avoid the competing [1,2]-Wittig rearrangement. The most popular method is direct lithiation using lithium diisopropylamide (LDA) or butyl lithium (BuLi); this method can be used for a wide variety of substrates including allyl benzyl ethers, allyl propargyl ethers, and bis(allyl) ethers. Clearly the methods must be compatible with the rest of the molecule to avoid occurrence of side products, whilst the α-protons must be relatively acidic. Both of these criteria can be overcome by transmetallation methods.

Transmetallation can be employed in order to avoid the use of strongly basic conditions. One such variant is the [2,3]-Wittig–Still rearrangement wherein stannyl ethers can be converted to homoallylic alcohols. Several examples of this tranformation in the synthesis of amino acid components of bioactive polyoxins have been reported by Ghosh.[34–36] In their synthesis of 5-*O*-carbomylpolyoxamic acid, a bioactive amino acid nucleoside, *E*- and *Z*-allylic stannyl ethers, such as **45**, derived from an isopropylidene *L*-threitol derivative, were subjected to the [2,3]-Wittig-Still rearrangement.

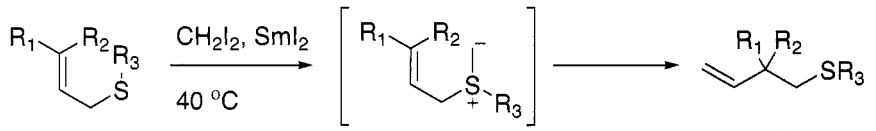


The *E*-allylic stannyl ether derivative gave better *syn*-diastereoselectivity (5.4:1) than the *Z*-isomer (2:1); this is most probably due to the competing electronically favoured and sterically favoured transition states.[9,36]

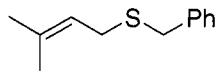
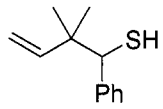
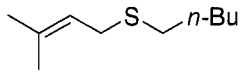
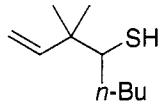
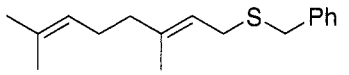
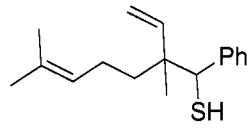
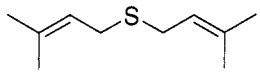
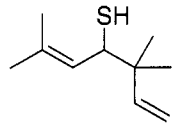
The [2,3]-Wittig rearrangement can be induced using samarium iodide *via* a 1,5-hydrogen atom transfer mechanism.[37] The mechanism begins by a single electron transfer from SmI_2 to the vinyl halide **47**. The radical then abstracts a hydrogen at the α'-carbon to the ethereal oxygen resulting in an α-allyloxy carbon radical **49** via a six-membered transition state. Reduction with SmI_2 then affords the corresponding anion **50**, which undergoes the 2,3-sigmatropic rearrangement to give homoallyl alcohol **51**.



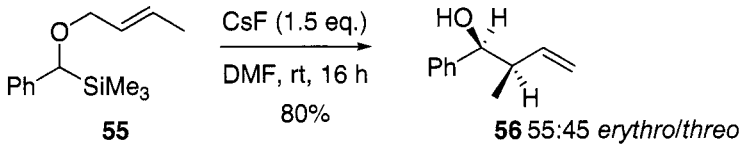
The generation of allyloxy carbanions by a net two-electron reduction of diallyl acetals **52** by SmI_2, which can then undergo a [2,3]-Wittig rearrangement has also been demonstrated.[38] Similarly, the addition of samarium carbenoids to allylic sulfides results in allylic sulfonium ylides which can then undergo the [2,3]-Wittig rearrangement. These methods are very attractive as they allow regioselective and base-free generation of the requisite carbanion species necessary for the rearrangement.[39]



52 **53** **54**

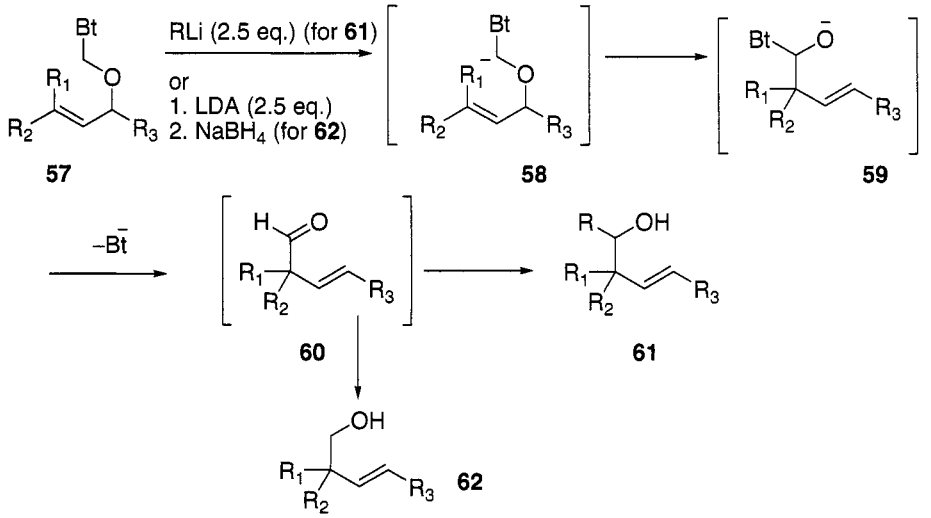
Reactant	Product	Time (min.)	Yield %
		90	97
		15	79
		15	92
		15	80

Meleczka and Geng have reported several examples of CsF and TBAF promoting the [2,3]-Wittig rearrangement of α-alkoxysilane substrates, such as **55**.[40] The authors found that TBAF was not very efficient at promoting the rearrangement and low yields were realised. However, the use of cesium fluoride gave primarily [2,3]-rearrangement products with very little, if any, contamination by [1,2]-Wittig rearrangement products. The yields were found to be comparable to analogous lithium anion-initiated rearrangements.[41,42]



55 **56** 55:45 *erythro/threo*

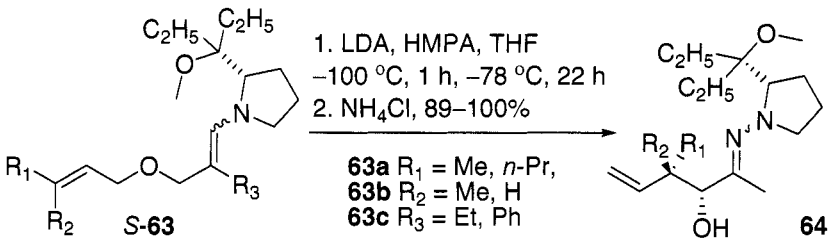
The stereocontrolled synthesis of homoallylic alcohols and unsaturated ketones *via* a benzotriazole-mediated [2,3]-Wittig rearrangement has been reported by Katritzky and coworkers.[43] This protocol can be used with a wide variety of readily available allylic alcohols **57** to give primary (**62**), secondary (**61**), and tertiary alcohols thus increasing the synthetic utility of this approach.



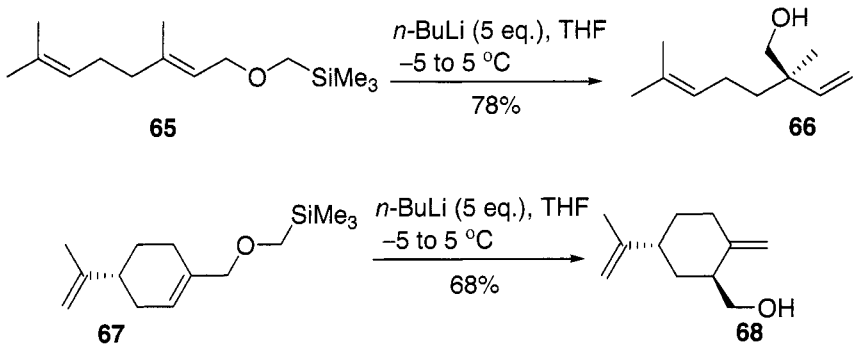
57			61		62
R_1	R_2	R_3	R	Yield %	Yield %
Me	Me	H	nBu	87	-
H	Ph	H	Me	81[a]	-
H	H	Et	-	-	56
H	H	nC_5H_{11}	-	-	60

[a]mixture of diastereoisomers 78:22

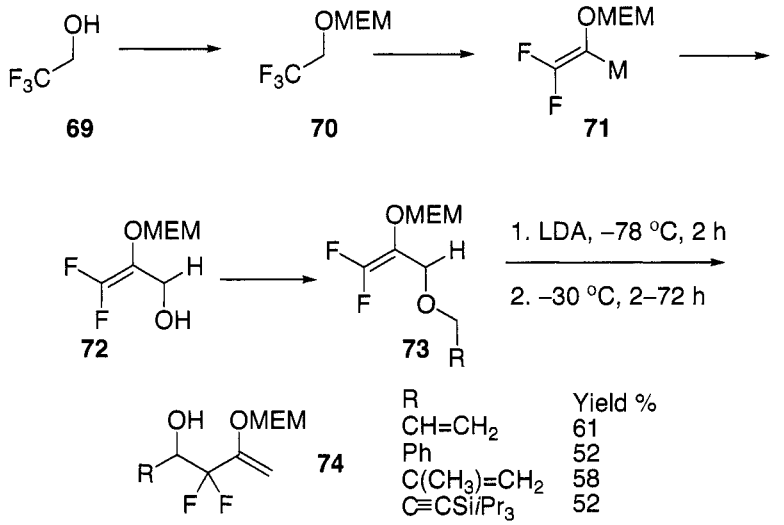
Chiral α-allyoxyhydrazones **63** have been shown to undergo asymmetric [2,3]-Wittig rearrangements with excellent yields and high *syn*-selectivities to give the corresponding α-hydroxyhydrazones **64**.[44]



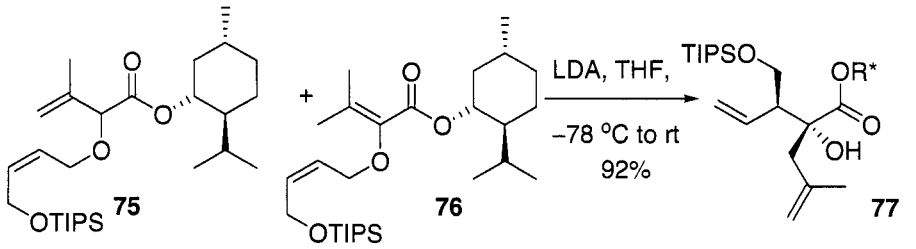
The [2,3]-Wittig rearrangement of (trialkylsilyl)methyl allyl ethers *via* the silicon-lithium exchange have been described by Mulzer and List.[45] The synthesis of the ether substrates resulted from deprotonation of the corresponding allylic alcohols with *n*-BuLi followed by addition of the (trimethylsilyl)methyl triflate. Thus, **65** and **67** were synthesised from geraniol and (*R*)-perilla alcohol, respectively. The [2,3]-Wittig rearrangement then proceeded smoothly upon treatment of the ethers with *n*-BuLi at low temperature. Alcohol **68** was obtained as a single diastereoisomer. This method alleviates the need to synthesise and use toxic stannane containing reagents.



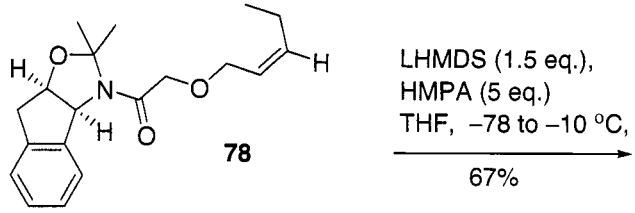
Percy and coworkers have reported the use of the [2,3]-Wittig rearrangement as a way in which to prepare highly functionalized molecules containing a mid-chain CF_2 group, **74**.[46] Ethers of difluoroallylic alcohols were synthesised in a few steps from commercially available 2,2,2-trifluoroethanol **69**.[47] These substrates **73** then underwent a [2,3]-Wittig rearrangement; thus in a few steps, synthetically useful products were obtained which can be used further in the synthesis of complex CF_2-containing unnatural targets/analogues.

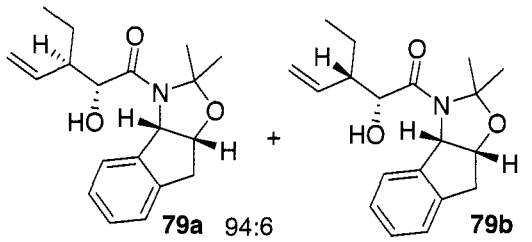


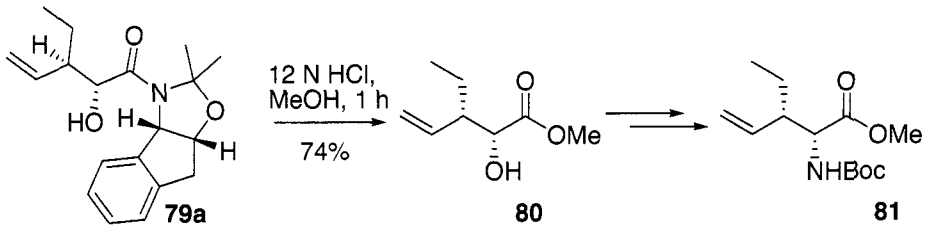
Hiersemann has reported the synthesis of 2-hydroxy-γ-lactones **77** by the [2,3]-Wittig rearrangement of ester dienolate substrates **75** and **76**. The products of the rearrangements were required as substrates for 3-oxy-Cope rearrangements, ultimately leading to the stereoselective synthesis of non-natural amino acids.[48]



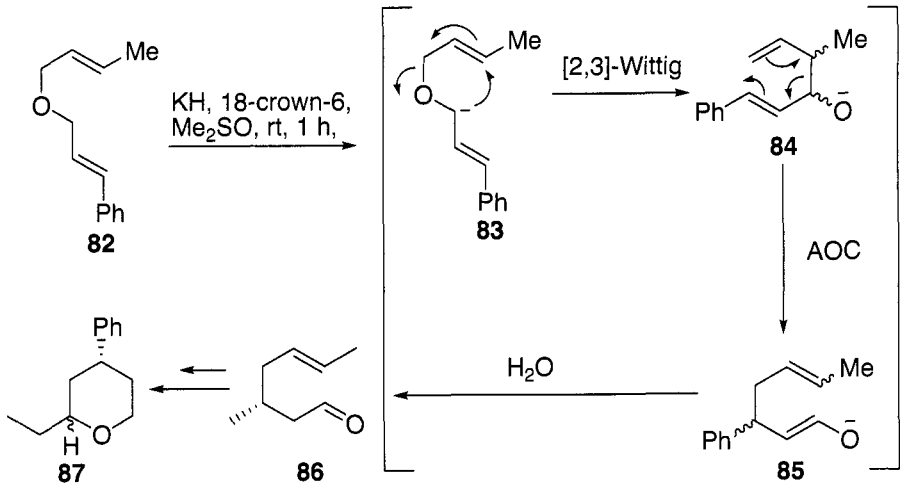
In a similar fashion, the [2,3]-Wittig rearrangement of amide enolates **78** can be carried out leading to α-hydroxy acids **79a** and **79b**, which can then be transformed into functionalized amino acids **81**.[49] The use of (1*S*,2*R*)-1-amino-indan-2-ol as a chiral auxillary for controlling the stereochemical outcome of the reaction was aptly demonstrated.



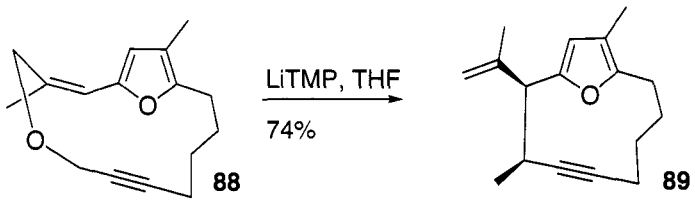




The synthesis of substituted tetrahydropyrans **87** *via* a stereoconvergent one-pot tandem [2,3]-Wittig-anionic oxy-Cope rearrangement has been reported by Greeves and coworkers.[50,51] If the alkyl group R is branched, for example, *t*-Bu or *i*-Pr, *E* geometry is obtained exclusively.[52] Reduction of the resulting aldehyde **86**, followed by stereoselective cyclisation, then reductive removal of the electrophile led to single diastereoisomers of the desired tetrahydropyrans. Trisubstituted *γ*-lactones can be synthesised if the [2,3]-Wittig-anionic oxy-Cope rearrangement aldehyde is oxidised then submitted to the procedure as above.[53]



In their synthesis of the pseudopterane 2,5-furanocyclic ring system, Marshall and Yu employed the [2,3]-Wittig reaction as a method for the ring contraction of bridged furan and dihydrofuran propargylic ethers, for example **88**.[54] After optimisation, an excellent yield of 73% was obtained with the product **89** as a single diastereoisomer. No other products were detected by TLC analysis of the reaction mixture. The racemic total synthesis of the pseudopterane (±)-kallolide B was subsequently reported using this protocol, followed by a enantioselective synthesis of the unnatural (–)-kallolide B.[55–57]

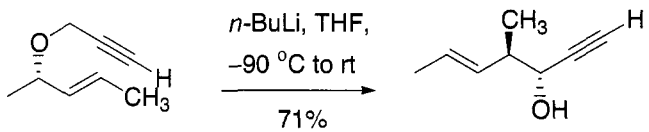


88 **89**

1.1.9.6 Experimental

[2,3]-Wittig rearrangement

(3*R*,4*R*)-4-Methylhept-5(*E*)-en-1-yn-3-ol[58]

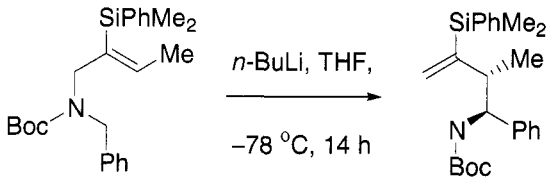


90 **91**

An aliquot of *n*-butyllithium in hexane (5.1 mL, 12.8 mmol, 2.4 M in hexanes) was evaporated *in vacuo* and the residue cooled to –90 °C. A solution of (*S*)-*trans*-2-(2-propynyloxy)-3-pentene **90** (454 mg, 3.66 mmol) in 10 mL of THF was slowly added. After the mixture was allowed to warm to room temperature overnight, the reaction was quenched with aqueous NH_4Cl. Extraction with Et_2O, drying, evaporation of the solvent, and purification of the residue on a silica gel column (5% Ethyl acetate/hexane) gave of (3*R*,4*R*)-4-methylhept-5(*E*)-en-1-yn-3-ol **91** as a colourless oil (322 mg, 71%).

Aza-[2,3]-Wittig rearrangement

(1*S*, 2*R*)-*N*-*tert*-Butoxycarbonyl-2-methyl-1-phenyl-3-(phenyldimethyl-silyl)-but-3-enylamine[27]



92 **93**

n-Butyllithium (0.66 mL of 1.7 mmol, 1.2 eq. 2.M in hexanes) was added dropwise to a stirred solution of (*Z*)-*N*-*tert*-butoxycarbonyl-*N*-[2-(phenyldimethylsilyl)but-2-enyl]-benzylamine **92** (0.55 g, 1.4 mmol) in THF (11 mL) at −78 °C. After stirring for 14 h at −78 °C, the reaction was quenched by the addition of methanol (0.1 mL) and warmed to room temperature. The reaction mixture was then partitioned between saturated aqueous sodium hydrogen carbonate (20 mL) and diethyl ether (15 mL), the organic layer was separated and the aqueous layer further extracted with diethyl ether (3 × 15 mL). The combined extracts were dried over magnesium sulfate and concentrated in vacuo to give a viscous pale yellow oil (0.63 g) which was purified by flask column chromatography (7% ethyl acetate-light petroleum) to give the title compound **93** as a colourless oil (0.44 g, 81%).

1.1.9.7 References

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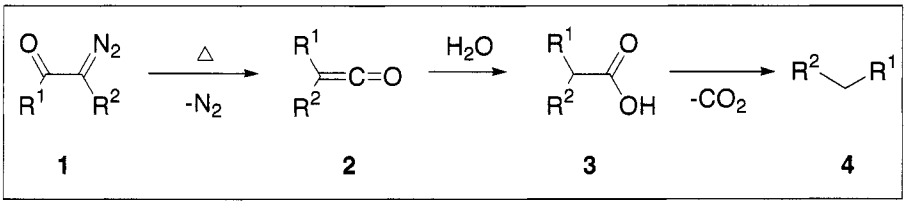
1.1.10 Wolff Rearrangement

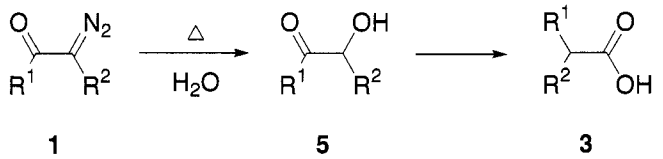
Raju Ranjith Kumar and Marudai Balasubramanian

1.1.10.1 Description

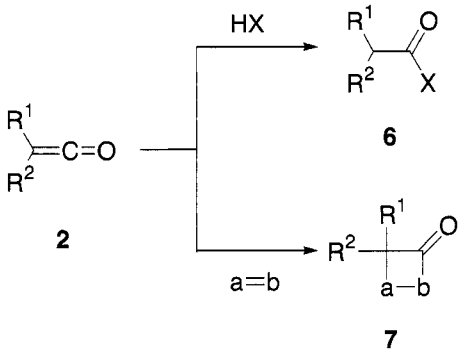
The formation of ketenes **2** from α-diazoketones **1** with the loss of nitrogen is known as Wolff rearrangement. The ketenes **2** afford carboxylic acids **3**, which upon decarboxylation give **4**.[1–13]



Initially, Wolff proposed that the α-diazoketones **1** afforded the alcohol **5**, which underwent double migration to form the acid **3**.[1] The involvement of ketene **2** as intermediate in this reaction was proposed by Schroter in 1909.[4]



Ketenes **2** are highly reactive and react either with nucleophiles to give carboxylic acid homologues **6** or undergo [2+2] addition with olefins to give **7**.



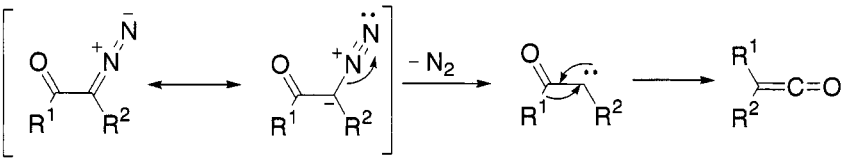
1.1.10.2 Historical Perspective

Ludwig Wolff (1857–1919) was born in Neustadt in the Palatinate and was educated at the University of Würzburg and Munich Polytechnic. In 1891, he became Professor of Analytical Chemistry at Jena, where he worked with Ludwig Knorr. His name is associated with the Wolff-Kishner reaction (1911) and the Wolff rearrangement (1912).

1.1.10.3 Mechanism

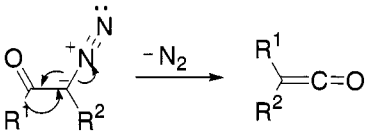
Wolff rearrangement of α-diazoketones to carboxylic acid derivatives proceeds *via* ketenes under photochemical, thermal or metal ion catalysis.[1–13] The extrusion of nitrogen and the 1,2-shift can occur either in a stepwise manner *via* a carbene intermediate **8** or through a concerted process.

(i) Stepwise mechanism



1 **8** **2**

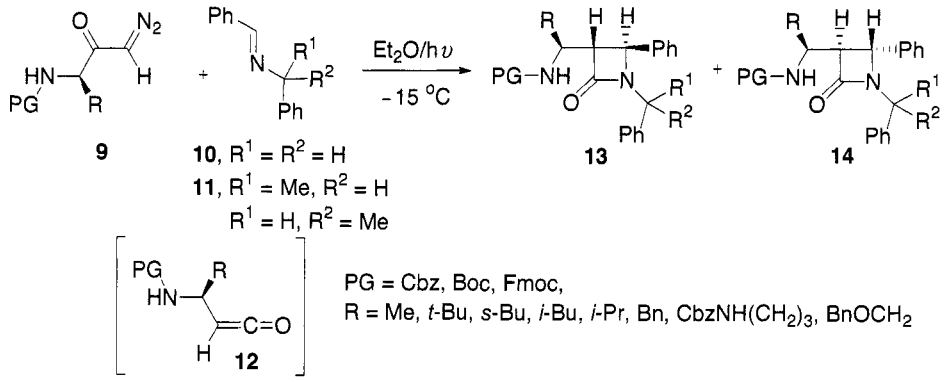
(ii) Concerted pathway



2

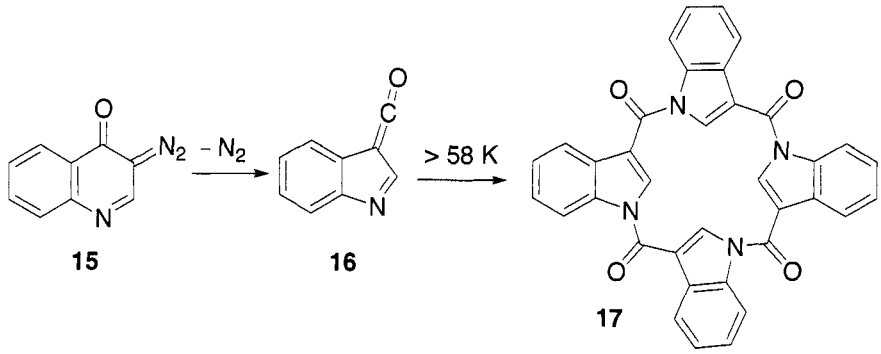
1.1.10.4 Variations and Improvements

The photochemical Wolff rearrangement of diazoketones **9** derived from protected amino acids led to the ketene intermediates **12**, which were trapped with *N*-benzylbenzaldimines **10** and **11** to afford β-lactams **13** and **14**.[14] Of the four possible diastereomers, only two were formed exclusively. The selectivity of this reaction depends on the bulkiness of the amino acid.



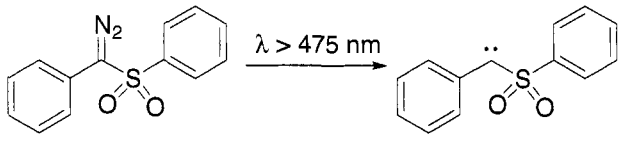
9 10, $R^1 = R^2 = H$; 11, R^1 = Me, $R^2 = H$; $R^1 = H$, R^2 = Me; 12; 13; 14

The ketene **16** generated by matrix photolysis of diazoketones **15** at low temperature tetramerized efficiently to give the porphyrin analog **17**.[15]

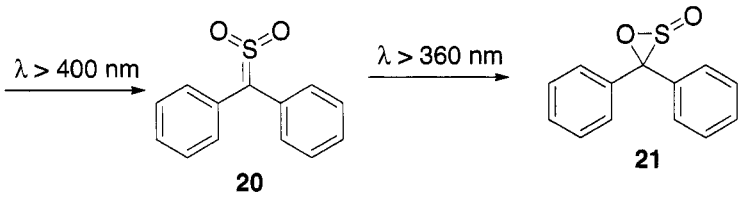


15 16 17

Photolysis of **18** with $\lambda > 475$ nm at 10 K in solid argon afforded carbene **19** as the major product along with a small amount of **20**. A photo induced hetero Wolff rearrangement of **19** was observed upon irradiation at λ 400 nm to give the sulfene **20**.[16] Further irradiation of **20** with $\lambda > 360$ nm afforded diphenyl-α-sultine **21**.

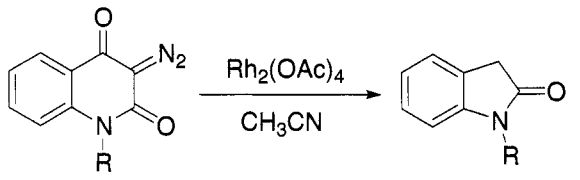


18 19



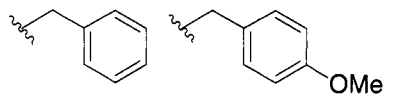
20 21

The diazoquinolinediones **22** were synthesized from the corresponding 4-hydroxy-2-quinolones through a diazotransfer reaction with mesyl azide. The rhodium(II) catalyzed Wolff rearrangement of the diones **22** in refluxing acetonitrile afforded oxindole derivatives **23** as a single product.[17]

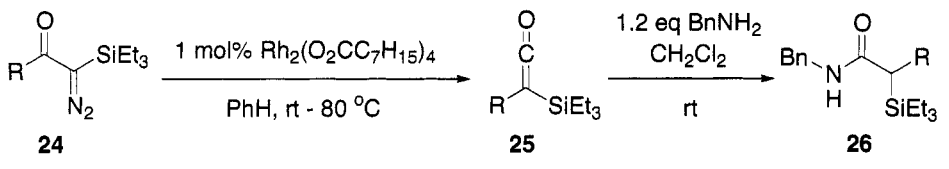


22 **23**

R = H, CH_3, CH_2CH_3, $(CH_2)_2CH_3$

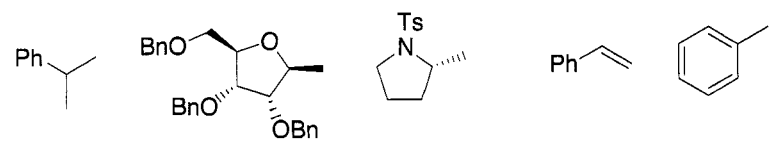


Wolff rearrangement has also been applied for the synthesis of silylketenes **25** from silyl diazoketones **24**.[18] The ketenes **25** upon further reaction with $BnNH_2$ afforded the corresponding α-silyl benzylamides **26** in good yields.

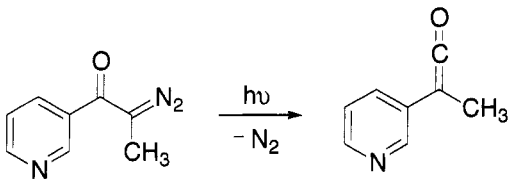


24 **25** **26**

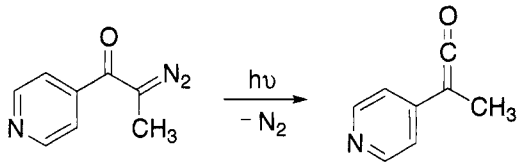
R = C_7H_{15},



The photo Wolff rearrangement of 3- and 4-substituted pyridyl α-diazoketones **27** and **29** to yield pyridylketenes **28** and **30** was effected by irradiation at wavelengths of 300–400 nm.[19]

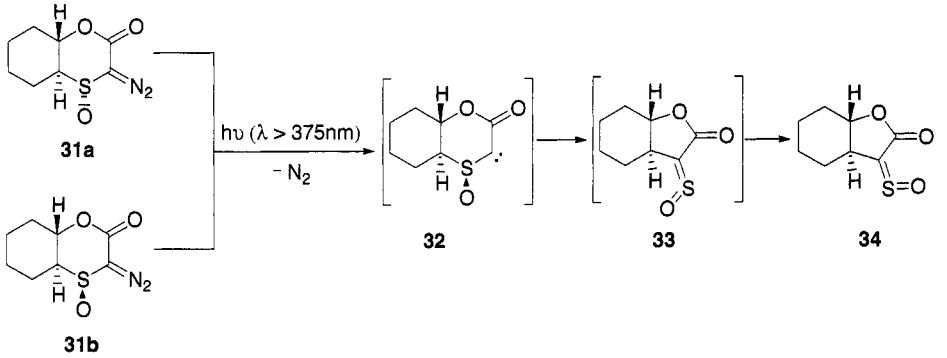


27 28



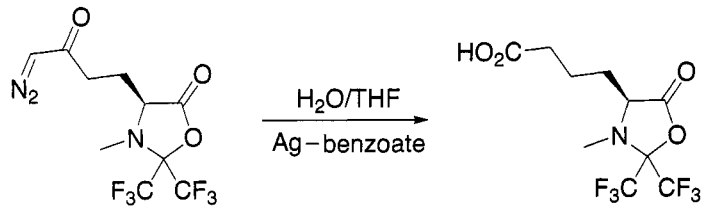
29 30

Irradiation at $\lambda > 375$ nm of the two diastereomeric diazo sulfoxides **31a** and **31b** underwent hetero Wolff rearrangement affording the α-oxo sulfine **34**. The carbene **32** has not been detected even in traces and the sulfine **34** is proposed to be formed from **31**, *via* dediazotization, hetero Wolff rearrangement and isomerization of domino sequence.[20]



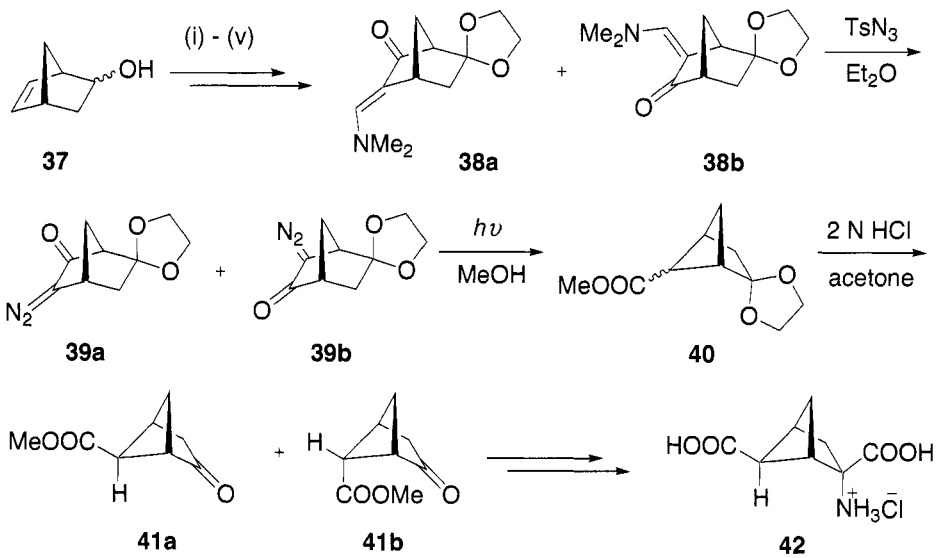
31a 31b 32 33 34

The base-free Ag^+ catalyzed Wolff rearrangement of 5-diazo-4-oxonorleucine **35** afforded the carboxylic acid **36** at room temperature on sonication using an ultrasound cleaning bath.[21]



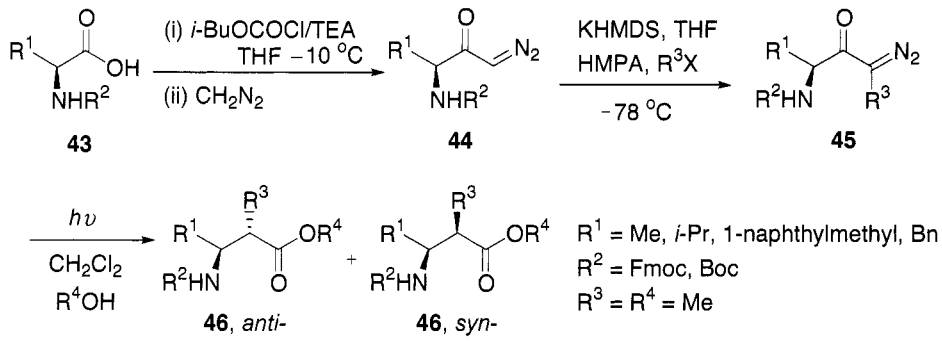
35 36

The 5-norbornen-2-ol **37** upon Swern oxidation and protection as ethylene ketal followed by introduction of second carbonyl via hydroboration of the double bond and oxidation with PCC afforded a mixture of ketones, **38a** and **38b**. These ketones were converted into a mixture of the corresponding α-diazo compounds **39a** and **39b** by alkylation with Bredereck's reagent followed by reaction with *p*-toluenesulfonyl azide. The α-diazo ketones **39** under Wolff rearrangement conditions underwent ring contraction furnishing **40** in an *endo*:*exo* ratio of 87:13, explicable to the preferred attack of methanol from the less hindered face of the ketene intermediate.[22] The *endo-exo* mixture **40** was hydrolyzed to afford the ketones **41a** and **41b**, which were separated through column chromatography. The exo isomer has been employed as the key intermediate for the synthesis of ABHxD-I (**42**), a potent mGluR agonist.



(i) Swern oxidation; (ii) $HOCH_2CH_2OH$, TsOH, toluene, reflux; (iii) BH_3•THF; (iv) PCC, CH_2Cl_2, reflux; (v) $(Me_2N)_2CHOt$-Bu

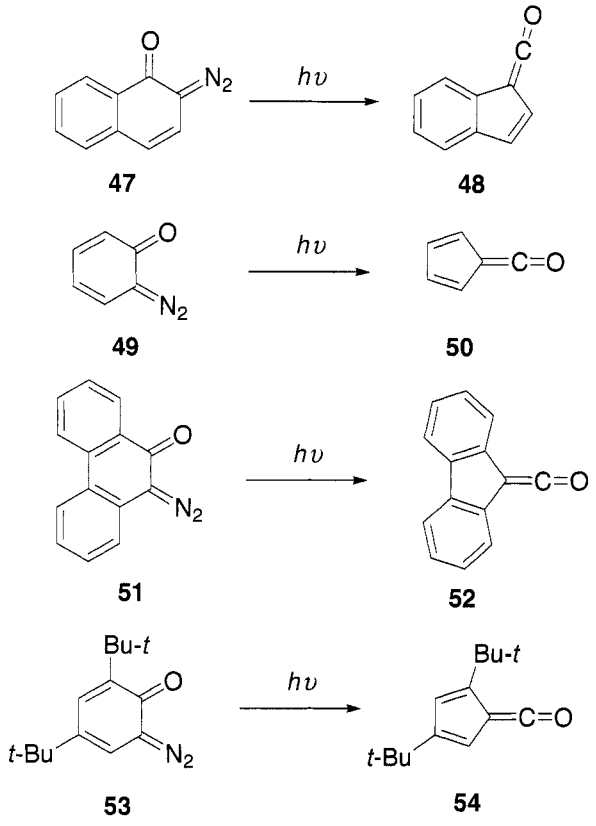
α-Alkyl-α-diazoketones **45** were obtained from the corresponding α-amino acids **43** in a two step sequence comprising diazocoupling followed by alkylation. The Wolff rearrangement of **45** was effected using UV light at –78 °C in dichloromethane affording the intermediate ketenes, which were trapped with suitable alcohols to furnish the α-methyl-β-amino acid derivatives **46**.[23] The stereochemistry of the major isomer was found to be anti by X-ray crystallographic study.



43 44 45

46, *anti*- 46, *syn*-

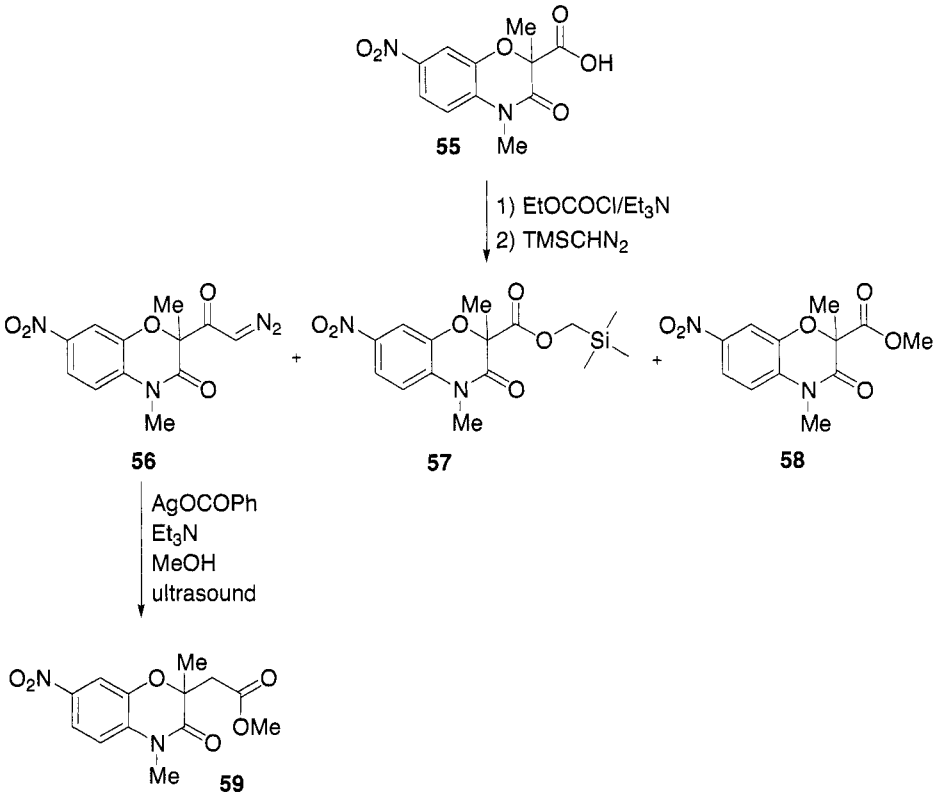
Photochemical Wolff rearrangement of 6-diazo-cyclohexadienones **47**, **49**, **51** and **53** led to the formation of 2,3-benzopentafulvenone **48**, pentafulvenone **50**, dibenzopentafulvenone **52** and 2,4-di-*tert*-butylpentafulvenone **54** respectively.[24]



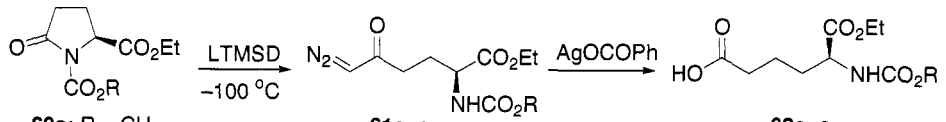
47 48 49 50 51 52 53 54

The benzoxazine **55**, a useful template for designing peptidomimetics, was converted to the diazoketone **56** in high yield by treatment with

ClCOOEt/Et_3N and two equiv. of $TMSCHN_2$. Apart from the diazoketone **56**, trimethylsilylmethyl ester **57** and methyl ester **58** were also formed as by-products, which did not exceed 10%. Ultrasound promoted Ag^+/base catalyzed Wolff rearrangement of the diazoketone **56** in methanol afforded the methyl ester **59**.[25] The ester by-products from the first step did not interfere in the rearrangement step.



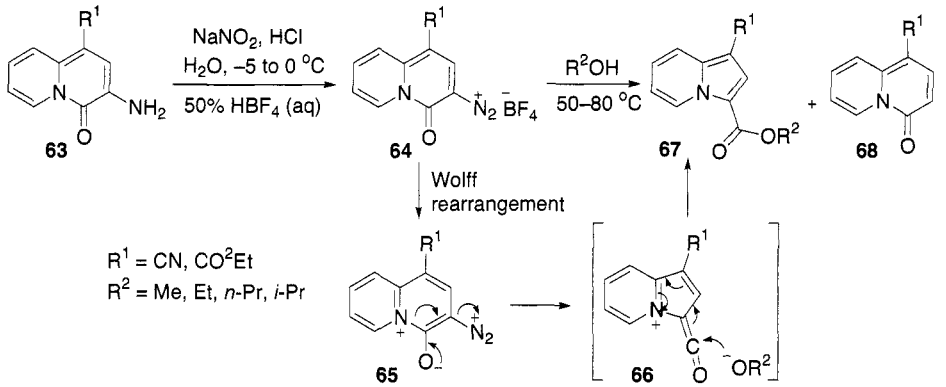
The ring-opening of *N*-alkoxycarbonylpyroglutamic acid esters **60** by lithium trimethylsilyldiazomethane at < -100 °C afforded diazo-norleucinates **61** with minimum formation of polymeric by-products. The Wolff rearrangement of **61** in the presence of silver benzoate in aqueous dioxane at 70 °C for 6 h led to the *N*-Boc α-ethyl ester of α-aminoadipic acid **62**. With the use of ultrasound, the reaction proceeded at ambient temperature furnishing good yields of **62a–c**.[26]



60a: R = CH_3
60b: R = $C(CH_3)_3$
60c: R = 9-fluorenylmethyl

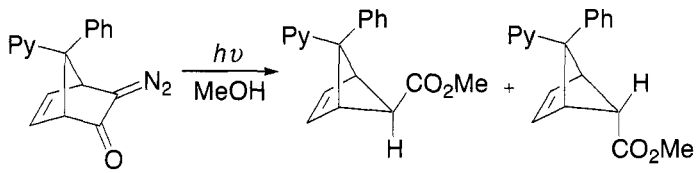
61a–c **62a–c**

The 3-diazoniumtetrafluoroborates **64** were obtained in good yields via nitrosation of 3-aminoquinolizines **63**. Treatment of **64** with anhydrous alcohol afforded a mixture of alkyl indolizine-3-carboxylates **67** and the 3-unsubstituted 4*H*-quinolizin-4-ones **68**. The product selectivity of this reaction depends upon the alcohol. The formation of indolizine **67** has been regarded as an aza Wolff rearrangement through ring contraction via **65** and **66**.[27]

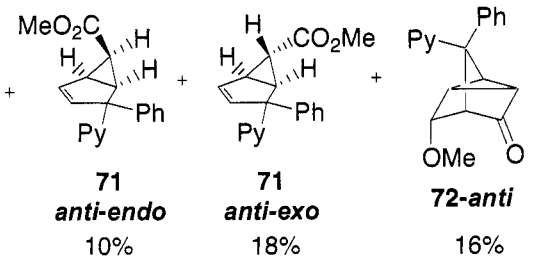


63 **64** **67** **68** **65** **66**

The Wolff rearrangement of *anti*- and *syn*- dehydronorbornyl compounds **69** in methanol resulted in the formation of unexpected rearranged products **70–72**.[28] The photolysis of **69**-*anti* gave five isomers *viz.* **70**-*anti-exo*, **70**-*anti-endo* and the unexpected products **71**-*anti-endo*, **71**-*anti-exo* and **72**-*anti*. The diazo ketone **69**-*syn* led to two abnormal Wolff products **71** and **72** in addition to the expected Wolff rearrangement product.



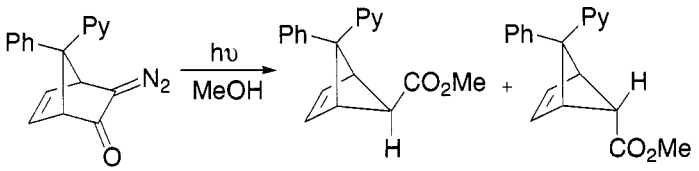
69-*anti* **70 *anti-exo*** 29% **70 *anti-endo*** 5%



71 ***anti-endo*** 10%

71 ***anti-exo*** 18%

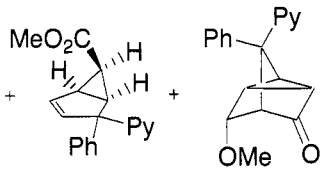
72-*anti* 16%



69-*syn*

70 ***syn-exo*** 23%

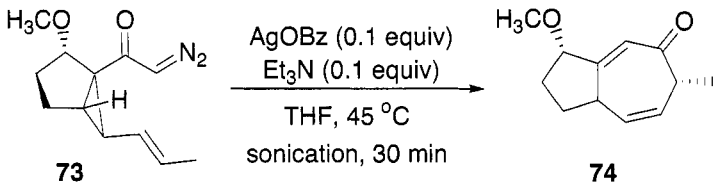
70 ***syn-endo*** 11%



71 ***syn-endo*** 43%

72-*syn* 8%

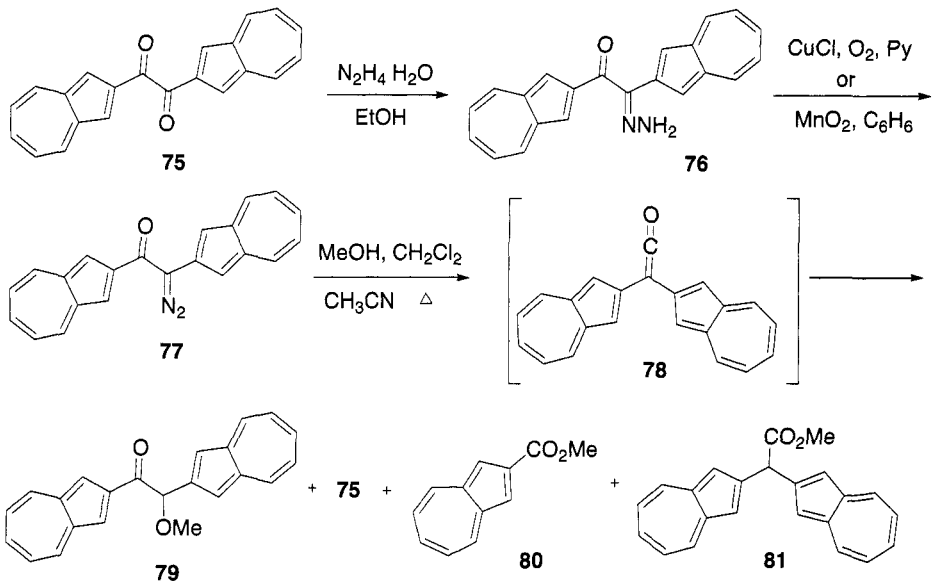
Sarpong *et al.*[29] reported a facile tandem Wolff-Cope rearrangement for the synthesis of fused carbocyclic skeletons. Treatment of diazo ketone **73** under modified Montero conditions employing AgOBz and Et_3N at 45 °C in THF with sonication for 30 min led exclusively to the desired Wolff-Cope rearrangement product **74** in 95% isolated yield.



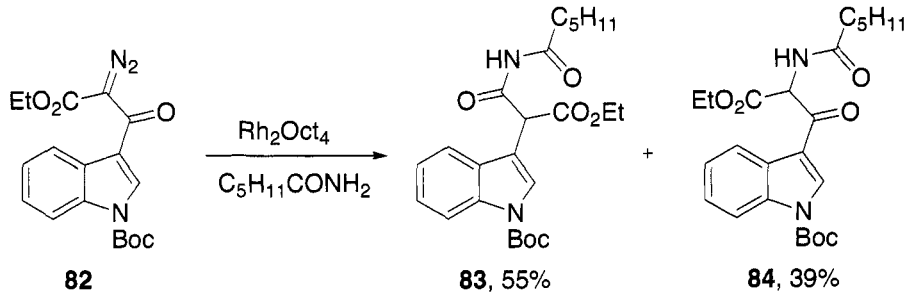
73 **74**

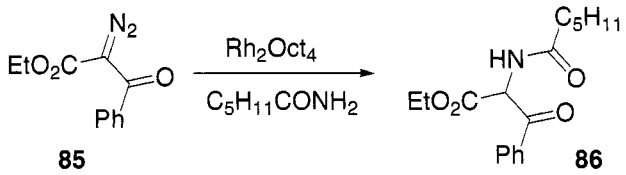
The reaction of diketone **75** with hydrazine afforded the monohydrazone **76**, which was further oxidized with copper(I) chloride, O_2 and pyridine or activated manganese dioxide to give the α-diazo ketone **77**. Thermal decomposition of **77** in methanol gave 2-azuloin methyl ether **79**,

methyl 2-azulenecarboxylate **80** and methyl di(2-azulenyl)acetate **81** via the Wolff rearrangement. The Wolff rearrangement presumably proceed via the ketene **78**.[30]



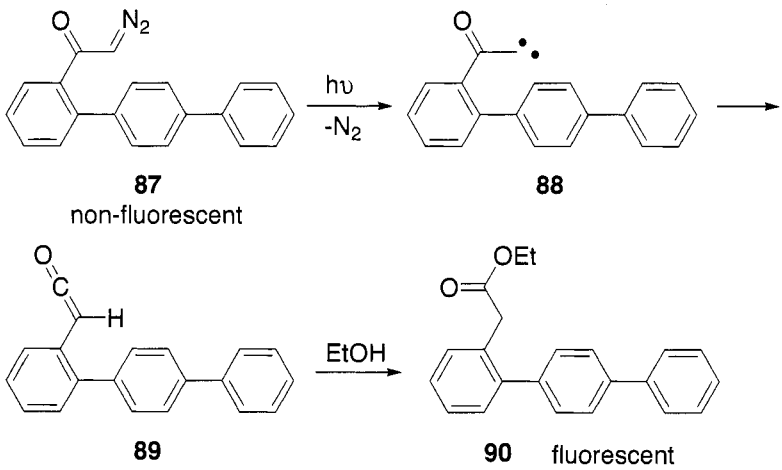
Dirhodium(II)-catalyzed reaction of 3-indolyl α-diazo-ketoester **82** in the presence of hexanamide afforded the Wolff rearrangement product **83** along with the formation of metal carbene N–H insertion product **84**.[31] It has been shown that the indole moiety is more prone to 1,2-rearrangement than the phenyl diazoketoester **85**, which led to the formation of N–H insertion product **86** exclusively under similar conditions.





85 **86**

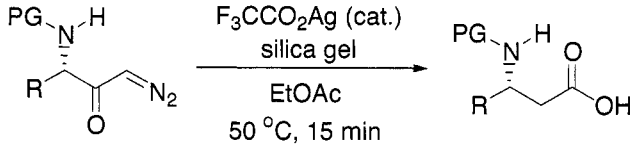
Two-photon induced Wolff rearrangement of a terphenyl diazo ketone **87** by focused laser pulses of 532 nm, furnished the ester derivative **90** via **88** and the ketene **89**. The diazo ketone a non-fluorescent compound, was converted to a fluorescent ester.[32]



87 non-fluorescent **88**

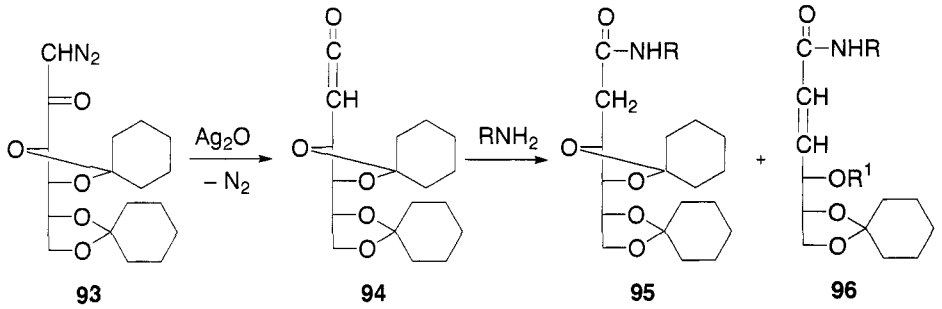
89 **90** fluorescent

The Wolff rearrangement of *N*-protected α-amino diazoketone **91** in the presence of silica gel and a catalytic amount of silver trifluoroacetate led to the formation of the *N*-protected acid **92**.[33]

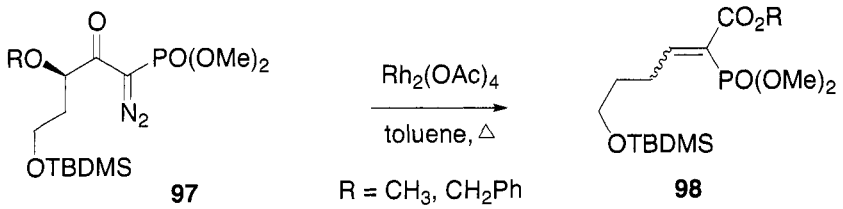


91 PG = Fmoc, Boc **92**
R = Me, *i*Pr, *i*Bu, *s*Bu, *t*Bu, Bn

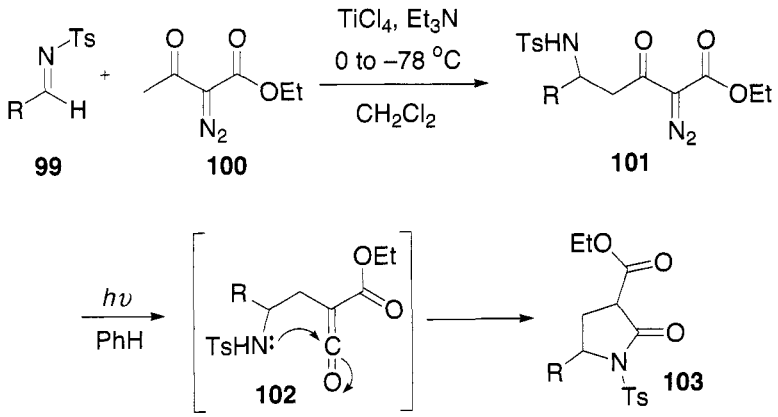
The Wolff rearrangement of 1-deoxy-1-diazo-3,4,5,6-di-*O*-cyclohexylidene-*D*-arabinohexulose **93** in the presence of ammonia and silver(I) oxide afforded 2-deoxyhexonamide **95**, whereas the reaction with benzylamine and *para*-substituted anilines resulted in the preferential formation of *N*-substituted 2,3-dideoxy-2-hexenonamides **96**.[34]



The diazo ketone **97** upon refluxing in toluene in the presence of Rh(II) catalyst underwent Wolff rearrangement to give *E/Z* mixture of ester **98**. The ester **98** results from the attack by the oxygen atom of the methoxy or the benzyloxy group on the ketene resulting from the Wolff rearrangement and β-elimination.[35]



The δ-*N*-tosylamino substituted α-diazo-β-keto carbonyl compounds **101** were obtained from the reaction between diazo ketone **100** and the tosylimine **99** in the presence of $TiCl_4$ in dichloromethane. The diazo ketone **101** underwent Wolff rearrangement in benzene upon irradiation with a high-pressure Hg lamp to afford **102**, which subsequently cyclized to give the expected γ-lactam derivatives.[36]

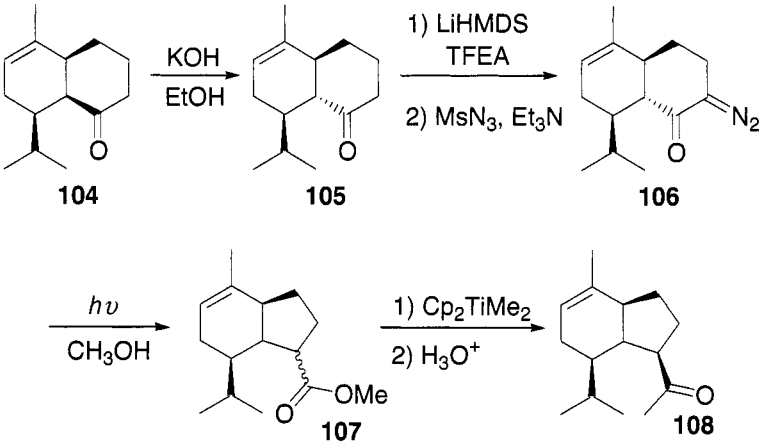


R = C_6H_5, *o*-MeC_6H_4, *p*-ClC_6H_4, 2-furyl, *n*-hexyl, *i*Bu

1.1.10.5 Synthetic Utility

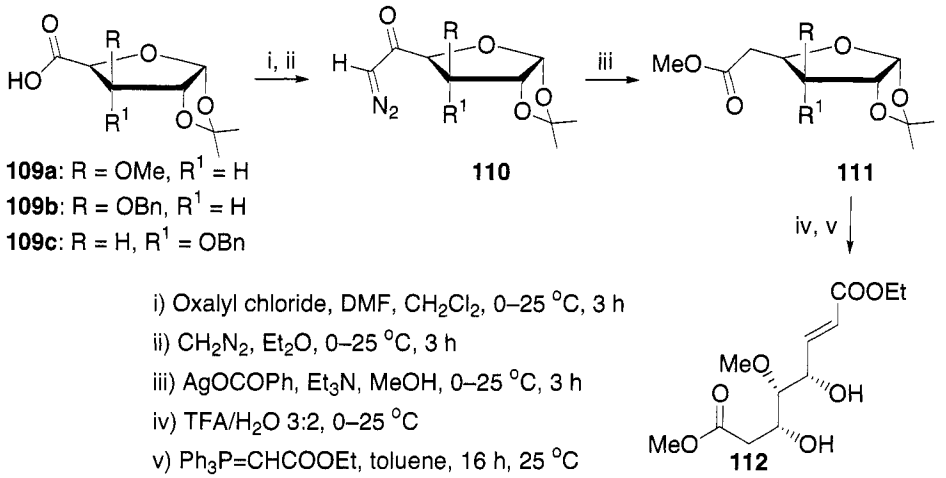
Synthesis of (±)-α-oplopenone.

Epimerization of the *cis*-ketone **104** gave predominantly the *trans*-ketone **105**, which was converted into diazoketone **106** in the presence of MsN_3 and triethylamine. The diazoketone **106** underwent Wolff rearrangement to afford the methyl ester **107**, which was converted to (±)-α-oplopenone **108** as a 4:1 mixture of diastereoisomers by methylenation and concomitant treatment of the product with aqueous acid.[37]



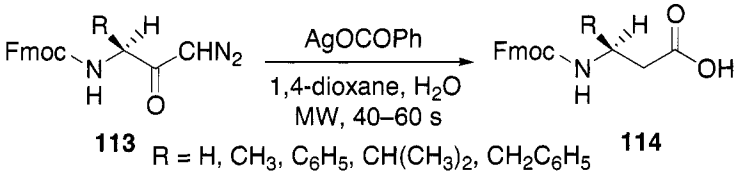
Synthesis of the right wing of carbonolide B.

The furanuronic acids **109**, obtained from *D*-glucose and *D*-mannose, were converted to the acid chloride by treatment with oxalyl chloride in dichloromethane. This acid chloride was treated with diazomethane in ether to afford the α-diazoketone **110**, which upon silver benzoate catalyzed Wolff rearrangement in the presence of triethylamine in dry methanol afforded the rearranged product **111**. Hydrolysis of **111** followed by Wittig olefination gave the α,β-unsaturated ester **112**, which served as a precursor for the synthesis of the right wing segment of carbonolide B, the aglycone of the 16 membered macrolide antibiotic carbomycin B.[38]



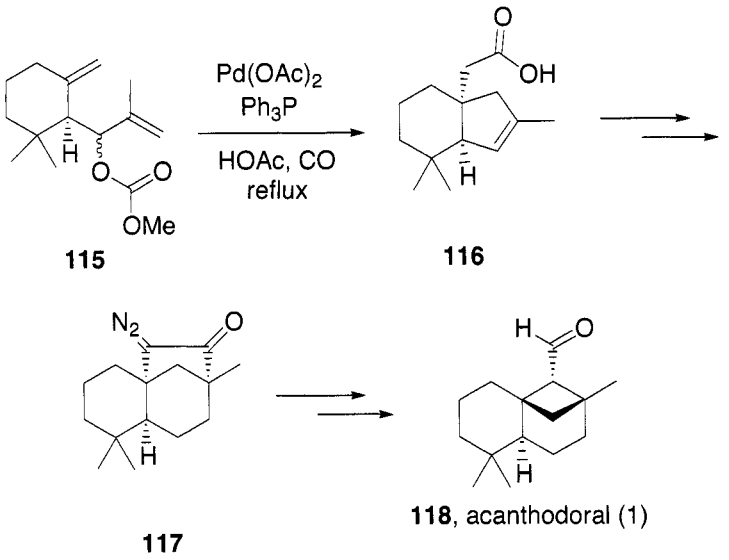
Synthesis of Fmoc-β-amino acids.

The Wolff rearrangement of diazoketones **113** in the presence of silver benzoate in 1,4-dioxane-water (7:3) under microwave exposure for 40-60 sec using an unmodified domestic microwave oven afforded the Fmoc-β-amino acids **114** in excellent yields (91–95%).[39]



Synthesis of (+)-acanthodoral

The first total synthesis of the antibiotic acanthodoral (1) **118** has been achieved from 3-methyl-2-cyclohexen-1-one in 19 steps in 2.1% overall yield. This synthesis involves the use of a Pd-ene reaction in the presence of CO to form the endocyclic alkene **116**, a nonreductive acyl radical cyclization and ring contraction by the Wolff rearrangement of **117**.[40]



115 **116**

117 **118**, acanthodoral (1)

1.1.10.6 Experimental

To a solution of α-diazo ketone **110a** (0.75 g, 3.1 mmol) in anhydrous MeOH (12 mL) was added drop-wise a solution of silver benzoate (150 mg, 0.62 mmol) in Et_3N (1.5 mL) at r.t. (25 °C) under N_2 atm. The mixture was stirred at the same temperature for 2.5 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography to give **111a** as a colorless liquid.[38]

1.1.10.7 References

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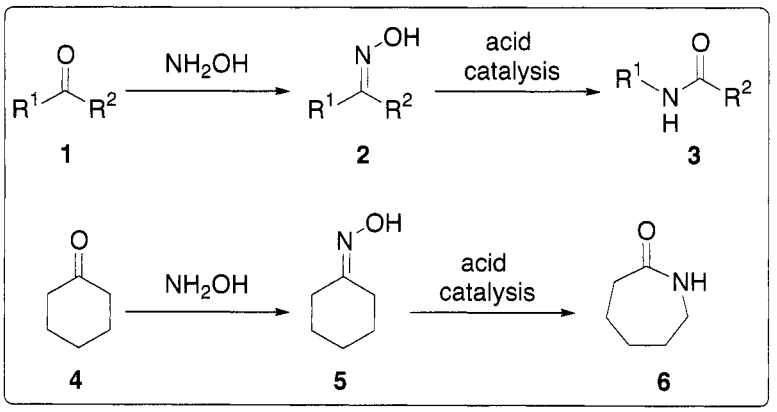
1.2.1 Beckmann Rearrangement

Raju Ranjith Kumar, K. Angaiyarkanni Vanitha and Marudai Balasubramanian

1.2.1.1 Description

The acid-catalyzed rearrangement of an oxime **2** to an amide **3** is named after the German chemist Ernst Otto Beckmann.[1–40] The rearrangement of cyclic oxime **5** results in ring expansion affording lactam **6**, which is a reaction performed on an industrial scale since the product is used as a monomer for manufacturing synthetic fibers. The catalyst employed for Beckmann rearrangement includes sulfuric acid, formic acid, liquid sulfur dioxide, silica gel, polyphosphoric acid, acetic acid, hydrochloric acid and acetic anhydride. Reagents like phosphorous pentachloride and thionyl chloride initially convert the hydroxyl group of the oxime **2** into a good leaving group. Substituents R^1 and R^2 at the oxime can be H, alkyl or aryl. The oximes can be obtained from the reaction of either aldehydes or ketones with hydroxylamine.



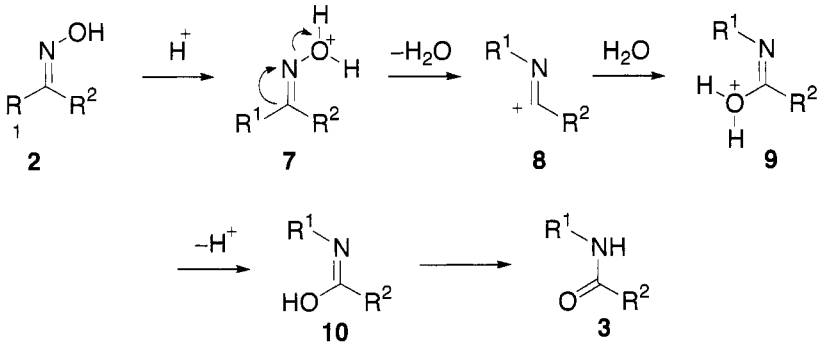
1.2.1.2 Historical Perspective

Ernst Otto Beckmann was born in Solingen, Germany on July 4, 1853 to a family headed by Johannes Friedrich Wilhelm Beckmann. At the age of 17, Beckmann was persuaded by his father to study pharmacy by arranging an apprenticeship at Elberfeld in 1870. In 1874 Beckmann joined the school of Remigius Fresenius in Wiesbaden, and moved to the University of Leipzig the following year when Fresenius became a Professor there. At Leipzig, Beckmann came into contact with the renowned chemist Hermann Kolbe. Although Beckmann wanted to study chemistry, he finished his studies with

Fresenius, passing his pharmacy examination in 1877. He then joined Kolbe, and his assistant, Ernst von Meyer, and started work on the oxidation of dialkyl sulfides. For this research Beckmann received his PhD in July 1878. Beckmann tried to apply an already-known reaction to discriminate between aldehydes and ketones. This reaction involved the use of hydroxylamine to convert benzophenone into an oxime. Treating this oxime with phosphorus pentachloride he converted it into a substance already characterized by Wallach. This reaction is now known as the Beckmann rearrangement.

1.2.1.3 Mechanism

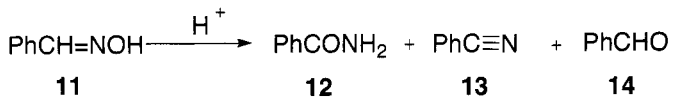
Initially, the hydroxyl group of the oxime **2** is protonated upon treatment with a protic acid to give the oxonium ion **7**. The migration of R^1 and loss of a water molecule occur simultaneously to afford the cation **8**, which reacts with water to give the iminol **10**. In general the substituent *trans* to either the hydroxyl or the leaving group migrates. Tautomerization of **10** results in the more stable amide **3**.



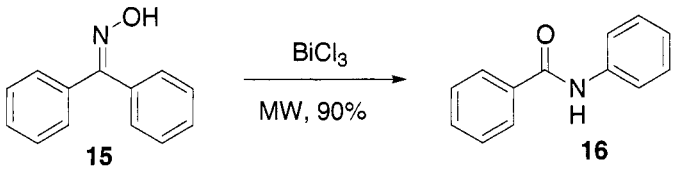
1.2.1.4 Variations and Improvements

(i) Microwave-assisted Beckmann rearrangement

Loupy *et al.*[41] reported the Beckmann rearrangement of benzaldehyde oxime **11** in the presence of different acidic catalysts such as SiO_2, Al_2O_3, K-10 clay, KSF, TsOH, $ZnCl_2$ and $SnCl_2$ under focused microwave irradiation. Best results were observed when $ZnCl_2$ was used as the acidic agent affording 92% yield of the rearrangement product **12**.

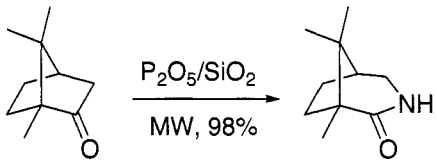


Benzophenone oxime **15** underwent the Beckmann rearrangement to afford amide **16** under microwave irradiation in the presence of bismuth trichloride within 8 min.[42] Aluminum trichloride afforded the product **16** in 15 min. under the same condition.



15 **16**

The one pot synthesis of amide **18** was accomplished within 2 min. by P_2O_5/SiO_2 catalyzed Beckmann rearrangement of the ketone **17** under microwave irradiation.[43] Other ketones such as cyclohexanone, benzophenone, acetophenone and benzil furnished the rearranged products in excellent yields.



17 **18**

Moghaddam *et al.*[44] reported that the Beckmann rearrangement of oximes **2** (R^1 = alkyl or aryl and R^2 = aryl) in the presence of $AlCl_3$–$ZnCl_2$ mixture supported on silica gel under microwave irradiation in solvent-free conditions furnished the corresponding amides **3** in excellent yields.

A silica sulphate (SiO_2–OSO_3H)-supported Beckmann rearrangement of oximes **2** (R^1 = R^2 = H, alkyl, aryl and heterocyclyl) under microwave irradiation in acetone was reported by Li *et al.*[45] This recyclable catalyst upon simple workup procedure furnished amides **3** rapidly with high selectivity.

(ii) Vapor-phase Beckmann rearrangement of cyclohexanone oxime

The Beckmann rearrangement of cyclohexanone oxime **5** affords ε-caprolactam **6**, which is used as a precursor for the manufacture of nylon. The conventional method for the rearrangement utilizes fuming sulfuric acid. Several publications pertain to the replacement of the above process using different catalysts. Some of the recent examples are discussed below.

The gas phase rearrangement of **5** with B_2O_3/ZrO_2 as catalyst at 300–320 °C was found to be highly active and selective towards the synthesis of **6**.[46] The selectivity of the catalyst was also compared with other boron catalysts supported on Al_2O_3, TiO_2, SiO_2 and MgO.

Dai *et al.*[47] reported the Beckmann rearrangement of **5** catalyzed by H–USY with different SiO_2/Al_2O_3 ratios in methanol and 1-hexanol. It has been found that H–USY catalysts with SiO_2/Al_2O_3 ratios of 27 to 62 exhibited excellent catalytic activity and selectivity affording the lactam **6** in 1-hexanol.

The vapor-phase Beckmann rearrangement of **5** to **6** catalyzed by various metal oxide powders was reported using a flow reactor system.[48] The most effective catalyst for the rearrangement was niobium oxide. Other oxides employed were CaO, MgO, La_2O_3, ZnO, TiO_2, B_2O_3, SiO_2, WO_3, MoO_3 and Al_2O_3.

Mesoporous silica FSM-16 catalysts modified with various oxides were used in the vapor-phase Beckmann rearrangement of **5**.[49] The selective formation of the lactam **6** was improved by using FSM–16 supported by Al_2O_3, ZnO and CdO.

A novel tantalum-pillared ilerite-catalyzed vapor-phase rearrangement of **5** afforded **6** with 98.9% conversion rate and 89% selectivity at 350 °C.[50,51]

Ghiaci *et al.*[52] reported the synthesis of ZrO_2–TiO_2 mixed oxides with a Ti and Zr molar ratio of 1/1 under various conditions by sol–gel method followed by the preparation of catalysts containing 5–35% of H_3PO_4 using these oxides. These catalysts were used for the vapor-phase Beckmann rearrangement of **5** to **6**. The yield of lactam **6** increased with increasing H_3PO_4 content in the mixed oxide and reached a maximum value for the 15 wt% H_3PO_4 on the ZrO_2–TiO_2 (1/1) support. With further increase in H_3PO_4 content, the lactam yield decreased with the lowest value being observed for the 35 wt% H_3PO_4 on the ZrO_2–TiO_2 (1/1) support.

A novel super-microporous layered material, silica-pillared niobic acid, was prepared by a guest-exchange route. This pillard material was found to be an acid catalyst for the vapor-phase Beckmann rearrangement of **5** to **6** in 1-hexanol, which exhibited a 100% conversion of the oxime with a selectivity of lactam above 85% at 340 °C.[53]

The influence of different post-synthesis modifications on the catalytic performances of β-silicates in the vapor-phase Beckmann rearrangement of **5** to **6** was examined by Forni *et al.*[54]

H–β was synthesized by hydrothermal method followed by ion exchange and treated with aqueous solutions of ammonia. The obtained catalysts were characterized by BET surface area measurement, XRD and IR

and employed for the vapor-phase Beckmann rearrangement of cyclohexanone oxime **5**.[55]

(iii) Liquid-phase Beckmann rearrangement

The Beckmann rearrangement of cyclohexanone, cyclododecanone and acetophenone oximes has been studied in liquid phase at 130 °C over a series of β zeolites differing in the presence or absence of Al framework and internal silanol groups.[56] When the zeolites having internal silanol and with no Al framework exhibit oxime conversion, but the selectivity to the corresponding amide is low in some cases. In the β-zeolites lacking silanol groups but with Al framework, conversion and selectivity were found to be very high.

Phosphorous pentoxide effectively catalyzed the homogeneous liquid phase Beckmann rearrangement of cyclohexanone oxime **5** to lactam **6** in DMF.[57] The catalytic activity was significantly increased by addition of trifluoromethanesulfonic acid as a co-catalyst. This protocol was further extended to the rearrangement of acetone, acetophenone and cyclopentanone oxime to the corresponding amides.

Chung *et al.*[58] reported the liquid phase Beckmann rearrangement of 4-hydroxyacetophenone oxime using zeolite H–β catalyst. The reaction was found to be an example of active solvent participation. A solvent having higher dielectric constant or more polar nature is preferred in the rearrangement step.

The liquid phase Beckmann rearrangement of cyclohexanone oxime **5** in the presence of a series of mesoporous molecular sieves with various SiO_2/Al_2O_3 ratios has been reported.[59] The surface silanol groups ineffectively catalyzed the rearrangement, whereas the acid sites generated by incorporation of aluminium improved the activity and selectivity to lactam **6**.

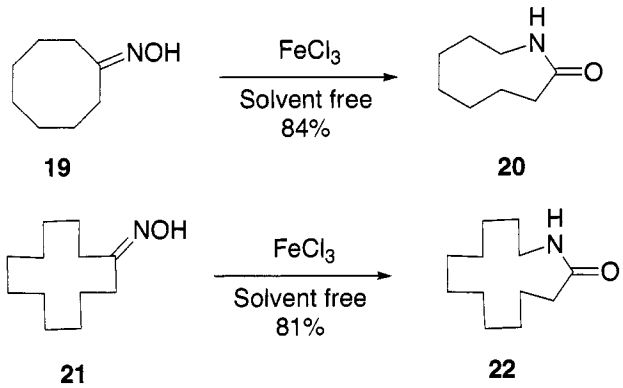
The liquid phase rearrangement of **5** to **6** was performed for the first time on arenesulfonic acid–functionalized SBA-15 (SBA–Ar–SO_3H) mesoporous silica.[60] The catalytic activity was compared with the activities of other solid acid catalysts such as propylenesulfonic acid–functionalized SBA-15, H–ZSM-5, H-mordernite, Al–MCM-41 and Al–SBA-15. The results revealed that SBA–Ar–SO_3H has higher catalytic activity and lactam selectivity.

The effect of various organic additives on the catalytic performance of zeolites and Al-containing MCM-41 in the liquid phase Beckmann rearrangement of cyclohexanone oxime **5** was investigated at 130 °C.[61] Over USY zeolite with a large amount of EFAL, the lactam yield was improved by adding ethanol, dimethyl sulfoxide, ammonia, diethylamine or pyridine to the

oxime solution. It has been rationalized due to the selective adsorption of these additives on the detrimental hydrolysis sites.

(iv) Solvent-free Beckmann rearrangement

The cyclic ketoximes **19** and **21** underwent Beckmann rearrangement in the presence of $FeCl_3$ to afford the amides **20** and **22**, respectively, under solvent free conditions.[62]



The solvent-free one step Beckmann rearrangement of ketones **1** and aldehydes in the presence of zinc oxide afforded the corresponding amides **3** (R^1 = alkyl, aryl, cycloalkyl; R^2 = H, cycloalkyl).[63] Symmetrical ketones furnished the amides in good to excellent yields. In the case of unsymmetrical ketones the reaction was selective and one of the two possible amides was formed. Aromatic and aliphatic aldehydes were converted to the corresponding primary amides.

The direct conversion of ketones **1** to secondary amides **3** from a solvent-free Beckmann rearrangement was accomplished by heating the ketones with hydroxylamine hydrochloride and anhydrous oxalic acid at 100 °C for 4–12 h.[64]

(v) Other Beckmann rearrangements

Beckmann rearrangement of cyclohexanone oxime and other oximes were also carried out in the presence of a variety of catalysts.[65–128] Some of the recent examples are discussed below.

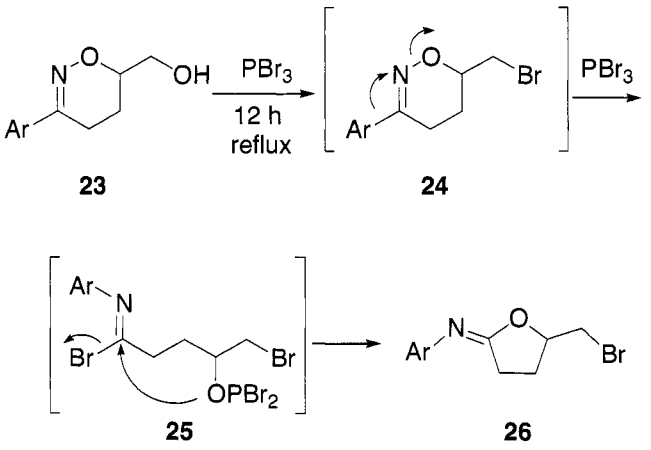
The caprolactam based Brønsted acidic ionic liquids such as [NHC][BF_4], [NHC][CF_3COO] and [NHC][NO_3] have been used to catalyze the rearrangement of cyclohexanone oxime to caprolactam and was found that with a 3:1 mole ratio of ionic liquid:oxime, the conversion increased to

78% and further to 95% at 100 °C when the reaction time was increased from 2 to 3 h. But the selectivity of the rearrangement decreased slightly.[129]

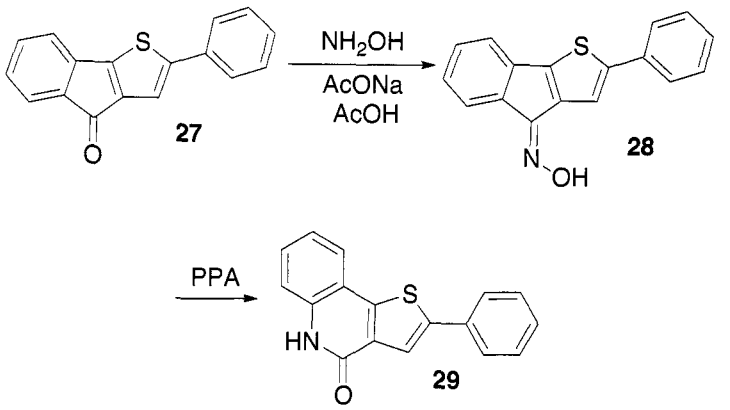
The solid state NMR study of the Beckmann rearrangement catalyzed by MFI–type zeolites with different acid catalysts disclose that the conversion of cyclohexanone oxime to caprolactam is catalyzed by SiOH, SiOH[B] and SiOHAl groups as in silicate-I, zeolites H–[B]ZSM-5 and H–ZSM-5.[130]

Alumina sulfuric acid (ASA) was found to be an effective catalyst for the solvent-free one pot Beckmann rearrangement of several alkyl and aryl aldehydes and ketones **1**. It has been reported that the electron rich aldehydes and ketones require shorter reaction times than the electron poor aldehydes. Cyclic ketones require longer reaction time than the aryl ketones ascribable to the steric factors.[131]

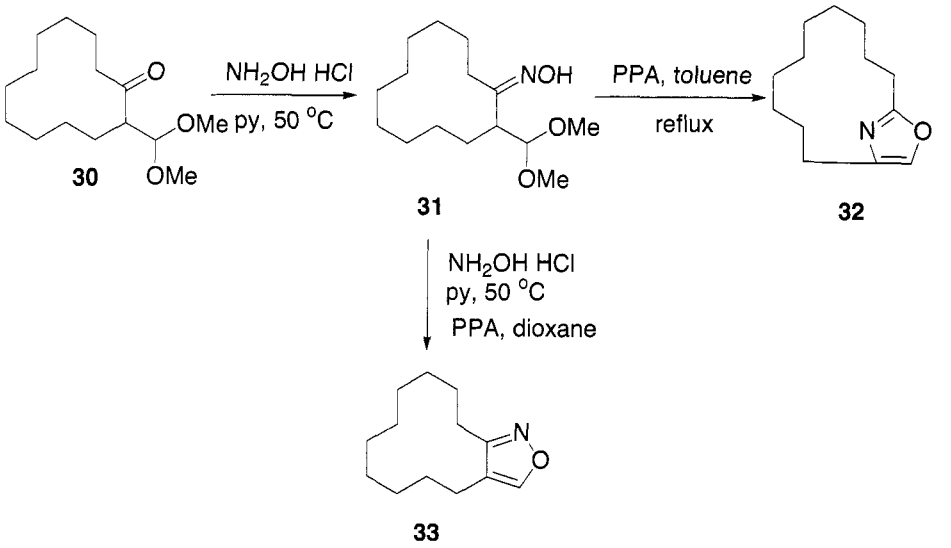
The reaction of 1,2-oxazine **23** with phosphorous tribromide afforded the 5-bromomethyl-2-(phenylimino)tetrahydrofuran **26** via an initial transformation of the alcohol into a bromide functionality **24** and subsequent Beckmann rearrangement via **25**.[132]



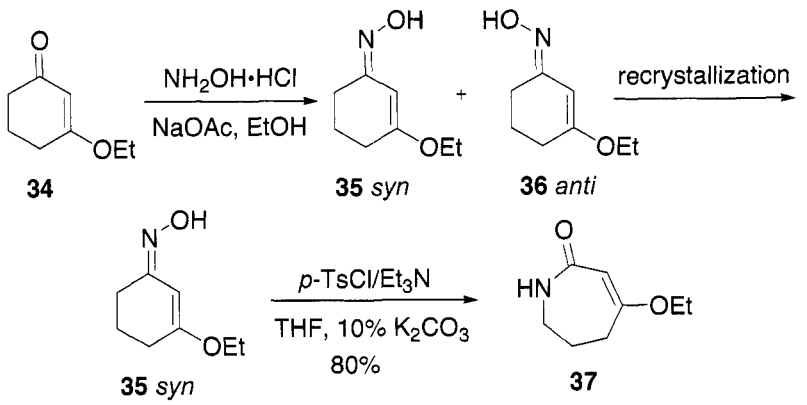
The indeno[1,2-*b*]thiophene **27** was converted to 2-phenyl-4*H*-indeno[1,2-*b*]thiophene-4-one oxime **28** by reaction with hydroxylamine in the presence of sodium acetate, which underwent the Beckmann rearrangement upon treatment with polyphosphoric acid to give 2-phenylthieno[3,2-*c*]quinoline-4(5*H*)one **29**.[133]



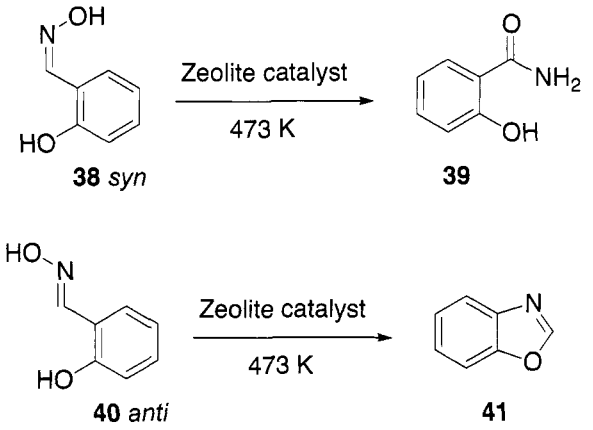
The ketone **30** was treated with hydroxylamine in refluxing toluene for 1 day and was subsequently treated with PPA to afford the oxazole **32** via a one pot Beckmann rearrangement and cyclization. Using dioxane as the solvent afforded isoxazoles **33** under similar reaction conditions. The selectivity has been attributed to the favorable geometry of intermediate oxime in dioxane.[134]



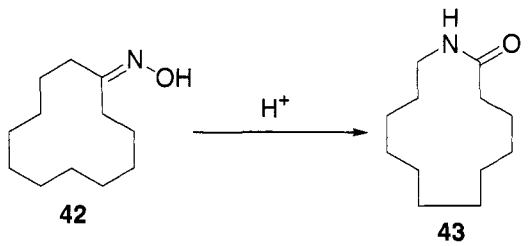
Treatment of ethoxy-2-cyclohexen-1-one **34** with hydroxylamine hydrochloride and sodium acetate in absolute alcohol resulted in the formation of a 2:1 mixture of *syn/anti* oximes **35** and **36**. This mixture upon recrystallization afforded a single oxime isomer **35**, which underwent Beckmann rearrangement in the presence of *p*-toluenesulfonyl chloride to furnish the lactam **37**.[135]



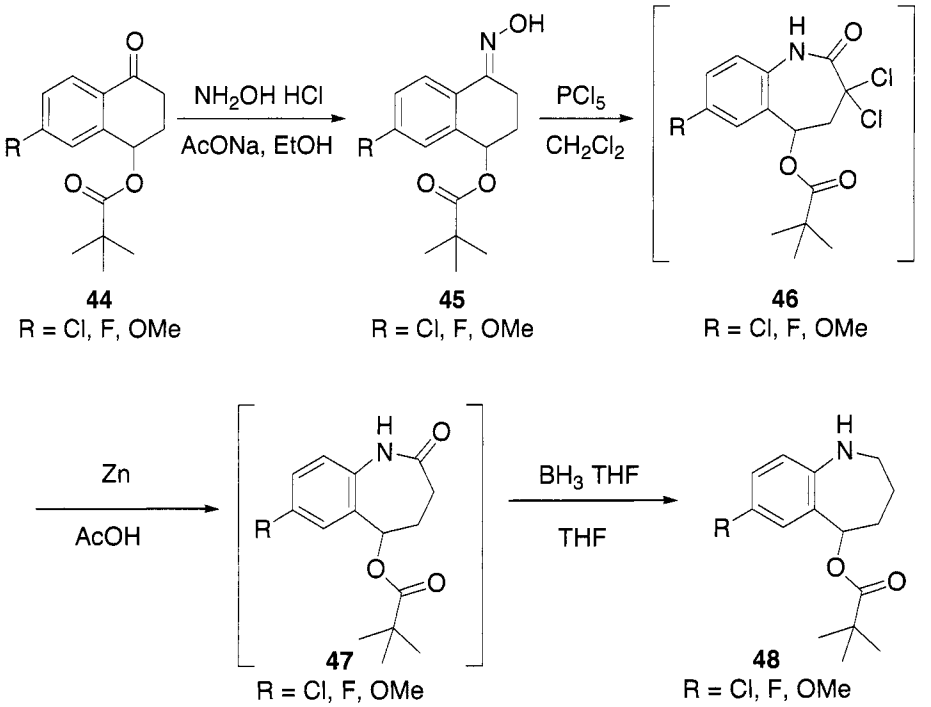
Salicylaldoximes **38** and **40** underwent isomerization followed by Beckmann rearrangement at 200 °C in the presence of K-10 montmorillonite clay and silica-alumina to afford *o*-hydroxybenzamide **39** and benzoxazole **41**, respectively.[136]



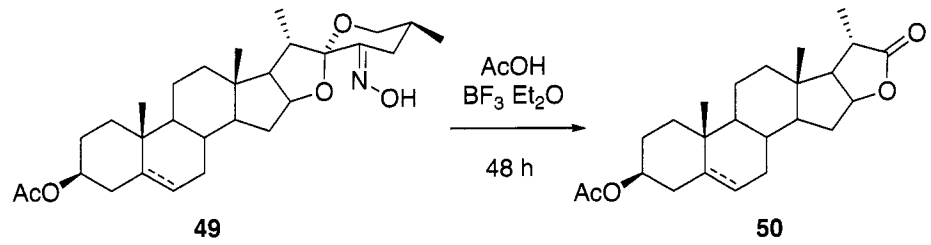
The rearrangement of cyclododecanone oxime **42** to laurolactam **43** has been achieved in the presence of siliceous and Al-containing MFI-type zeolites.[137]



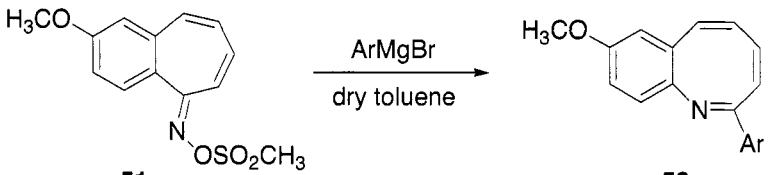
Oximes **45** were achieved from the reaction of **44** with hydroxylamine hydrochloride and sodium acetate in ethanol. The treatment of oximes **45** with excess of PCl_5 in dichloromethane afforded α,α-dichlorolactam **46**, which was reduced with zinc powder in acetic acid to give **47**. Selective reduction of the amide carbonyl by BH_3–THF complex furnished the benzazepine **48**, which served as an intermediate for the synthesis of tolvaptan.[138]



The treatment of oxime **49** in glacial acetic acid with BF_3•Et_2O at room temperature afforded solely the corresponding bisnorcholanic lactone **50**. The product arising from the nucleophilic attack of acetic acid or acetate ion to C-16 of **49** was not observed.[139]

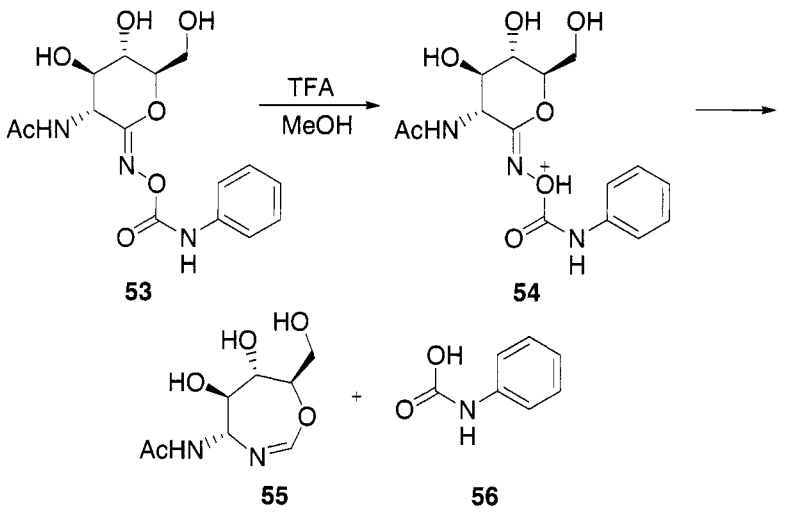


The Beckmann rearrangement of 2-methoxy-5*H*-benzo[*a*]cyclohepten-5-one oxime mesylate (**51**) in the presence of ArMgBr in dry toluene afforded 8-methoxy-2-phenyl-1-benzazocine (**52**).[140]



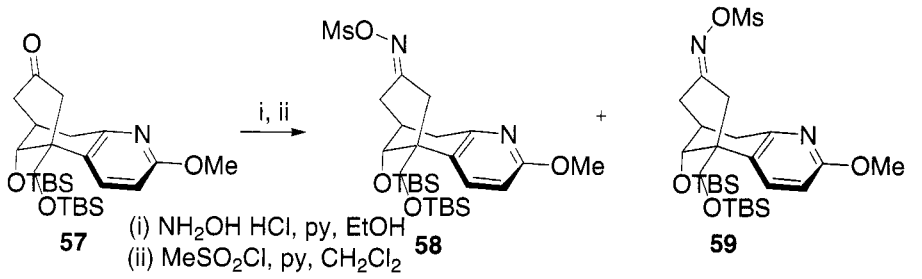
51 **52**

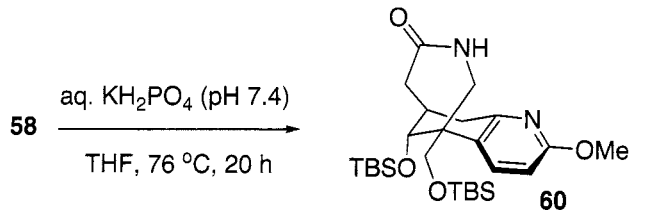
The reaction of *O*-(2-acetamido-2-deoxy-*D*-glucopyranosylidene)-amino-*N*-phenylcarbamate **53** with trifluoroacetic acid furnished the Beckmann rearranged product **55** and the acid **56**.[141]

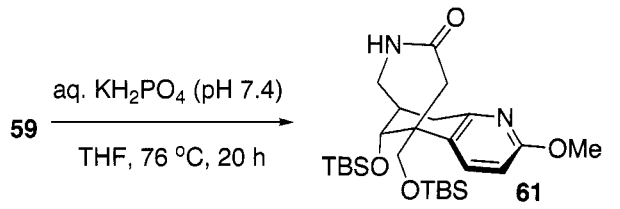


53 **54** **55** **56**

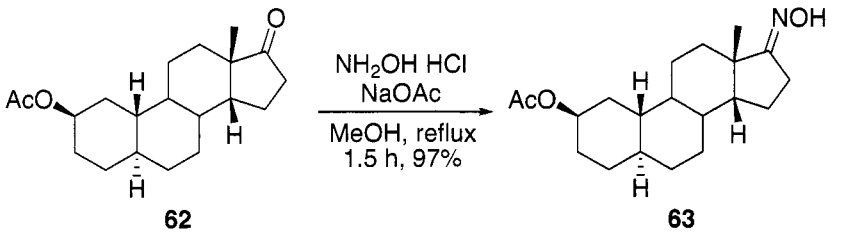
Ketone **57** upon reaction with hydroxylamine hydrochloride and subsequently with $MeSO_2Cl$ afforded the oxime mesylate isomers **58** and **59**, respectively. These mesylates separately underwent the Beckmann rearrangement in the presence of KH_2PO_4 in THF affording the tricyclic amides **60** and **61**, respectively.[142]

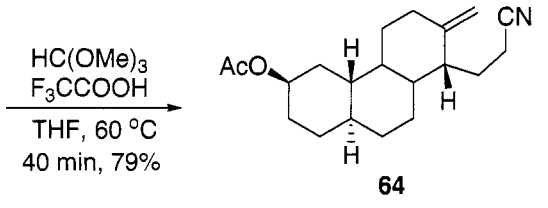




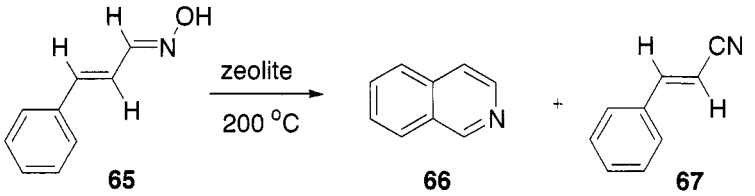


The reaction of ketone **62** with hydroxylamine hydrochloride and sodium acetate afforded the oxime **63**, which upon treatment with $CH(OCH_3)_3$/THA underwent an *abnormal Beckmann rearrangement* furnishing the carbonitrile **64**.[143]



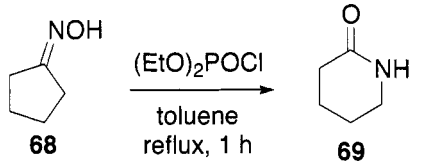


Cinnamaldoxime **65** in the presence of different H-zeolites, K-10 montmorillonite clay, amorphous SiO_2–Al_2O_3 and γ-alumina underwent the Beckmann rearrangement via the migration of the *anti*-styryl moiety to electron-deficient nitrogen followed by an intramolecular cyclization to afford the isoquinoline **66** as the major product. Cinnamonitrile **67** and cinnamaldehyde were obtained as minor products.[144]

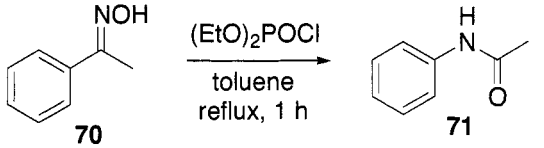


65 **66** **67**

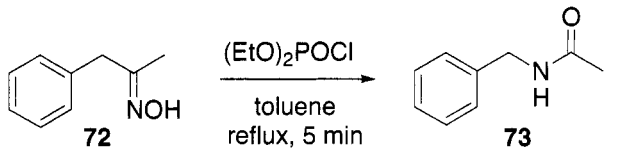
Sardarian *et al.*[145] reported that oximes **68**, **70**, **72** and **74** underwent the Beckmann rearrangement in the presence of diethyl chlorophosphate as catalyst to afford the corresponding amides **69**, **71**, **73** and **75** respectively.



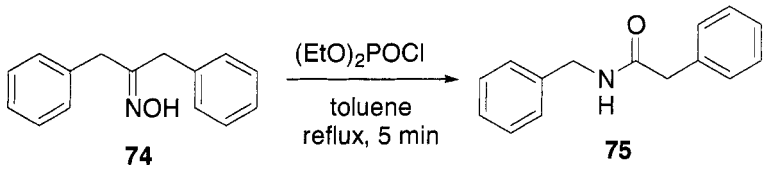
68 **69**



70 **71**



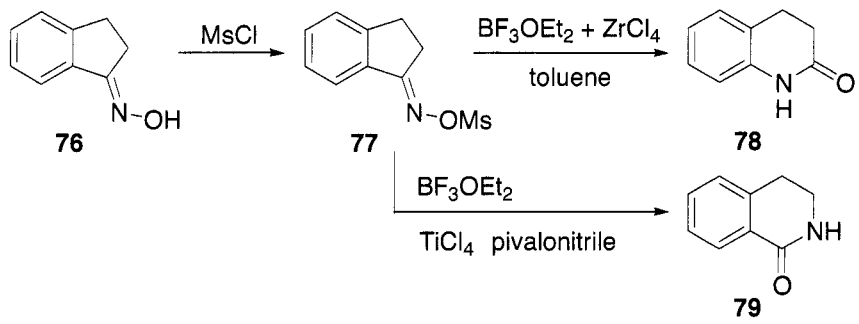
72 **73**



74 **75**

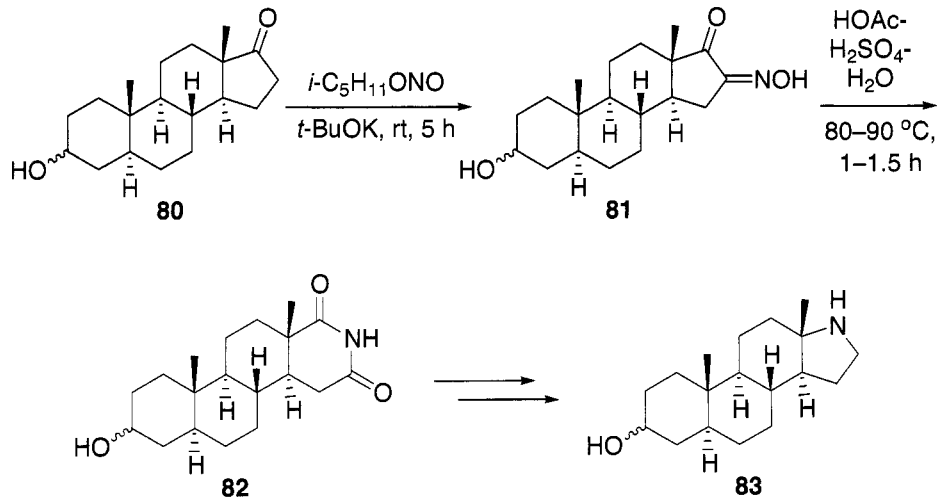
Mixed Lewis acid such as BF_3•OEt_2–$ZrCl_4$ in toluene or chlorotoluene has been found to be more efficient catalyst than $ZrCl_4$ for the Beckmann rearrangement of the oxime sulfonate **77** to the carbostyril **78**. The

oxime sulfonate was in turn derived from the oxime **76** by the reaction with MsCl.[146] The rearrangement of **77** in the presence of BF_3•OEt_2–$TiCl_4$ led to the formation of isocarbostyril **79**.[147]

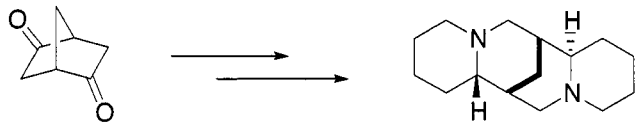


1.2.1.5 Synthetic Utility

(5α)-17-Aza-androstan-3-ol **83** was obtained from **80**, through a Beckmann rearrangement of the oxime **81**, to give **82** followed by a Hofmann rearrangement.[148]

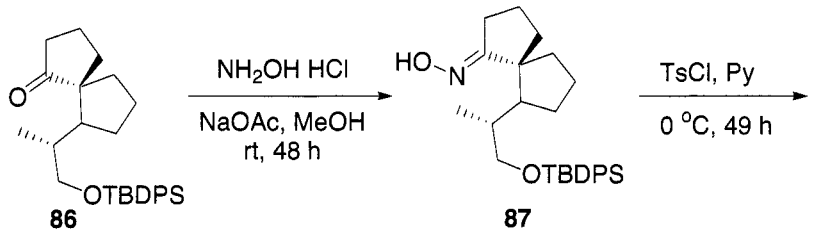


The total synthesis of (+)-sparteine (**85**) was achieved from 2,5-norbornadione **84** in 15 steps. The key steps in the synthesis were the two ring expansion reactions, one involving an intramolecular Schmidt reaction and the other a variant of the photo-Beckmann rearrangement ring-expansion.[149]

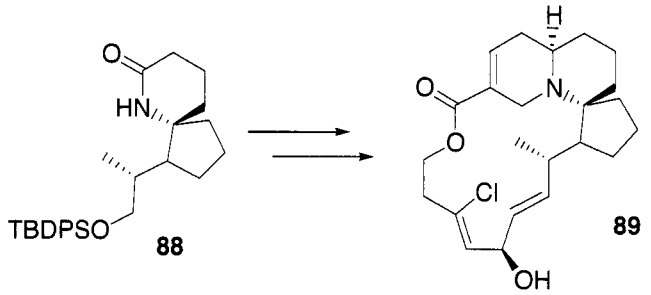


84 85

The Beckmann rearrangement of oxime **87** in the presence of TsCl afforded the corresponding [5.4.0]azaspirobicyclodecane **88**, which served as a key intermediate towards the synthesis of the marine alkaloid halichlorine (**89**).[150]

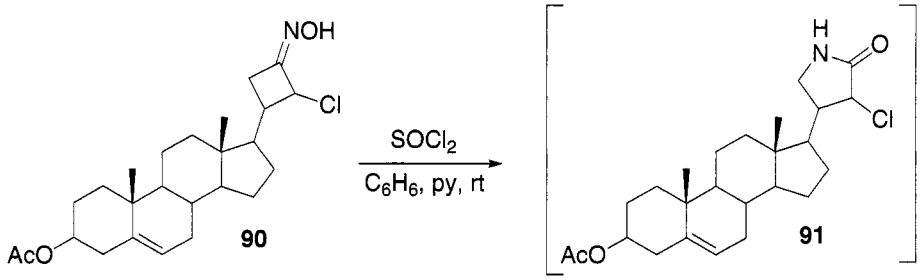


86 87

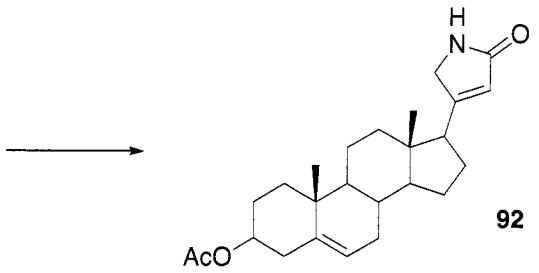


88 89

The treatment of α-chlorocyclobutanone oxime steroidal derivative **90** with thionyl chloride in benzene afforded azacardenolide **91** via **92**.[151]



90 91



92

1.2.1.6 Experimental

*Synthesis of **69**, **71**, **73** and **75***

For each reaction, the oxime (5 mmol) and toluene (1 mL) were charged into a 50 mL two necked round-bottomed flask equipped with a magnetic stirrer and condenser. The reaction was heated to reflux and diethyl chlorophosphate (5 mmol) was added to the mixture. The reaction mixture was heated for 20–120 minutes and then cooled to room temperature. The crude mixture was neutralized with aqueous solution of sodium hydroxide (10 mL, 5%) and then extracted with diethyl ether (10 mL). Drying the ethereal layer over anhydrous sodium sulfate and removal of the solvent gave the crude product, which was purified by short column chromatography over silica gel using *n*-hexane and ethyl acetate (9:1–5:5) as eluent.[145]

1.2.1.7 References

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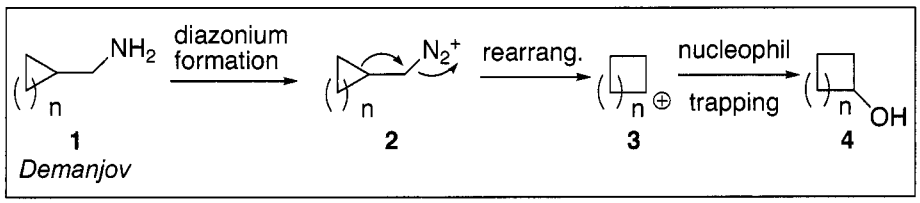
1.2.2 Demjanov and Tiffeneau–Demjanov Rearrangement

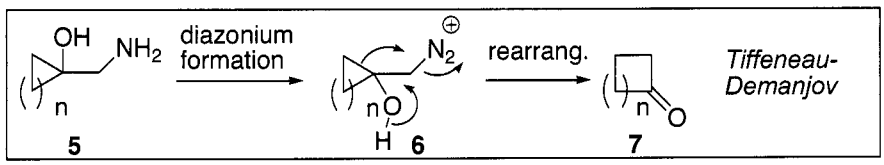
Timothy T. Curran

1.2.2.1 Description

The Demjanov and Tiffeneau–Demjanov rearrangements are the reaction of a primary alkyl amine with a diazotizing reagent to form the diazoalkane **2**. The alkyl azide suffers loss of N_2 to form the primary cation which rearranges normally by ring expansion, when the starting amine **1** is a cycloalkylmethylamine, rearrangement occurs to a more stable cation. In the case of the Demanjov rearrangement, solvent acts to trap the rearranged cation typically leading to mixtures of isomeric alcohols **4**.



In the case of the Tiffeneau–Demjanov rearrangement, the starting material is an aminomethylalkanol **5**; thus after formation of the diazoalkane **6**, the neighboring alcohol serves as an electron source to provide an "electron push" to satisfy the formed cation. In this sense, the Tiffeneau–Demjanov rearrangement resembles a pinacolic deamination process and provides a ketone **7**.

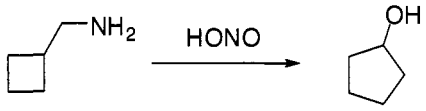


In this review, both cyclic and acyclic work will be considered with focus predominantly on cyclic work.

1.2.2.2 Historical Perspective

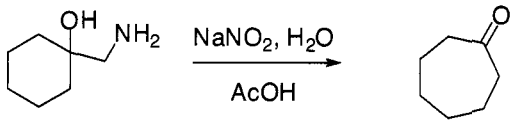
Demjanov described the rearrangement initially in 1901, but the reaction was not recognized until 1903 when he reported the rearrangement of

cyclobutylmethylamine **8** to cyclopentanol **9**.[1,2] This reaction has been applied to many ring systems since then providing ring expanded products.



8 **9**

Tiffeneau and co-workers[2,3] reported their discovery of the reaction in 1937 for the ring expansion of hydroxy-cyclohexylmethyl amine **10** to form cycloheptanone **11**. This reaction also has been applied to numerous cases in which a ring expanded ketone was formed.



10 **11**

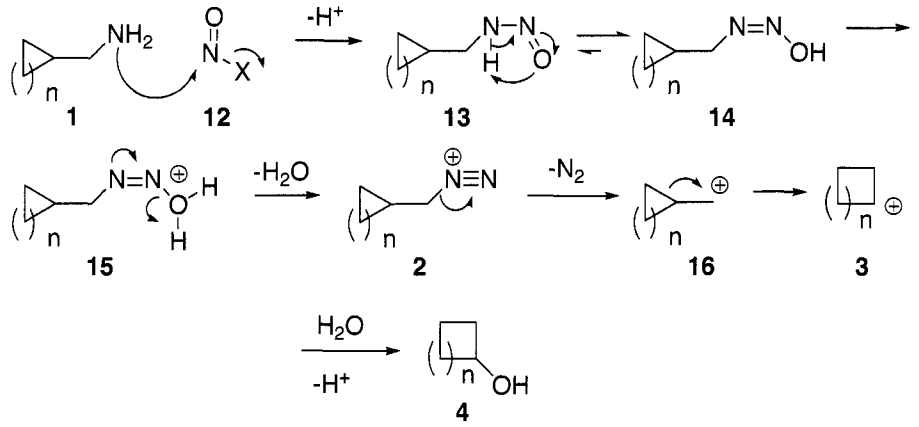
Over time, conditions have not significantly changed the selectivity, but more moderate conditions and improved methods to prepare the amino-alcohols or the use of alternative reagents to achieve a similar reaction have been developed.[4] In addition, new reagents have been developed to accomplish an analogous transformation. For example, the addition of diazoalkanes to ketones suffers a similar fate to the formation of the diazonium compound derived from amino-alcohols.[5] A better understanding of the rearrangement, what drives the migration and which group migrates have been achieved.

1.2.2.3 Mechanism

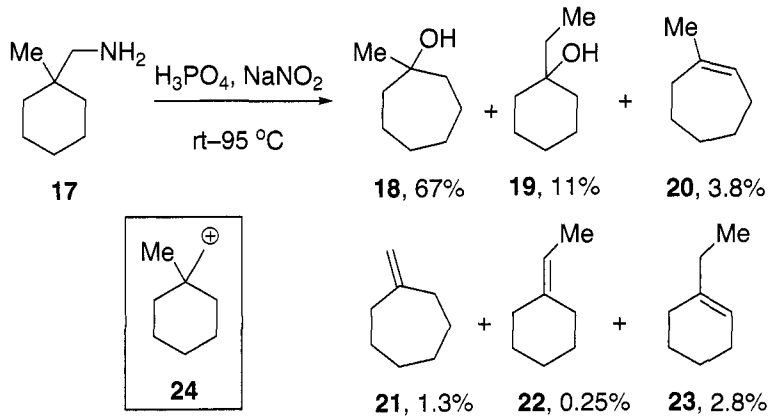
The mechanism for the Demjanov reaction is a well accepted mechanism. The formation of the diazonium occurs as outlined. Reaction of the amine **1** with activated NOX **12** (X is thought to be ONO)[6] delivers the *N*-nitroso compound **13**, which undergoes rearrangement to provide hydroxyl-diazo material **14**. Protonation of **14** and loss of water provides the diazonium, which suffers loss of N_2 to provide cation **16**. Carbocation **16** then undergoes rearrangement to provide **3**, which traps a nucleophile (typically water sometimes nucleophilic co-solvents or acid counterions like acetate) and provides the alcohol **4**.

Since the carbocation like **16** and **3** are formed, there will be instances in which rearrangement may proceed in a fashion that is not desired. Due to this fact, the Demanjov reaction has oftentimes led to mixtures of products or

merely solvolysis of the diazonium. For example, reaction of methylcyclohexylmethylamine **17** provided several products including the desired rearranged methyl cycloheptanol **18** in 67% yield.[7]

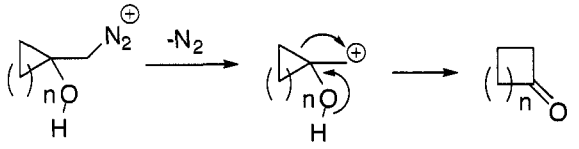


Along with the desired product, dehydration under the reaction conditions provided **20** and **21**. Methyl migration from the formed methyl carbocation **24** provides the second major product **19**, which also produces dehydration products **22** and **23**.



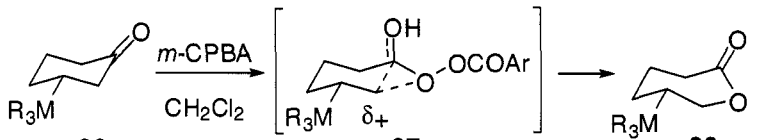
The Tiffeneau–Demjanov rearrangement is analogous through the formation of the diazonium **6**. Loss of N_2 provides the carbocation, which undergoes rearrangement. The amount of "push" from the internal bond migration and the amount of concertedness of the rearrangement which would lead to predictable stereochemical outcome is dependent upon the

stability of the carbocation and the conformational effects of the surrounding migration.



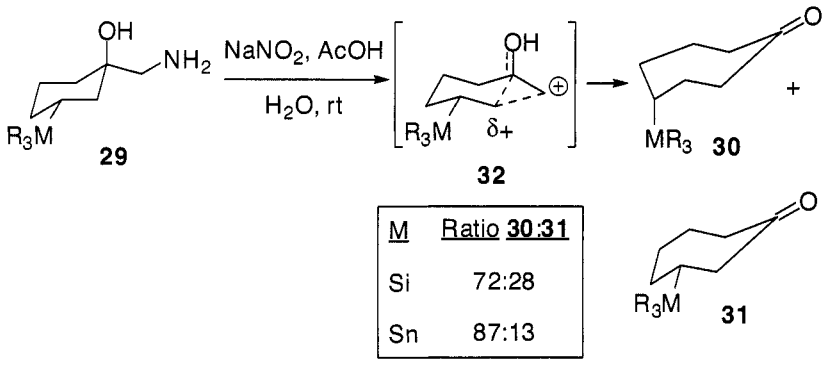
25 **7**

Just as in the Demjanov rearrangement, the Tiffeneau–Demjanov rearrangement can also provide a variety of products. However, the by-products are typically fewer, but due to the carbocationic nature of the reaction, the potential for by-product formation remains. A comparison of the β-Si/β-Sn effect on the Tiffeneau–Demjanov rearrangement has been compared to observations of the Baeyer–Villiger oxidation. While stabilization of the developing positive charge does manifest itself, the effect was not as pronounced as in the Baeyer–Villiger oxidation.[8] For example, the Baeyer–Villiger oxidation of ketone **26** containing a silyl or stannyl group beta to the carbonyl, gave predominantly lactone **28** due to the the directing effect of Si or Sn.



26 **27** **28**

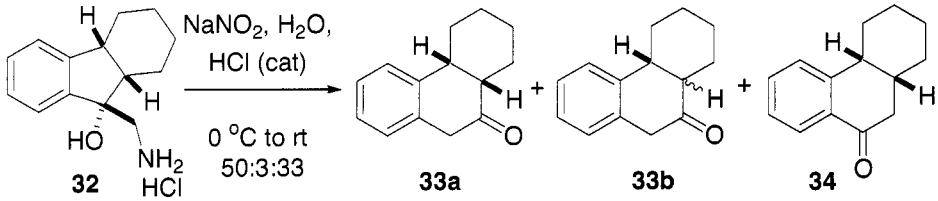
While one can draw a very similar transition state for the Tiffeneau–Demanjov rearrangement, the selectivity observed gave mixtures of cycloheptanones **30** and **31**. In acyclic systems studied in this same report, selectivities were again more inferior for the Tiffeneau–Demjanov rearrangement than for the Baeyer–Villiger rearrangement. The authors rationalized this lack of selectivity due to the high reactivity of the diazonium as a leaving group in comparison to the acyl group and the low degree of positive charge built-up on the migrating carbon.



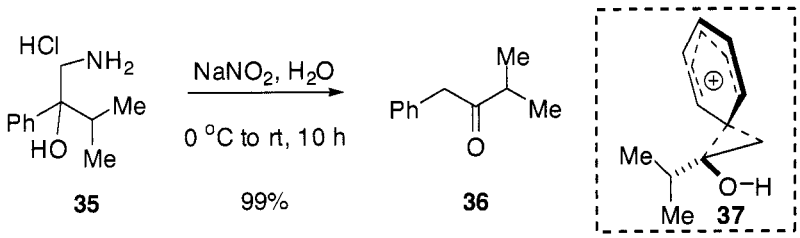
M	Ratio **30**:**31**
Si	72:28
Sn	87:13

The Tiffeneau–Demjanov rearrangement did not require a significant electron push while the Baeyer–Villiger reaction requires electron push with a greater build-up of positive charge on the migrating carbon; and therefore, stabilization of the building positive charge has a greater impact.

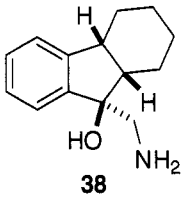
Rearrangement of fused cyclic systems has been studied and migratory aptitudes compared. For example, in the fused system **32**, diazonium formation and rearrangement provided a mixture of **33a**, **33b**, and **34** arising from phenyl migration and cyclohexyl migration in a 50 : 3 : 33 ratio.[9]



While the phenyl group predominantly migrated, in the acyclic case, phenyl migration was the only migrating group providing exclusively **36** from **35**.[9,10] The authors proposed a "steric control" exerted in a rigid-fused system of **32**, preventing the stabilizing overlap of the phenyl ring coupled with the inability of the cyclohexyl ring to adopt a stabilized chair transition state during migration (consider **37**).



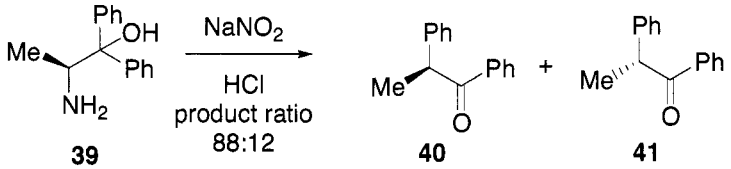
Additionally, diastereomer **38** provided a ratio of phenyl:cyclohexyl rearrangement products similar to **32**. This signifies that the stereochemistry in this instance has little impact on altering the outcome of the reaction, or that orbital alignment in this system was not changed significantly to enhance or diminish selectivity.



55:0.7:26
33a:**33b**:**34**

38

A test to ascertain the concertedness of this reaction in an acyclic, stereochemical experiment has shown that some retention of configuration at the carbon containing the diazonium leaving group has occurred. While the configuration of the migrating group is believed to retain its configuration, in this example, if the reaction were concerted, inversion of configuration would be expected at the carbon with the diazonium as leaving group. Thus, diazotization of **39** should have led entirely to **40** only. However while inversion was predominant (88%), 12% of the reaction failed to proceed through the bridged phenyl ring.[6]

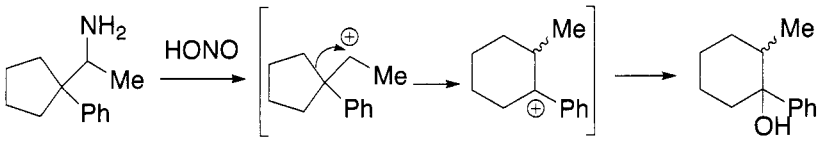


39 **40** **41**

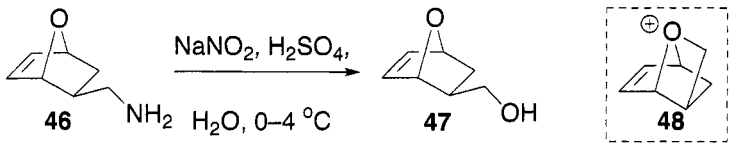
1.2.2.4 General Selectivity

Overall, the general ease of migration or the migratory aptitude of groups is: Ph, vinyl > Me_3C > allyl, benzyl > $MeCH_2$ > Me. For the Tiffeneau–Demjanov rearrangement, this mirrors the pinacol–pinacolone rearrangement. When considering bridged-bicyclic structures, typically a methlyene group migrates in preference to a bridgehead carbon. As mentioned in the previous section, many factors contribute to the preference for migration. The ability for the molecule to access a conformation to enable migration is critical. In addition, as rings increase in size, yields of products tend to diminish. For example, conversion of the 12-membered hydroxymethylaminocyclodoecane gave the 13-membered cyclic ketone in 50–60%.[11]

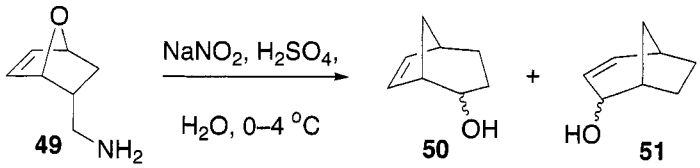
For the Demjanov rearrangement, the course of rearrangement or reaction is governed by the relative stability of the rearranged carbocation and whether or not the system provided enough energy to achieve the rearrangement. For example, Demjanov rearrangement of **42** provided a *cis*- and *trans*-mixture of alcohols **45**. The intermediate carbocation rearranged with ring-expansion to the more stable cation which traps water.[12]



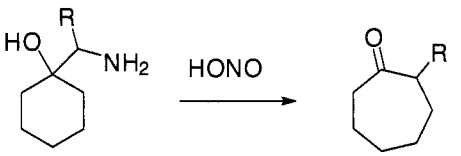
In addition, if the initially formed cation produced a more stable cation than anything that would undergo rearrangement or ring expansion, solvent trapping then provided the alcohol. For example, diazotization of **46** yielded only **47**; no trace of Demjanov rearrangement occurred. The authors of this work suggested that structure **48** may be the participating culprit which prevented rearrangement.[13]



Interestingly, the *endo*-methylamine **49** gave rearranged product and yielded a 1 : 1 mixture of methylene and bridgehead migration products **50** and **51**.[13]



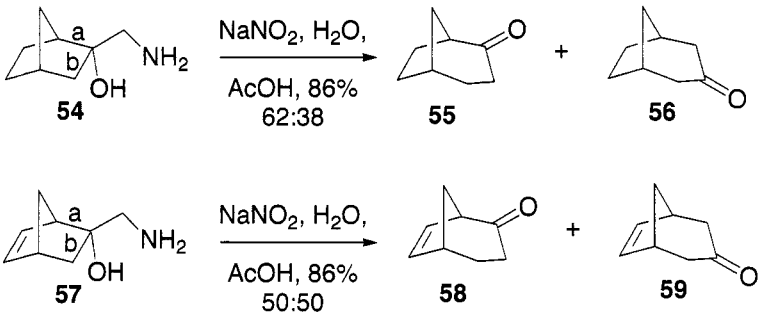
For the Tiffeneau–Demjanov rearrangement, substitution of the carbon bearing the amine group was shown to stabilize the forming carbocation and thereby extinguish the driving force for ring expansion. However, when there are additional driving forces, like formation of a more stable carbocation or relief of strain, ring expansion has occurred. For example, diazotization of **52** provides the rearranged cyclo-2-alkanone **53**.[2]



52 **53**

Substitution within the cycloalkane ring typically did not have a great influence on the rearrangement other than stabilization of δ^+ carbon of the migrating group. Other subsituents on the cycloalkane ring could have a conformational effect which may alter selectivity.

Tiffeneau–Demjanov rearrangement of norcamphor and dehydronorcamphor has been studied by McKinney *et al.*[14] Diazotization of *exo*-methylamine norcamphor derivative **54** led to a 62:38 ratio of **55** and **56**; while, for the dehydro case, compound **57** gave a 1:1 mixture of **58** and **59**. The difference in selectivity was suggested to be attributed to the stabilization of the bridgehead migrating group in **57** leading to **59** (migration of bond a). Also noted was destabilizing interactions for the migrating methylene group (migration of bond b).



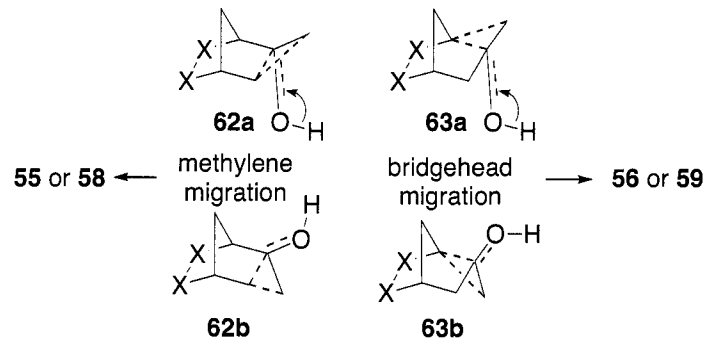
54 **55** **56**

57 **58** **59**

Evaluation of the *endo*-methylamines of norcamphor derivatives **60** and **61** was also studied. Diazotization of **60** gave a 91:9 mixture of **55** and **56**, while dehydro **61** gave a 77:23 mixture of **58** and **59**. Again, noted was the increased propensity for the allylic group to undergo migration in comparison to the saturated system.

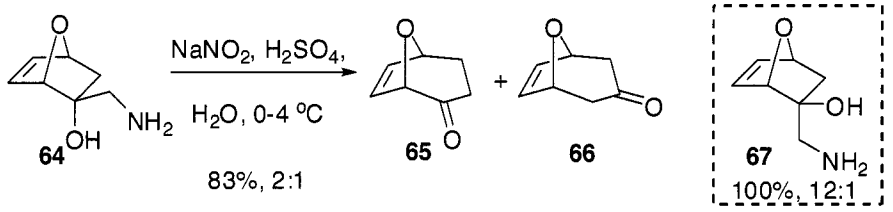
60 **61**

54%, 91:9 49%, 77:23



Comparison of the *endo*-methylamine **60** with *exo*- **54** also illustrated a preference for migration of the methylene group in preference to the bridgehead. Rationale for the difference was suggested to be a "least motion" argument, that the less the molecule has to flex or move bonds the easier for the rearrangement to occur. Additionally, conformational analysis shows that the *endo*-methylamine has a chair-like conformation while the *exo*- has a boat-like conformation (bond b led to steric interactions between the bridge methylene and the transferring bond; compare **62a,b** with **63a,b**).[5,14]

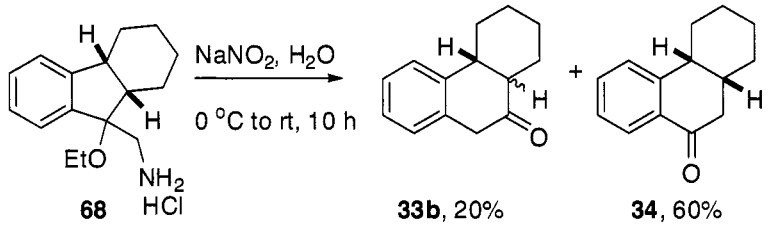
Reaction of the oxa-bicyclo system was shown to follow the same trend. Thus, migration of the methylene group was preferred in a 2:1 ratio for the *exo*-methylamine oxabicyclo compound **64**, while the *endo*-methylamine provided a 12:1 mixture of **65** and **66**.[13]



1.2.2.5 Variations and Improvements

Variations and improvements on the Demanjov and Tiffeneau–Demjanov reaction have been limited. Variations have come in different methods to generate diazonium salts using various acids containing non-nucleophilic counter ions. The use of weaker acids for the Demanjov rearrangement led to diminished amounts of olefinic by-products. Understanding how facile the reaction was at lower temperature also provided higher yield and fewer by-products.

Alkoxymethylamines **68** rather than hydroxymethylamines **32** and **38** have been shown to undergo the Tiffeneau–Demjanov rearrangement. This served to modestly alter the selectivity.[10]



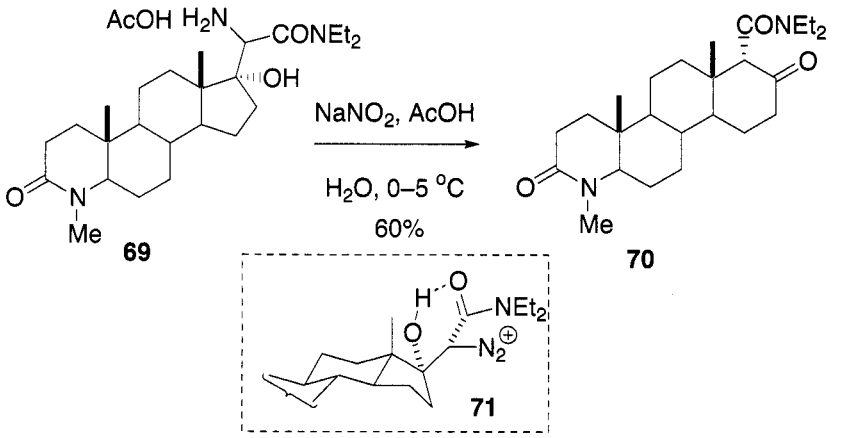
68 **33b**, 20% **34**, 60%

Another significant contribution has come by new and general methods to generate cycloalkylmethylamines and hydroxycycloalkylmethylamines. This work has led to further exploration of these rearrangements.[4,5]

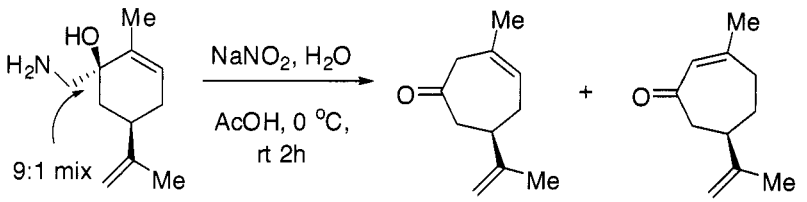
1.2.2.6 Synthetic Utility

General Utility

In general, these reactions have been utilized to generate molecules from existing backbones or to form interesting bicycles which would otherwise be difficult. For example, diazotization of pregnane derivative **69** led to amide **70** in 60% yield. This example showed the retention of configuration of the migrating carbon and (at least some) inversion of stereochemistry at the carbon that had the diazonium. The authors suggested that the selectivity was due to a low energy conformation which minimized non-bonding steric interactions with the C18 methyl group, and a hydrogen bonding network served to stabilize and more highly populate conformation **71** leading to the observed product **70**.[15]



69 **70** **71**

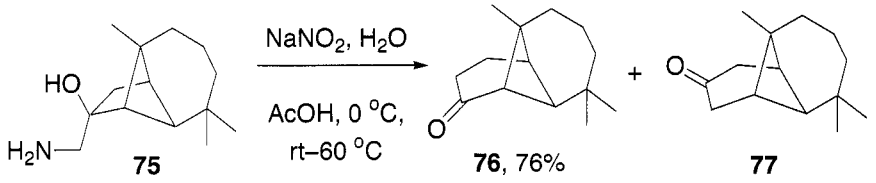


72 **73**, 68% **74** 10%

Another example of the utility of this reaction is the formation of enantiopure cycloheptenones from optically pure natural products like *R*-carvone. Hydroxylaminomethylcyclohexene **72** derived from *R*-carvone rearranged to provide two compounds resulting from selective rearrangement of the vinyl carbon. While the alkene migrated into conjugation under the reaction conditions providing 10% of **74**, the Tiffeneau–Demjanov reaction provided entry into optically-enriched cycloheptenones.[16]

Applications in Total Synthesis

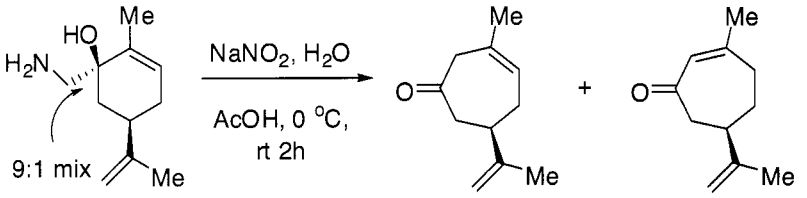
The Tiffeneau–Demjanov rearrangement has been utilized in the total syntheis of terpenoids (±)-α- and β-longipines.[17] The ring expansion was applied late in the synthesis and was high yielding and selective. Diazotization of **75** gave after rearrangement a 90:6 ratio of **76** and **77**, providing **76** in 76% isolated yield. Migration of the methylene group occurred in preference to the bridgehead.



75 **76**, 76% **77**

1.3.7 Experimental

Preparation of (*R*)-6-Isopropenyl-3-methyl-cyclohept-3-enone (73) **and (*R*)-6-isopropenyl-3-methyl-cyclohept-2-enone** (74)[16]



72 **73**, 68% **74** 10%

A mixture of compounds **72** (10.05 g; 55.4 mmol) in 10% aqueous AcOH (110 mL) at 0 °C was treated with a 1.29 M aqueous solution of $NaNO_2$ (29 mL). The reaction mixture was stirred for 30 min at 0 °C and 2 h at room temperature. The solution was again cooled to 0 °C and treated with 15% aqueous solution of NaOH to bring the pH to 10. The aqueous phase was extracted with Et_2O, and the combined etherial extracts were washed with brine and then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel using *n*-hexane–EtOAc (9.5:0.5) as eluent to first give **73** (6.34 g, 68%) and **74** (0.71 g, 10%).

1.3.8 References

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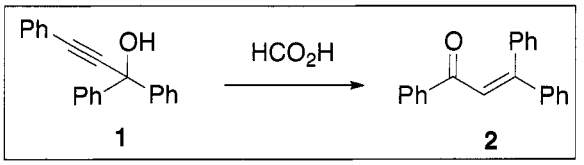
1.2.3 Meyer–Schuster Rearrangement

Richard J. Mullins and Nina R. Collins

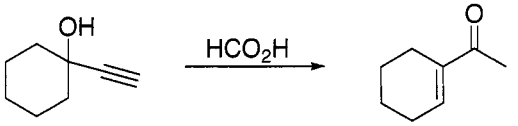
1.2.3.1 Description

The Meyer–Schuster rearrangement is the isomerization of secondary and tertiary α-acetylenic alcohols to α,β-unsaturated carbonyl compounds.[1]



1 2

Similarly, the Rupe rearrangement is the reaction of tertiary α-acetylenic alcohols to α,β-unsaturated ketones in the presence of an acid catalyst.[2]

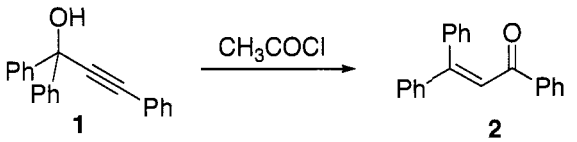


3 4

Although a variety of acid catalysts are employed in the Meyer–Schuster and Rupe rearrangements, formic acid is commonly used to effect the respective transformations.[3]

1.2.3.2 Historical Perspective

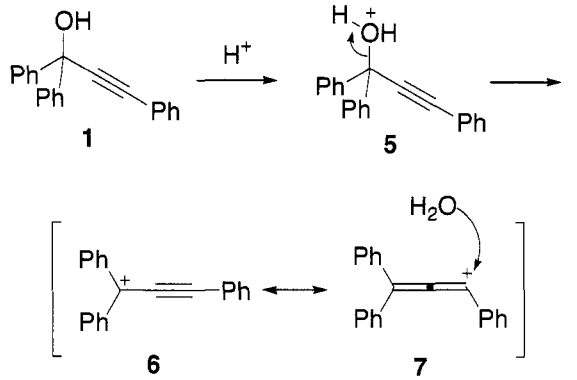
Meyer and Schuster discovered the rearrangement that carries their names in an attempt to convert α-acetylenic alcohols such as **1** to the respective tertiary chloride in the presence of an acetyl chloride catalyst.[1] Rather than the expected chloride products, α,β-unsaturated ketone **2** was obtained via a previously unknown acid-catalyzed rearrangement. Further research demonstrated the ability of a variety of acid catalysts (i.e., acetic acid, concentrated sulfuric acid, ether saturated with dry hydrogen chloride, and acetic anhydride) to induce the observed transformation.[1]

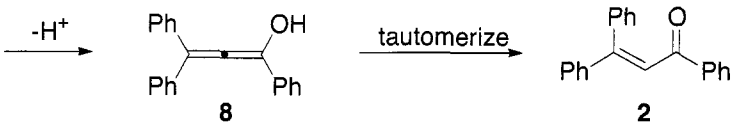


Following publication of Meyer and Schuster's findings, Rupe and co-workers conducted studies on the acid-catalyzed isomerization of an array of propargylic alcohols.[2,3] Their research led to the elucidation of a rearrangement pathway somewhat similar to that observed by Meyer and Schuster. While the Rupe rearrangement also leads to the formation of α,β-unsaturated ketones, it does so via a different mechanism than that of the Meyer–Schuster rearrangement. Initially, α,β-unsaturated aldehydes were thought to be the isomerization product.[3,4] However, further experimentation by Chanley[5] and others[3,6] indicated that ketones were the major product of the Rupe rearrangement. A comprehensive review on the history of the Meyer–Schuster and Rupe rearrangements through 1971 has been written.[3]

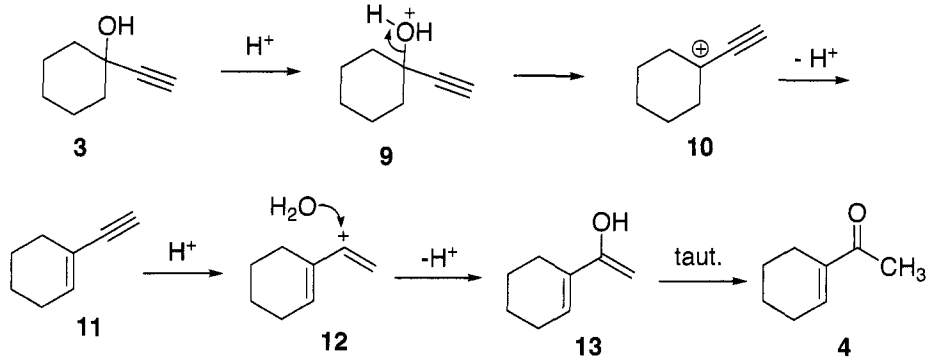
1.2.3.3 Mechanism

Studies aimed at the elucidation of the Meyer–Schuster and Rupe reactions followed. Equally important was the discovery of subtle structural differences in the reacting propargylic alcohols leading to the respective rearrangement pathways. Early observations indicated that the Meyer–Schuster rearrangement occurred with secondary and tertiary propargylic alcohols such as **1**. Acid-catalyzed dehydration of **1** results in the formation of propargylic cation **6**. Lacking an expellable proton on the adjacent carbon, addition of water to the alternate allenyl cation resonance form **7** is followed by deprotonation to give allenol **8**. Tautomerization then results in formation of α,β-unsaturated ketone **2**.[3]





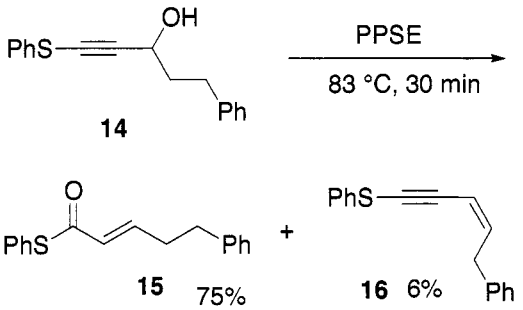
In contrast, tertiary propargylic alcohols with an expellable proton such as **3** will instead proceed via the Rupe rearrangement. Following dehydration to propargylic cation **10**, elimination occurs to give enyne **11**. Subsequent hydration of the alkyne gives **13**, which tautomerizes to the α,β-unsaturated ketone **4**.



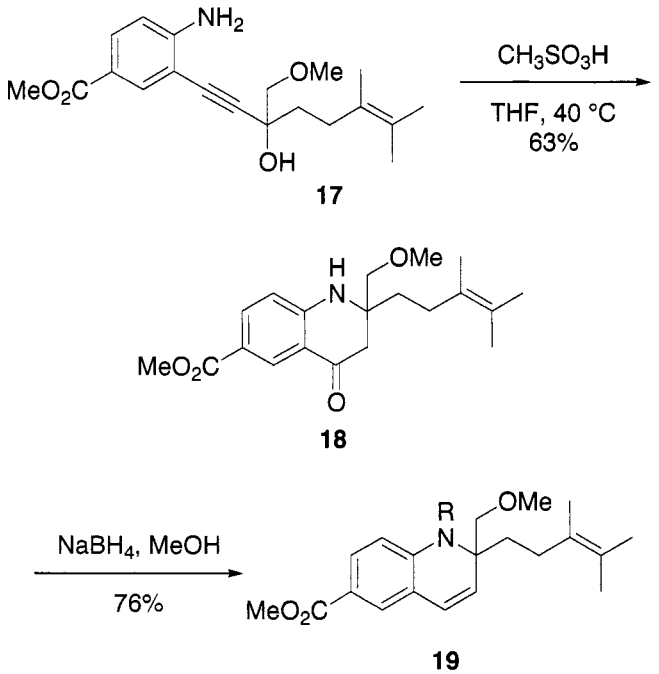
Although the proposed dehydration-hydration sequence above is generally accepted, the presence of enyne intermediate **11** was originally questioned.[3] Specifically, Ansell and coworkers[7] supported an alternate mechanism[8] involving a 1,2-hydroxy shift, bypassing the need for the enyne intermediate. Ultimately, further experimentation and spectroscopic data supported the presence of enyne intermediates, and the initially proposed mechanism was accepted.[9]

1.2.3.4 Synthetic Utility

Yoshimatsu and coworkers employed the Meyer–Schuster rearrangement as a novel effort for the synthesis of α,β-unsaturated thioesters,[10] compounds of interest as a result of their insecticidal activities[11] and their use in the synthesis of macrocyclic lactones.[12–14] While these reactions are plagued by competitive formation of an enyne byproduct, in the case of **14**, treatment with polyphosphoric acid trimethylsilyl ester (PPSE) resulted in the desired α,β-unsaturated thioester **15** in good yield. Except in the reaction of tertiary propargylic alcohols, where the enyne was favored, the yield of the thioester significantly exceeded that of the by-product in most cases.

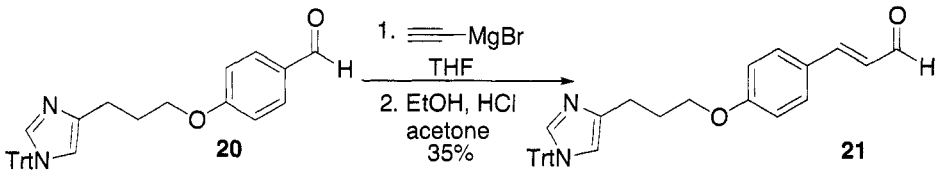


The synthetic practicality of the Meyer–Schuster rearrangement was demonstrated in the synthesis of (±)-virantmycin,[15,16] a metabolite of *Streptomyces nitrosporeus*, which has been shown to possess antiviral activity.[17,18] When the attempted conversion of **17** to **19** via a hydrogenation/cyclization sequence was unsuccessful, an alternate pathway utilizing the Meyer–Schuster reaction was explored. Treatment of **17** with acid was presumed to give the α,β-unsaturated ketone which underwent a spontaneous Michael reaction to give **18**. Reduction of the resulting ketone **18** was followed by dehydration to provide **19**.

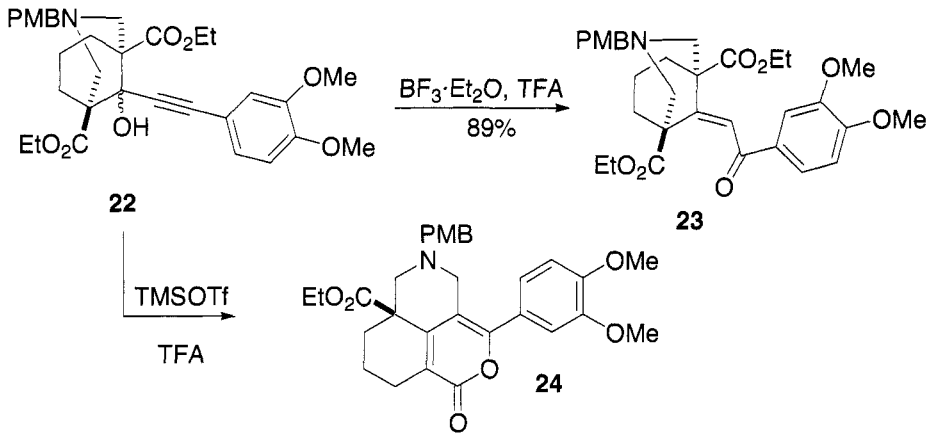


Holger and coworkers employed the Meyer–Schuster rearrangement in their synthesis of a novel histamine H_3-receptor antagonist.[19] Addition of

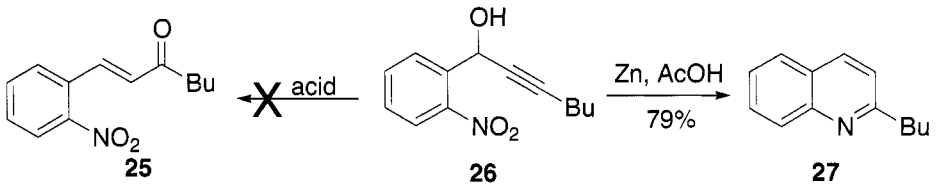
ethynyl magnesium bromide provided a propargylic alcohol, which was readily converted to α,β-unsaturated aldehyde **21** via the Meyer–Schuster protocol.



The Meyer–Schuster rearrangement provided an efficient route to compounds such as **23**, prepared in order to fully investigate the photochemical rearrangement of the 3-azabicyclo[1.3.1]nonane skeleton.[20,21] BF_3•OEt_2 proved to be quite effective resulting in an 89% yield of the Meyer–Schuster product. Interestingly, similar conditions (TMSOTf in TFA) resulted in low yields of the Meyer–Schuster product along with **24**, arising via a [1,3]-sigmatropic shift of the expected Meyer–Schuster product and subsequent ring closure.

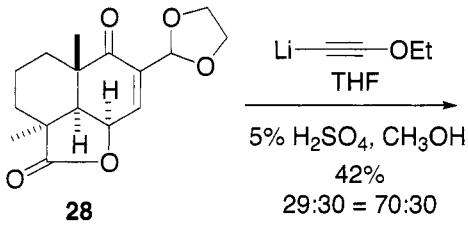


Deshong and Sandlier found that nitrochalcones, such as **26,** were resistant to the Meyer–Schuster reaction under a variety of conditions.[22] Fortunately reduction of the nitro group prior to the rearrangement proved to be a more effective strategy. Enhanced reactivity, due to the more electron rich aniline, allowed for Meyer–Schuster rearrangement which was immediately followed by cyclization to **27**. While tertiary alcohols react more efficiently, this one-pot preparation of quinolines has proven general for a variety of nitroarenes.



25 26 27

The addition of alkoxyacetylides to aldehydes and ketones has emerged as a powerful olefination strategy for the production of α,β-unsaturated carboxylic esters. This technique was first reported in the synthesis of an antifungal mold metabolite isolated from the fermentation of an *acrostalagmus* species. Addition of the acetylide anion to **28** and subsequent Meyer–Schuster rearrangement completed the synthesis of the metabolite **29** along with its anomer **30**.[23]



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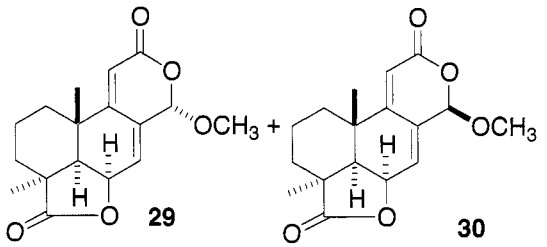
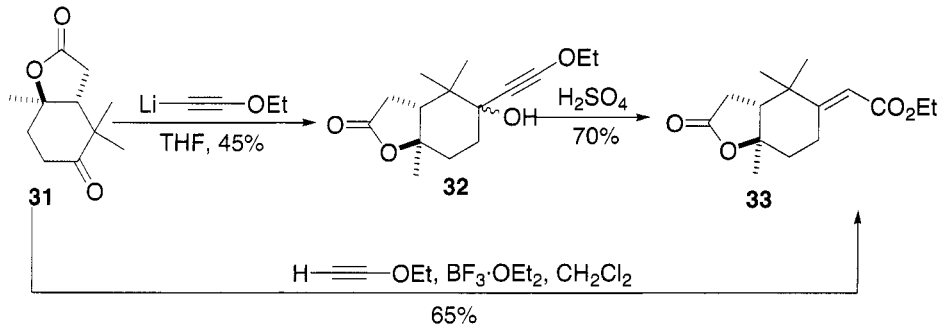
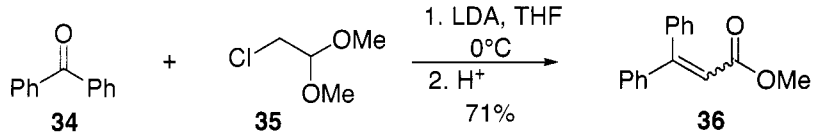


29 **30**

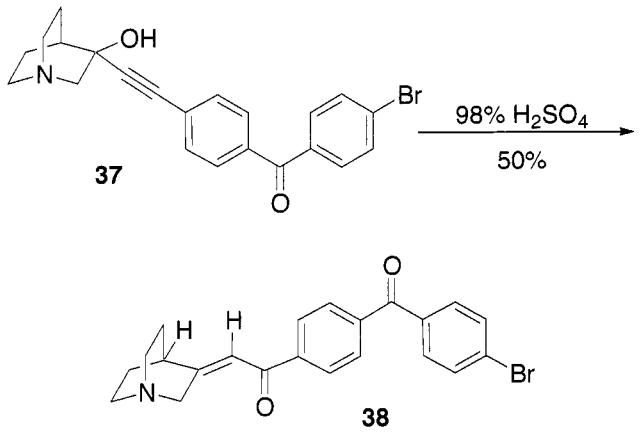
Similarly, Crich and colleagues' synthesis of the taxol AB ring system utilized this methodology, converting propargylic alcohol **32** into the corresponding ester.[24,25] The addition of lithium ethoxyacetylide was followed by rearrangement to **33** in modest yield. To improve this conversion, the Vierregge modification[26] of the Meyer–Schuster rearrangement was employed. Treatment of ketone **31** with ethoxyacetylene in the presence of BF_3•OEt_2 resulted in the direct synthesis of **33** in greatly improved yield. Notably, both of these processes resulted in a single olefin isomer. Recovery of the starting material and incomplete reaction was attributed to the difficulty in handling and purifying the commercially available ethoxyacetylene.[27] A similar process was utilized, albeit less successfully, in the synthesis of lancifolol.[28]



An interesting solution to the problem described above was put forth by Olah[29] and others.[27] In situ generation of methoxy acetylide precludes the use of methoxyacetylene, and provides for the efficient one-pot conversion of **34** to **36**. The acetylide anion can be efficiently generated under a variety of conditions,[27] including sodium in ammonia[30] or LDA in THF.[29]

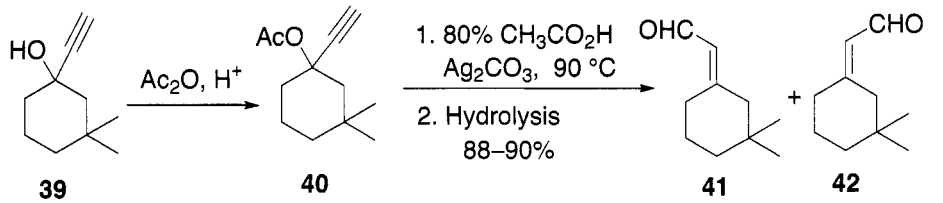


Brown and coworkers found use for the Meyer–Schuster rearrangement in their synthesis of quinuclidine inhibitors of 2,3-oxidosqualene cyclase/lanosterol synthase (OSC).[31] The rearrangement was the last step in the synthesis of one such inhibitor, utilizing concentrated H_2SO_4 to carry out the transformation from **37**.



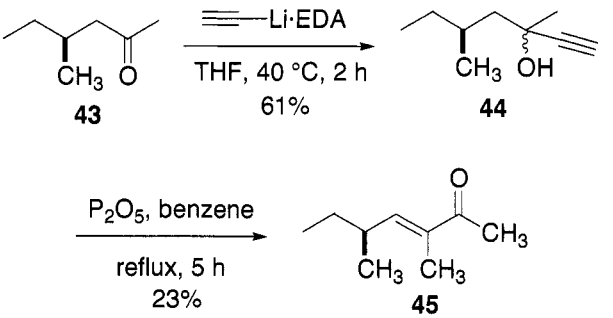
The practicality of the Meyer–Schuster and Rupe rearrangements has been further demonstrated in synthetic efforts toward insect pheremones.

Specifically, the synthesis of the cyclohexyl components of the boll weevil sex pheromone featured the Meyer–Schuster reaction of **40**, prepared via acetylide addition and acetylation of the resulting tertiary alcohol.[32] Treatment of **40** with silver(I) carbonate in acetic acid resulted in smooth formation of aldehyde isomers **41** and **42** (47:53) in excellent yield.



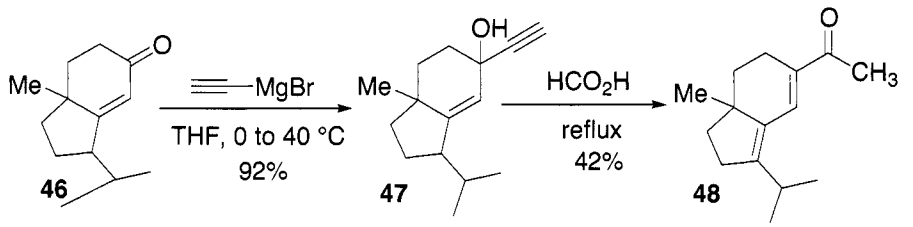
39 **40** **41** **42**

Conversely, Bestmann and coworkers[33] utilized the Rupe reaction to prepare normanicone[34,35], a mandibular gland pheromone in the North American ant species *manica mutica* and *manica bradley*. In a manner similar to above, acetylide addition produced alcohol **44** which was treated with P_2O_5 to yield the Rupe product **45**, albeit in low yield.

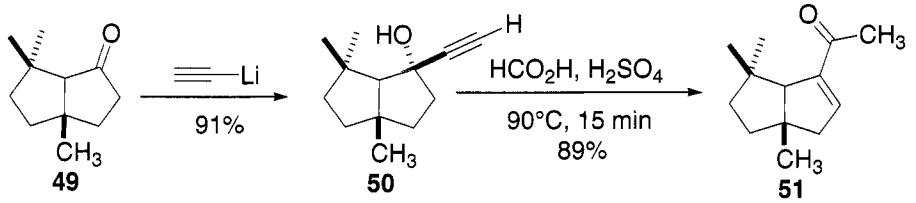


43 **44** **45**

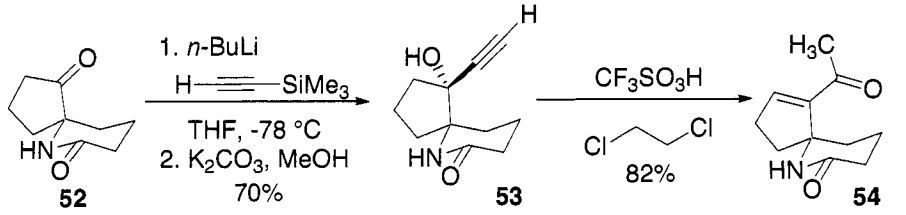
This homologation and rearrangement process emerges as a commonly observed theme with regard to the Rupe protocol.[36-42] Following acetylide addition to a ketone, treatment with acid typically results in production of an α-substituted α,β-unsaturated ketone via the Rupe rearrangement. In this manner, the Rupe reaction has found utility in the synthesis of the tricyclic skeleton of cyathins,[43] a family of biologically active natural products, featuring a unique 5-6-7 ring system. Treatment of alcohol **47** with refluxing formic acid resulted in a modest yield of **48**.



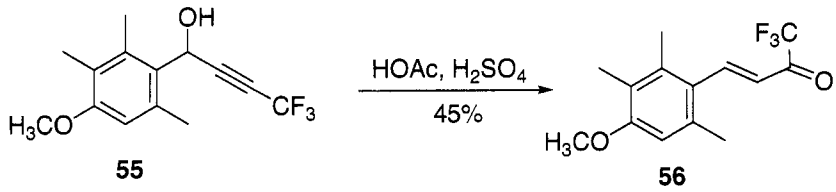
Similarly, Paquette's stereoselective synthesis of a marine sesquiterpene from the capnellene family[44–47] utilizes this addition/rearrangement protocol.[48] Alcohol **50**, produced by lithium acetylide addition to **49**, underwent smooth rearrangement to provide **51** in excellent yield.



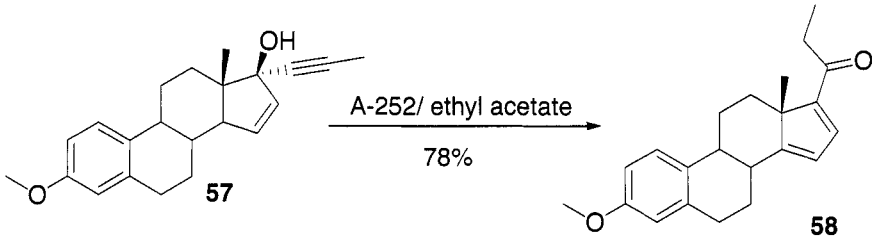
Alternatively, following addition of the silyl acetylide anion and deprotection to provide **53**, a triflic acid mediated Rupe rearrangement in dichloroethane was effected to give **54**.[49] These conditions were discovered when more typical conditions (H_2SO_4, HOAc) failed to produce significant quantities of **54**.



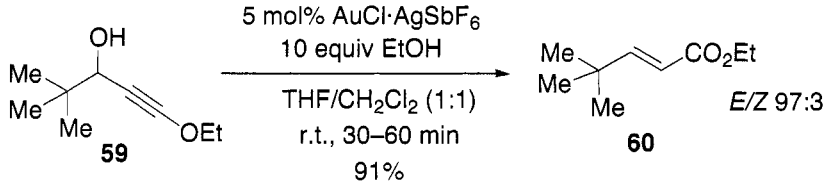
Additionally, the synthesis of fluorinated analogues of retinoic acid featured the conversion of **55** to **56** under standard conditions, as a key step in the work of Pawson and coworkers.[50]



The utility of the Rupe reaction has been impressively demonstrated in its large scale pilot plant implementation for the synthesis of steroid intermediate **58**.[51] Using the strongly acidic Amberlyst type resin A-252 in ethyl acetate, the reaction proceeded to produce **58** from **57** in 78% yield and 98% purity. Notably, the reaction has been accomplished on 64 kg scale, in a manner more inexpensive and environmentally benign than previously described.[52]

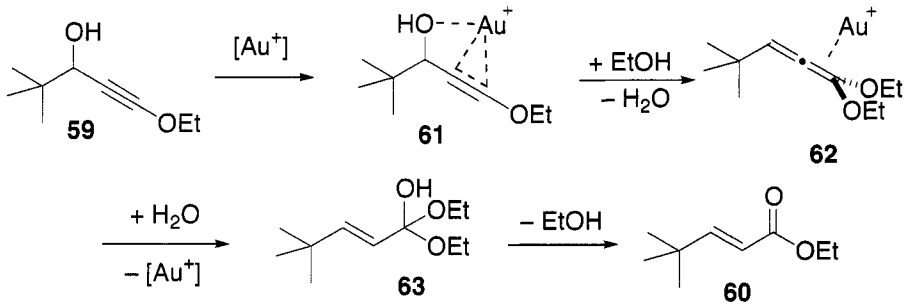


Although classic Meyer–Schuster and Rupe rearrangements have been useful in many synthetic endeavors, the harsh conditions required to initiate the aforementioned rearrangements as well as poor selectivity limit their applicability. In light of this, different catalytic systems have been explored in order to bring about the transformations under milder reaction conditions. One such emerging catalytic system which has received a substantial amount of attention involves using gold(I) and gold(III) salts. Pioneers in the field, Dudley and coworkers have reported olefination of hindered ketones via addition of ethoxyacetylide followed by subsequent gold-catalyzed Meyer–Schuster rearrangement.[53] As a demonstration of this approach, secondary propargylic alcohol **59** was smoothly converted to **60** in good yield and with high olefin isomer selectivity.[54] The same reaction conditions, having been meticulously optimized, were also successful in promoting the rearrangement of tertiary propargylic alcohols via the Meyer Schuster rearrangement.

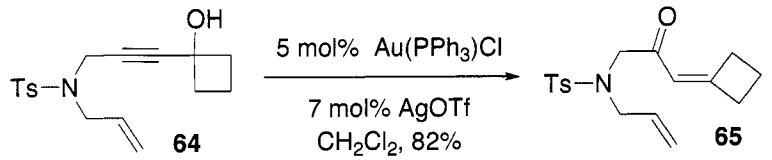


While these reactions can be thought of as Meyer–Schuster reactions, as a result of the products formed, it is likely their mechanism is somewhat different. Dudley and coworkers have proposed a hypothetical mechanism for this variant of the reaction.[54] The gold catalyst is presumed to coordinate

with the ethoxyalkyne which promotes addition of ethanol and loss of water to give 1,1-diethoxyallene **62**. Hydration of the allene and gold decomplexation results in **63**. It is uncertain whether the gold catalyst plays a role in the reincorporation of water in this step which determines the stereochemistry of the final product. Finally, elimination of ethanol results in formation of α,β-unsaturated ester **60**.

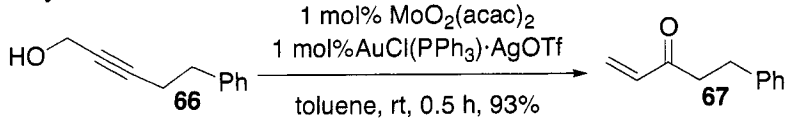


Chung and colleagues also employed gold(I) catalysts in their study focused on the rearrangement of cycloalkynols to α,β-unsaturated ketones.[55] For example, **65** is smoothly produced from **64** under the conditions shown. Although the exact mechanism of the transformation was unknown, it was surmised that dehydration of the alcohol and subsequent addition of water to a cumulene intermediate may be involved.

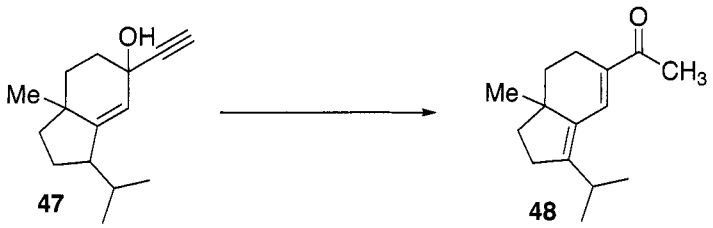


Similarly, Zhang and co-workers employed gold-catalyst $Au(PPh_3)NTf_2$ to effect the formation of α,β-unsaturated ketones from propargylic acetates.[56] As in the other examples, high levels of *E*-selectivity and good yields were observed.

Research by the Akai group led to the discovery that a combination of Mo and cationic Au catalysts increases both the rate and yield of Meyer–Schuster rearrangements.[57] Generally reactions occurred at room temperature within an hour and afforded, when applicable, high *E*-selectivity. For example, reaction of **66** under the described conditions resulted in **67** in excellent yield.



1.2.3.5 Experimental



3-Acetyl-6-methyl-9-(1-methylethyl)bicyclo[4.3.0]nona-2,9-diene (48)[43]
Ethynylalcohol **47** (1.00 g, 4.60 mmol) was dissolved in HCO_2H (10 mL) and refluxed for 15 min. The mixture was poured into saturated aqueous $NaHCO_3$, and extracted with pentane. Combined organic phases were successively washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 80 g; elution with 8:1 hexane–AcOEt) to give **48** (419 mg, 42%) as a colorless plate.

1.2.3.6 References

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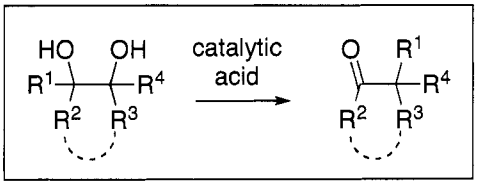
1.2.4 Pinacol Rearrangement

Brian Goess

3.2.4.1 Description

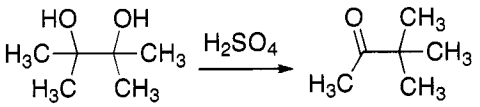
When a vicinal diol is treated with catalytic acid, an E1-type dehydration and subsequent [1,2]-shift of an adjacent bond generates an aldehyde or ketone in a transformation known as a pinacol rearrangement.



When the leaving group is something other than water, the transformation is known as a semipinacol rearrangement. Semipinacol rearrangements are more commonly used than pinacol rearrangements and are generally higher-yielding. Semipinacol rearrangements can be stereoselective, especially in cyclic systems. Furthermore, when the migrating bond is part of a ring, the transformation leads to either ring enlargement or ring contraction. As a result of these and other useful characteristics, semipinacol rearrangements have found widespread use in organic synthesis.

1.2.4.2 Historical Perspective

The first pinacol rearrangement was conducted by Fittig in 1860, though he did not know the precise constitutions of the starting material and product at the time of the experiment. On treatment of 2,3-dimethylbutane-2,3-diol (pinacol) with sulfuric acid, 3,3-dimethylbutane-2-one (pinacolone) was formed.[1]

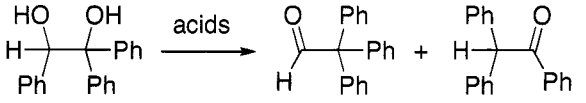


pinacol pinacolone

In 1873, Butlerov proposed the now-accepted mechanism for this reaction in which he suggested the involvement of a carbon skeleton

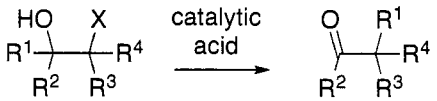
rearrangement.[2] This was a bold suggestion considering skeletal rearrangements were not well-known at the time.[3]

Subsequent to its initial discovery, the pinacol rearrangement was found to be general for a wide range of 1,2-diols, including both cyclic and acyclic diols. However, due to the intervention of carbocationic intermediates, asymmetric 1,2-diols often generate mixtures of constitutional, regio-, and stereoisomers, along with elimination by-products. When the effect of the concentration of various protic acids on the yield of the pinacol-pinacolone rearrangement was measured, the amount of elimination by-products were found to increase as the dilution of aqueous protic acid increased.[4] Furthermore, when diol **1** is treated with sulfuric acid two pinacol products are formed in varying amounts depending on the identity and concentration of the acid.[5] These and similar concerns mitigate the synthetic utility of the pinacol rearrangement. Initial reaction development efforts focused on determining which structural features of 1,2-diols favor predictable and high-yielding reactions.



1

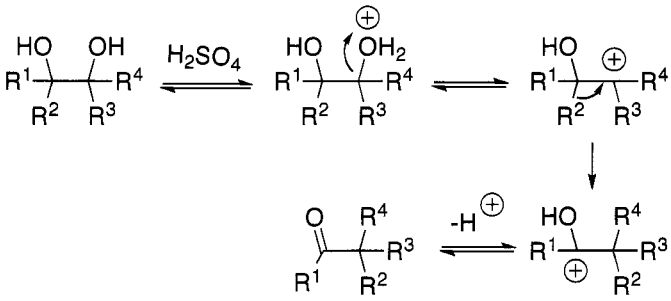
The synthetic utility of the pinacol rearrangement was greatly enhanced when variants bearing leaving groups other than water were developed. In such semipinacol rearrangements,[6] dramatically enhanced regioselectivities are often observed. Semipinacol rearrangements continue to find applications in modern total syntheses, especially in cases where the transformations are also stereoselective.



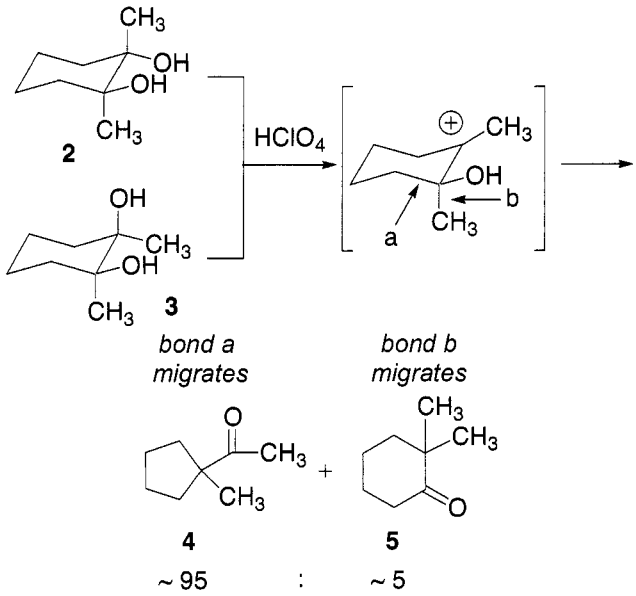
X = halogen, OSO_2R, SR, N_2^+

1.2.4.3 Mechanism

The fundamental mechanism of the pinacol rearrangement is widely accepted and consists of protonation of an alcohol, departure of water to generate a carbocation, [1,2]-migration of an adjacent alkyl group, aryl group, or hydride, and deprotonation.

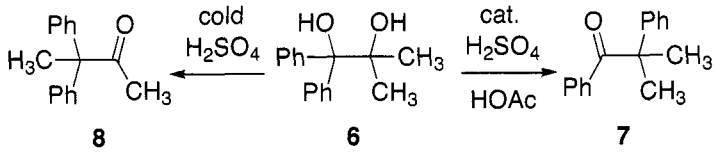


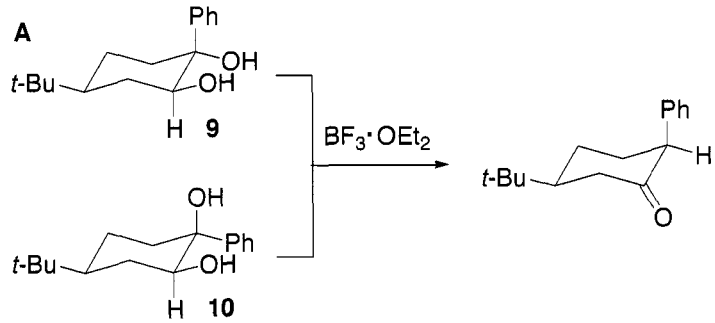
Evidence supporting carbocation intermediates in pinacol rearrangements was provided when diastereomers **2** and **3** were found to produce similar product ratios on treatment with dilute perchloric acid (**4**:**5** ca. 95:5).[7] A non-concerted mechanism with a common cationic intermediate that yields two different products depending on which adjacent bond migrates would be expected to produce such a result. There is, however, computational data that some pinacol rearrangements, especially those involving a hydride migration, may occur instead via concerted, hydrogen-bridged transition states.[8]

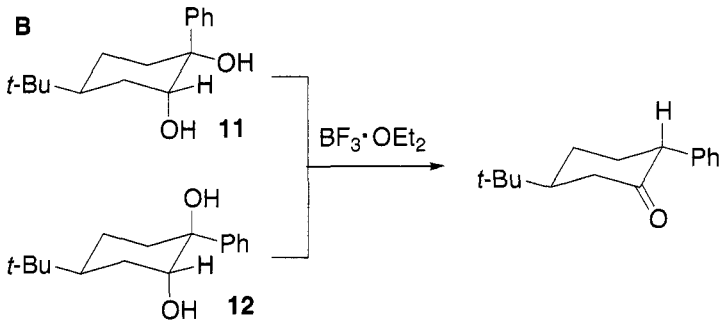


The pinacol rearrangement of unsymmetrical 1,2-diols is usually regioselective, which is the result of two factors: (1) the reaction proceeds via the most stable carbocation intermediate, and (2) groups that better stabilize developing positive charge migrate preferentially (aryl, H, vinyl > 3° > 2°> 1°).[9] The high migratory aptitude of aryl groups may be due in part to their

ability to provide anchimeric assistance[10] in departure of the leaving group. Exceptions to these trends are not uncommon, and modifications to the experimental conditions can produce divergent result. The behavior of **6** under two similar sets of conditions illustrates this dichotomy.[11] **7** is generated when a phenyl, the group with the higher migratory aptitude, migrates; however, **8** is generated when the more stable carbocation is formed initially and a methyl group migrates.



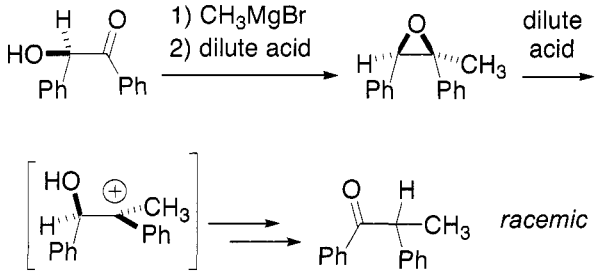




Due to the symmetry of the carbocation intermediate, pinacol rearrangements of acyclic substrates are rarely stereoselective. However, conformational constraints in cyclic systems can lead to high stereoselectivities. The reactivity of the set of conformationally-locked stereoisomers **9–12** when treated with a Lewis acid is illustrative.[12] Regardless of the stereochemistry at C-1, both C-2 (*S*) diastereomers (**9** and **10**) yield only the ketone α-(*S*) stereoisomer, indicating hydride migration proceeds stereoselectively from the bottom face of the ring system (pathway

A). In contrast, both C-2 (*R*) diastereomers (**11** and **12**) yield only the ketone α-(*R*) stereoisomer, indicating hydride migration proceeds stereoselectively from the top face of the ring system (pathway **B**).

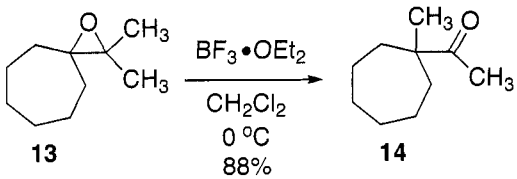
The carbocation intermediate in a pinacol rearrangement could be stabilized by intramolecular electron donation from the adjacent hydroxyl group to form a protonated epoxide. Indeed, epoxides have, on occasion, been isolated under pinacol rearrangement conditions and have been implicated as intermediates as well.[13] For example, when (–)-benzoin was treated with methylmagnesium iodide followed by dilute acid, an optically-active epoxide was isolated.[14] Further treatment of the epoxide with acid generated a racemic ketone.



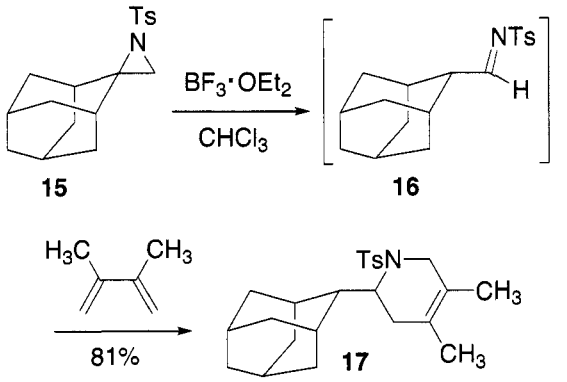
1.2.4.4 Variations, Improvements and Modifications

Although dilute sulfuric acid is the most common acid used in pinacol rearrangements, the examples in the accompanying sections demonstrate that many protic and Lewis acids can be employed effectively. Solid acids such as alumina and montmorillonite clays have also been shown to be effective heterogeneous catalysts of the pinacol rearrangement.[15] Selectivities are highly dependent on the identity of the catalyst. Radical cation-catalyzed pinacol rearrangements have also been reported using aminium salts[16] and nitrosyl tetrafluoroborate,[17] though doubt has been cast on the significance of the mechanistic distinction between organic cation and cation radical pathways.[18]

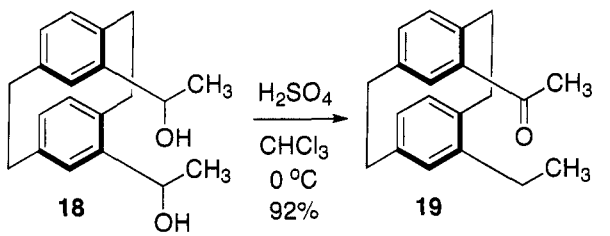
Rearrangements analogous to the pinacol rearrangement can be effected through opening of an activated epoxide. For instance, when epoxide **13** is treated with boron trifluoride-diethyl etherate, ketone **14** is produced.[19]



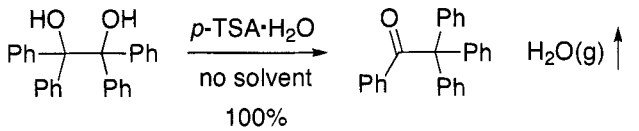
An analogous transformation with *N*-tosyl aziridines produces *N*-tosyl imines.[20] When aziridine **15** was treated with boron trifluoride-diethyl etherate in the presence of 2,3-dimethylbutadiene, amine **17** was produced via imine **16**.



Through-space pinacol rearrangements have also been observed. When paracyclophane **18**, a diol with hydroxyl groups in pseudo-vicinal proximity, was exposed to acid, a surprising transannular pinacol-like hydride migration occurred to yield ketone **19**.[21]

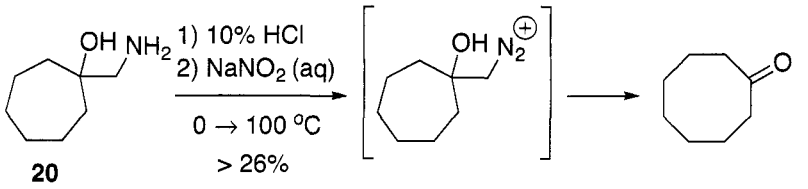


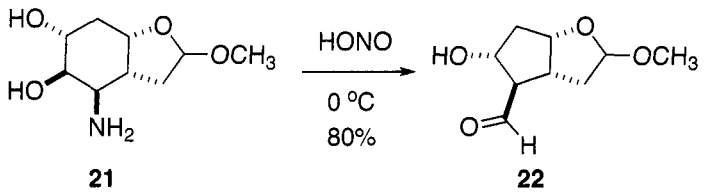
Pinacol reactions were found to proceed effectively in the solid state, and the mechanism of this reaction was investigated by atomic force microscopy.[22] The rate of the reaction was enhanced dramatically if water was continuously condensed out of the reaction mixture.



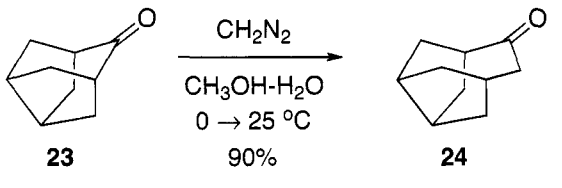
The most synthetically useful variations of the pinacol rearrangement are the so-called semipinacol rearrangements,[6] in which the hydroxyl leaving group is replaced with another leaving group. In general, semipinacol

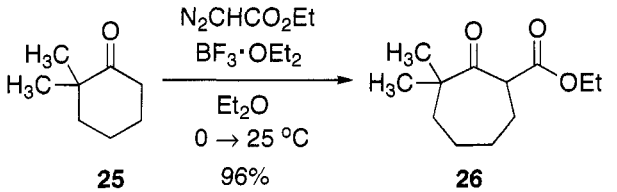
rearrangements proceed under milder conditions and with enhanced selectivities when compared to the corresponding pinacol rearrangements. One of the best-known examples of a semipinacol rearrangement is the Tiffeneau–Demjanov rearrangement, which is often used to conduct ring-enlargements. On treatment of cyclic vicinal amino-alcohol **20** with HONO, diazotization of the amine followed by ring-bond migration generates cyclooctanone.[23] Furthermore, inversion of configuration is generally observed, and, in certain cases, ring-contraction is possible (**21** → **22**).[24]



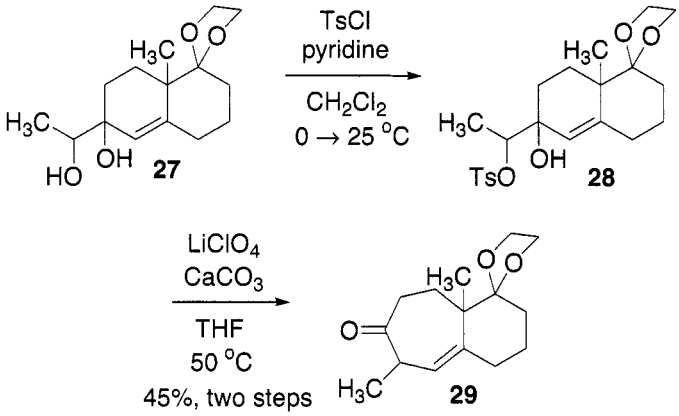


A related transformation involves treatment of a ketone with a diazo compound (**23** → **24**).[25] Formation of epoxide by-products is minimized in polar, aprotic solvents or with Lewis acid catalysis. Ethyldiazoacetate can also be used to transform ketones to γ-keto esters under the influence of Lewis acids (**25** → **26**).[26] As is the case with most Tiffeneau–Demjanov and related rearrangements, the least substituted group migrates preferentially.



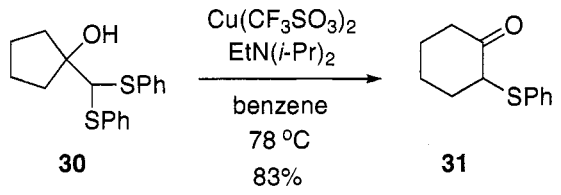


Group VI elements are frequently employed as leaving groups in semipinacol rearrangements. A unsymmetrical vicinal diol that might not react with high regioselectively in a traditional pinacol rearrangement may undergo a semipinacol rearrangement with high regioselectivity if one of the alcohols in the diol can be selectively activated. For instance, selective tosylation of the less hindered secondary alcohol in **27** affords tosylate **28** which undergoes a regioselective pinacol rearrangement to generate ketone **29**.[27] Note the preferential migration of the vinyl group, in accord with the expected relative migratory aptitudes.



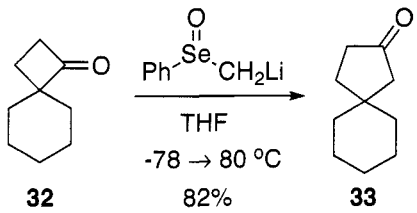
27 **28** **29**

A thiol leaving group can also be employed in semipinacol ring-expansion reactions. When dithiophenoxymethyl anion is added to cyclopentanone, cyclohexanone **30** is produced. Treatment of **30** with copper(II) triflate and diisopropylethylamine results in cyclohexanone **31**.[28]



30 **31**

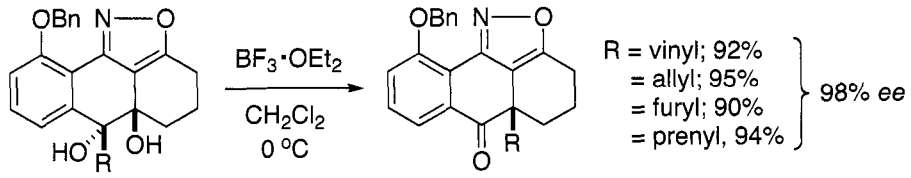
A similar transformation has been developed for selenium. When cyclobutanone **32** is treated with a lithiated alkyl selenoxide, cyclopentanone **33** is produced.[29]



32 33

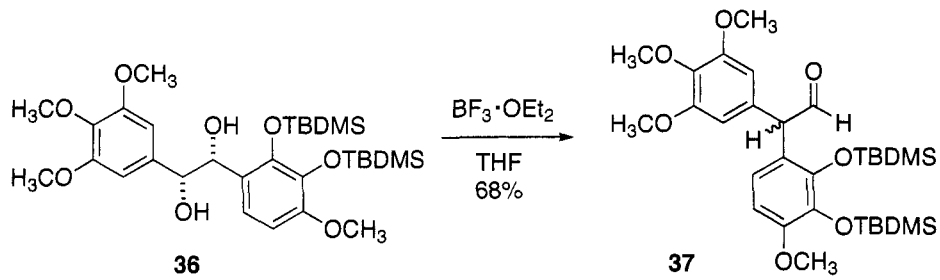
3.2.4.5 *Synthetic Utility*

The classic pinacol rearrangement can be used to set the stereochemistry of angular carbons in systems where an isoxazole moiety is correctly positioned to stabilize a developing carbocation.[30] Thus, when diols **34** were exposed to a Lewis acid, ketones **35** were regio- and stereoselectively generated.



34 35

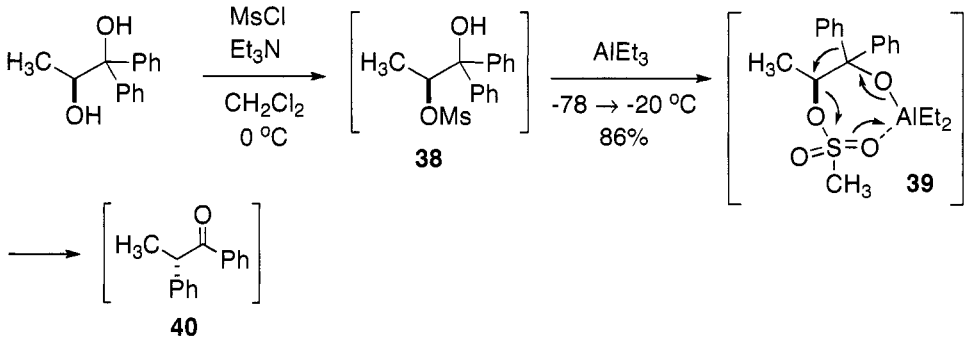
The pinacol rearrangement is a key step in a total synthesis of hydroxyphenstatin.[31] The authors were attempting to form the dimethylacetonide of **36** using boron trifluoride-diethyl etherate and 2,2-dimethoxypropane and found a pinacol reaction had taken place instead. They were able to optimize the yield by leaving out the 2,2-dimethoxypropane.



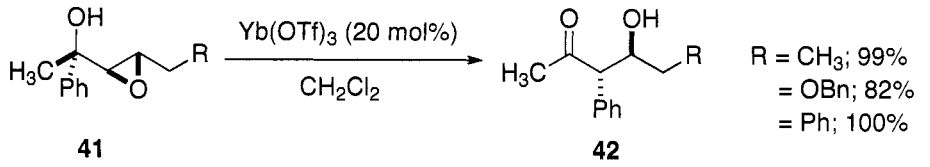
36 37

A number of synthetic methods have been developed that take advantage of the potential stereoselectivity of semipinacol rearrangements. For instance, treatment of mesylate **38** with triethylaluminum results in the stereoselective formation of ketone **40** via a Lewis acid-bridged cyclic intermediate **39**.[32] This strategy of selectively activating the less hindered

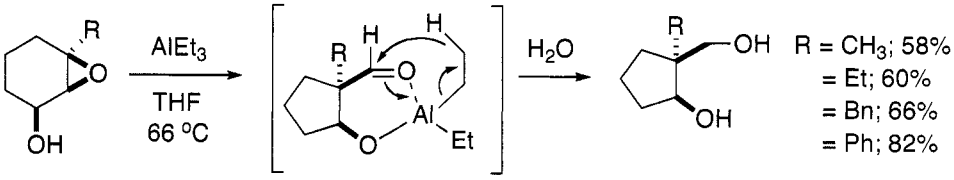
alcohol of a vicinal diol and inducing a semipinacol rearrangement on the product was employed in a synthesis of longifolene (see **27** → **29**).[27]



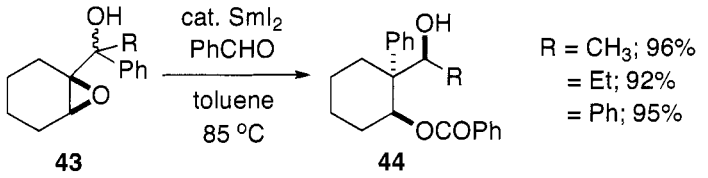
A large family of semipinacol rearrangements have been developed for the stereoselective transformation of non-racemic α-hydroxy epoxides.[33] These reactions are usually Lewis acid-promoted, as in the case of the conversion of **41** to **42**.[34]



A Lewis acid-promoted tandem rearrangement/reduction of non-racemic α-hydroxy epoxides yields 2-quarternary-1,3-diols.[35] This reaction also successfully transforms α-hydroxy-*N*-tosyl aziridines into *N*-tosyl-1,3-amino alcohols.

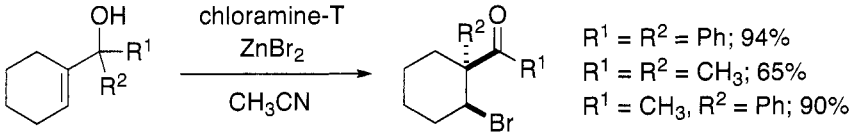


A related reaction transforms non-racemic α-hydroxy epoxides (**43**) into 2-quarternary-1,3-diol monoesters (**44**) under the influence of samarium iodide and an aldehyde.[36] Though **43** was used as a mixture of diastereomers, only one product diastereomer was observed.



43 44

Allylic alcohols may be converted to α-quaternary-β-bromoketones via a semipinacol rearrangement on the corresponding bromonium ions.[37]



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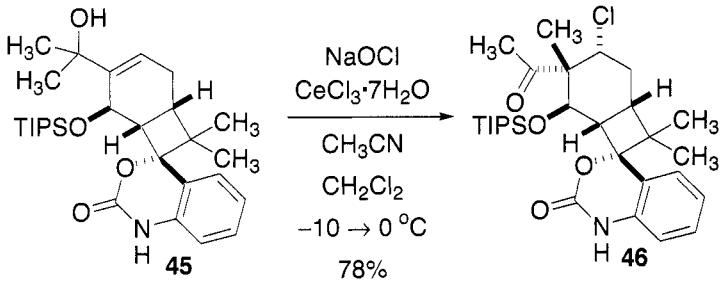
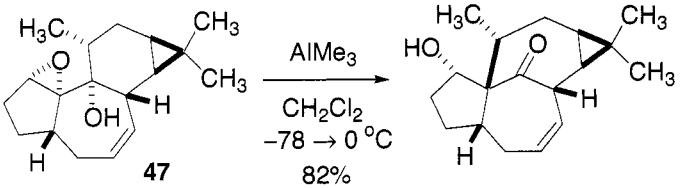
A related reaction was used in a total synthesis of racemic welwitindolinone A isonitrile.[38] Allylic alcohol **45** was treated with sodium hypochlorite and cerium trichloride heptahydrate, which led to formation of rearranged ketone **46**.



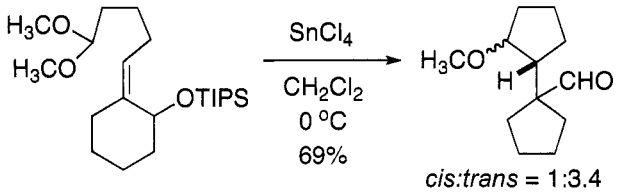
45 46

Many additional applications of semipinacol rearrangements on α-hydroxy epoxides have been developed,[33] and these reactions have found use in complex molecule synthesis. For example, α-hydroxy epoxide **47** underwent a Lewis acid-mediated semipinacol ring expansion to set the challenging in-out intrabridgehead stereochemistry of the ingenol core.[39]

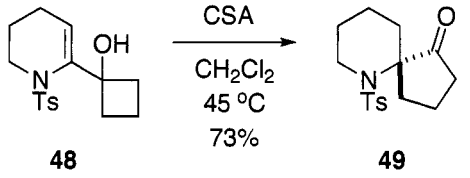


47

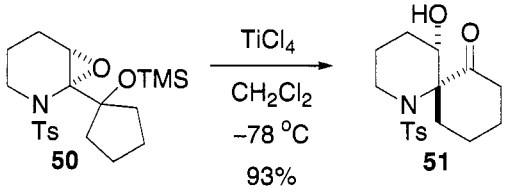
Oxonium ions generated *in situ* from the Lewis acid-promoted collapse of acetals can serve as migration termini for semipinacol rearrangements in a tandem Prins/semipinacol ring-contraction process.[40]



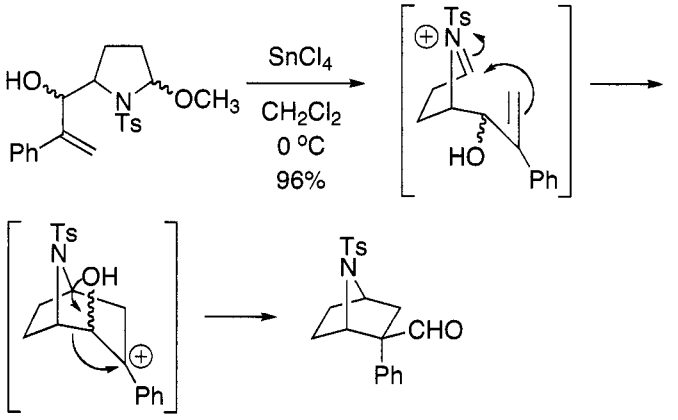
Iminium ions generated *in situ* can also serve as migration termini for semipinacol rearrangements. For instance, azaspirocyclic ketones are generated from appropriately-substituted *N*-tosyl enamides (**48** → **49**).[41] The corresponding reaction with a cyclopentanol in place of the cyclobutanol led primarily to elimination side reactions, but this was overcome by pre-forming the *O*-silyl epoxide (**50** → **51**).



48 **49**

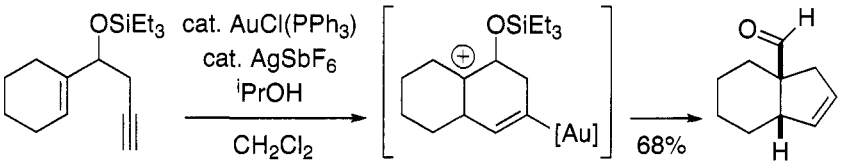


50 **51**



Tandem Prins/semipinacol rearrangements have been developed for complex molecule synthesis.[42] A tandem aza-Prins/semipinacol rearrangement strategy was used in the preparation of a key intermediate in the synthesis of racemic epibatidine.[43]

3-silyloxy-1,5-enynes undergo a gold-catalyzed, tandem 6-*endo*-dig cyclization/semipinacol rearrangement to yield functionalized cyclopentenes.[44]



1.2.4.6 Experimental

The examples presented illustrate two of the common ways pinacol reactions are run. The first is a classic pinacol rearrangement; the second is a semipinacol rearrangement.

Aldehyde (37).[31]
$BF_3 \cdot OEt_2$ (0.82 mL; 6.7 mmol) was added dropwise to a stirred solution of **36** (2.1 g; 3.3 mmol) in anhydrous THF (20 mL) under argon at room temperature. After 1 h, saturated $NaHCO_3$ was added to the mixture before extraction with EtOAc (4 × 15 mL) and drying of the combined organics. Evaporation of the solvent *in vacuo* afforded a light brown oil, which was subjected to flash column chromatography (15:1 hexanes/EtOAc) to generate **37** as a clear oil that crystallized from CH_3OH as a colorless solid (1.3 g; 68%).

Aldehyde (44).[36]
A solution of SmI_2 (0.1m in THF, 0.4 mL) was added dropwise to a solution of **43** (R = Ph) (112.0 mg, 0.4 mmol) and freshly distilled benzaldehyde (1.6 mmol) in dry toluene (4 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred for 4 h at 80 °C, after which TLC analysis showed the starting material had disappeared completely. Then a saturated solution (3 mL) of sodium hydrogen carbonate was added. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent and column chromatography of the crude product on silica gel (petroleum ether/ethyl acetate 30:1 to 15:1) afforded **44** (R = Ph) (147.0 mg, 0.38 mmol, 95%).

1.2.4.7 References

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Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100.
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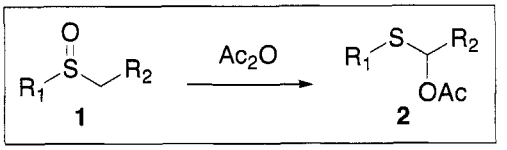
1.2.5 Pummerer Rearrangement

Nadia M. Ahmad

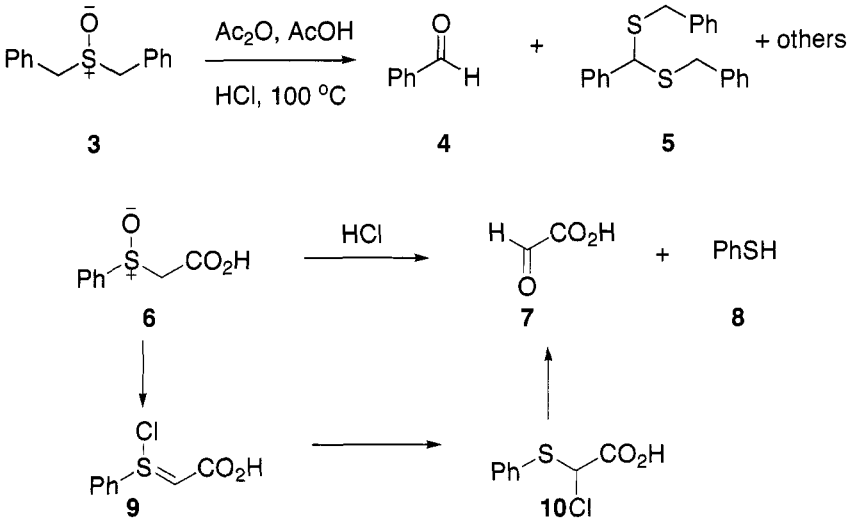
1.2.5.1 Description

The Pummerer rearrangement is the formation of α-acyloxythioethers by the transformation of sulphoxides using acetic anhydride. The sulfur is reduced with concommitant oxidation of the α-carbon.



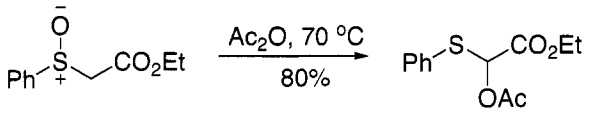
1 2

1.2.5.2 Historical Perspective



The Pummerer rearrangement was reported by Rudolf Pummerer in 1909 when he published a paper in Chemische Berichte.[1] Earlier in the same year, Smythe had reported the reaction of dibenzyl sulfoxide **3** with acetic anhydride and hydrochloric acid to give benzaldehyde **4** and thioacetal **5**, among other products.[2] Smythe was apparently unable to explain the product distribution, which was then left to Pummerer do so in his much-cited paper later that year. Pummerer published the reaction of sulfinyl acetic acid **6** with hydrochloric acid to give glyoxylic acid **7**. The formal oxidation of the

α-carbon was explained by the formation of the intermediate sulfurane **9** followed by the 1,2-chloride shift product **10**.

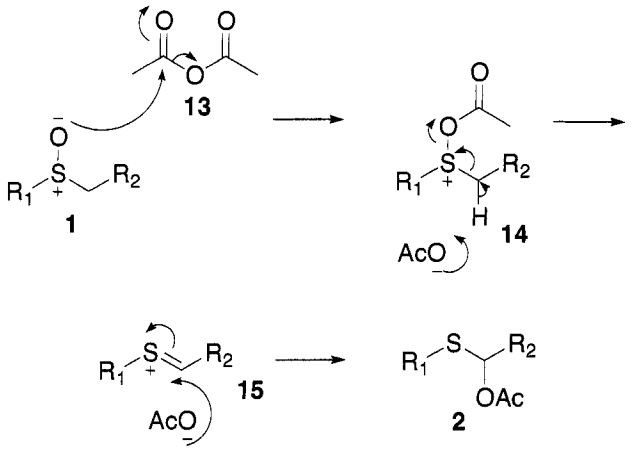


11 **12**

Pummerer wrote only one further paper on this chemistry, in 1910.[3] The reaction of sulfoxide **11** with acetic anhydride was shown to afford sulfide **12** in what is now recognised as the classical Pummerer rearrangement. From these two reports, the scope of the Pummerer rearrangement has been investigated by many prominent groups who have spent much time and effort in extending the utility of this illustrious reaction. This is perhaps best exemplified by the considerable number of reviews on the Pummerer rearrangement.[4–13]

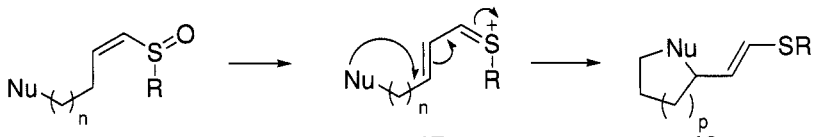
1.2.5.3 Mechanism

The mechanism of the Pummerer rearrangement begins with attack of the sulfoxide oxygen onto acetic anhydride, thereby causing the release of an acetate ion. The acetate ion subsequently acts as a base by removing a proton from the α-carbon resulting in sulfurane **15**. This then undergoes nucleophilic attack by a second acetate anion, leading to the sulfide product **2**.



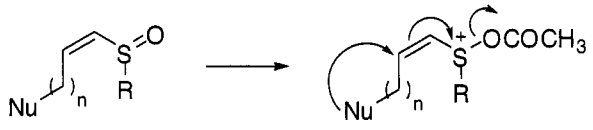
More recently, two distinct mechanistic pathways for the Pummerer rearrangement have been described.[6,14] These are the vinylogous Pummerer pathway,[15] and the additive Pummerer sequence.[16] The vinylogous pathway

can be likened to S_N1 chemistry, as the *S–O* bond scission takes place prior to attack by the nucelophile. This is the classical mechanism for the Pummerer rearrangement.



16 **17** **18**

The additive Pummerer sequence proceeds *via* an S_N2-like displacement, that is, nucleophilic attack and alkoxide departure take place in a concerted manner. This pathway has been utilized more recently for the formation of heteroatom-carbon and carbon-carbon bonds, particularly in the synthesis of polycyclic natural products and drug-like molecules.

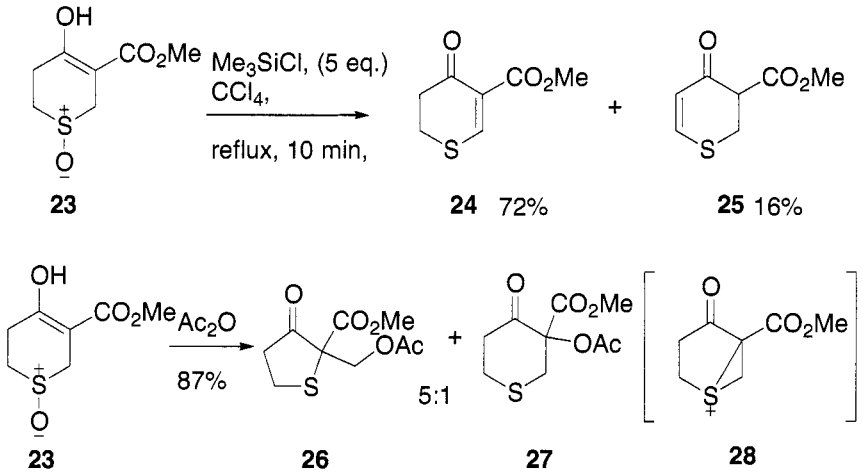


19 **20**

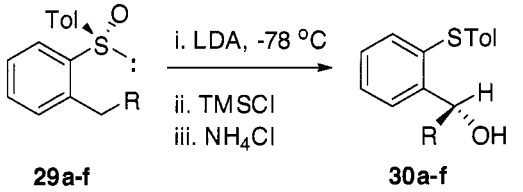
21 **22**

1.2.5.4 Variations and Modifications

Reagents other then acetic anhydride have been used to effect the Pummerer rearrangement. For example, heating sulfoxide **23** (which exists in its enol form) with chlorotrimethylsilane under reflux in carbon tetrachloride gave the desired 3-methoxycarbonylthian-4-one derivatives **24** and **25**.[17] Under standard Pummerer reaction conditions however, sulfoxide **23** underwent rearrangement to give acetates **26** and **27** in which the β-carbons rather then the α-carbons had been oxidised. Small traces of the desired alkenes were also detected. The formation of acetates **26** and **27** was thought to come from attack of the acetate anion on the thiiranium intermediate **28**; the five membered ring would be expected to be the main product due to nucleophilic attack of the acetate at the least sterically hindered position and this was observed.



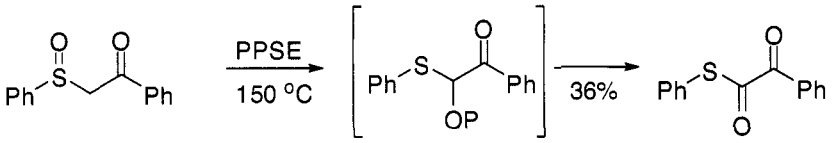
The use of trimethylsilyl halides has been expanded further to afford optically pure benzyl alcohols through a stereoselective vinylogous Pummerer rearrangement.[18] The reaction proceeds *via* a 1,4-migration of the sufinyl oxygen atom to give (*R*)-benzyl alcohols **30a–f** with > 98% *ee*.



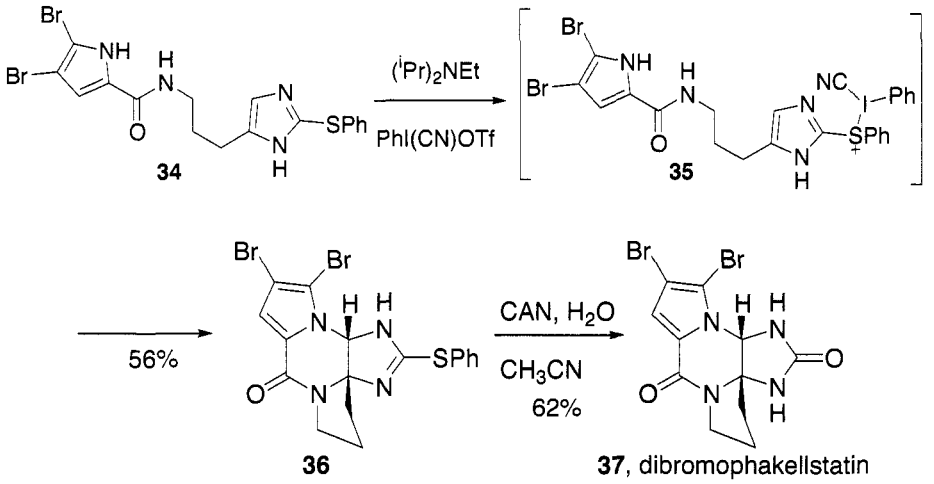
	R	Yield %
30a	CH_3	69
30b	CH_2CH_3	67
30c	CH_2Ph	51
30d	CH_2CH_2Ph	54
30e	$CH_2CH{=}CH_2$	65
30f	CH_2CH_2OH	56

The Pummerer rearrangement can also be invoked by the use of polyphosphoric acid trimethylsilyl ester (PPSE).[19] Using this method, Kakimoto and Imai reported the synthesis of the unusual product phenyl phenylthioglyoxylate **33**. The reaction was thought to proceed *via* phosphorylation of the sulfoxide oxygen rather than silylation as rearrangement did not take place when tris(trimethylsilyl)phosphonate was

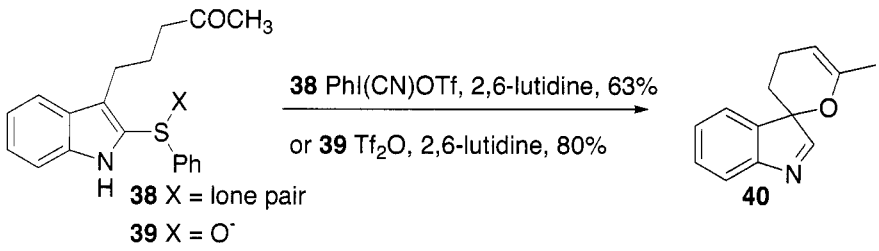
employed, whilst the use of polyphosphoric acid ethyl ester enabled the reaction to proceed.



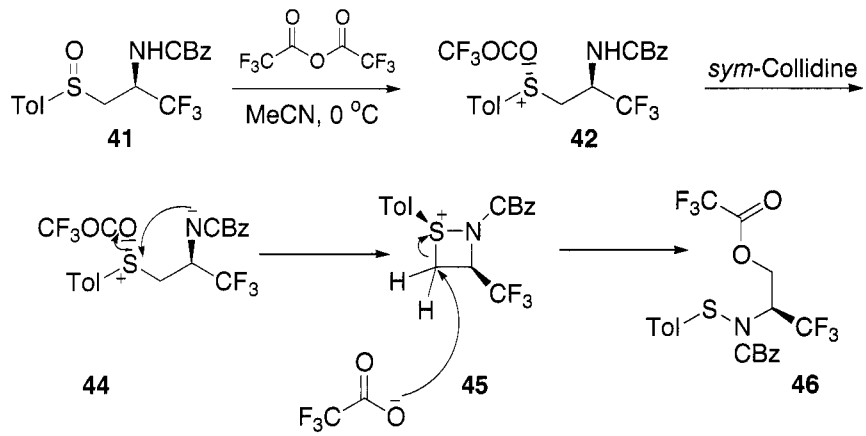
The application of a novel oxidative variant of the Pummerer rearrangement has resulted in the synthesis of the dihydrooroidin-derived natural product, dibromophakellstatin, **37**.[20] The oxidant of choice is Stang's reagent, PhI(CN)OTf.[21] The advantages of this procedure include the avoidance of overoxidation and regioselective nucleophilic addition. Sulfide **34** was converted to the tetracyclic species **36** upon treatment with Stang's reagent in 56% yield. The mechanism may involve a vinylogous Pummerer pathway, or an additive Pummerer sequence.

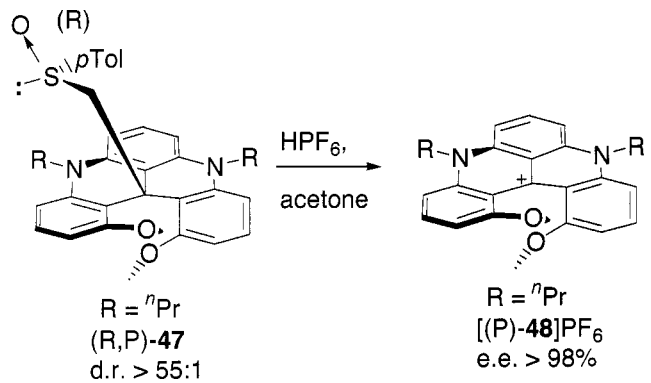


In a similar mode, spirocyclic oxindole derivatives such as **40** can be formed from the corresponding relevantly substituted indoles in good yield.[22–24] These transformations can be carried out using either the sulphide (**38**) and Stang's reagent or the sulfoxide (**39**) and acetic anhydride.



The non-oxidative Pummerer rearrangement of γ-trifluoro-β-aminosulfoxides has been reported in which the rearrangement follows an unusual pathway.[25] Removal of the trifluoroacetate anion occurs by an intramolecular nucleophilic displacement (**44**). The displaced anion then attacks the α-carbon to give the ring-opened aminosulfoxide product **46**.

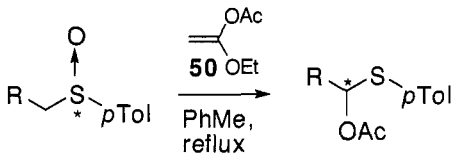




Lacour *et al.* have reported the unusual fragmentation of [4]heterohelicenium sulfoxides when treated under Pummerer rearrangement conditions.[26,27] In this case, instead of using acetic anhydride to enable the

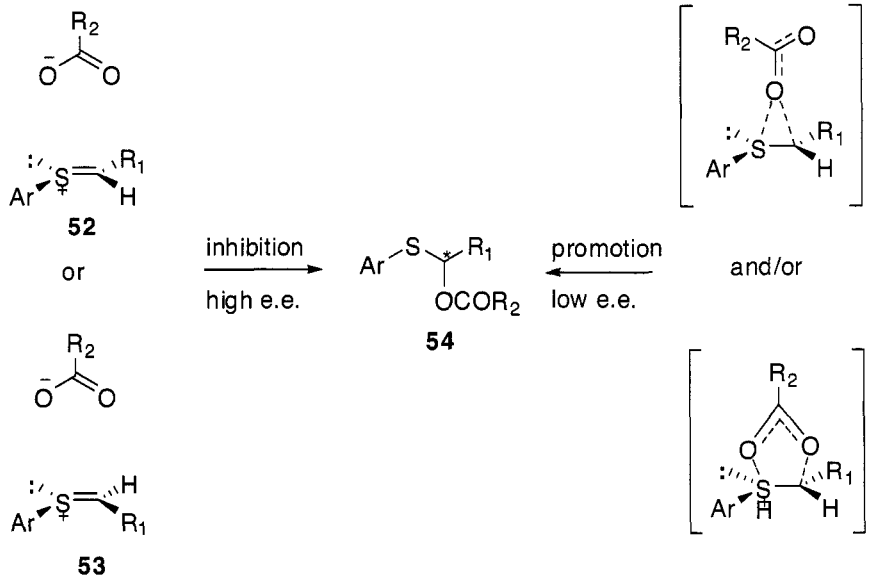
reaction to proceed, hexafluorophosphate HPF_6 was employed. Unlike the expected *β-C-H* bond cleavage, *β-C-C* bond fragmentation took place to give the stable cation **48**, whose presence was indicated by the formation of a deep green colour. The cation could be isolated and purified by silica gel column chromatography as the hexafluorophospate salt.

Kita *et al.* have reported an asymmetric Pummerer rearrangement of optically active sulphoxides, induced by ethoxy vinyl esters (EVE).[28] In particular ethoxy vinyl acetate **50** was used to effect the Pummerer rearrangement of sulfoxides **51a–b** in good yields and high enantioselectivity.



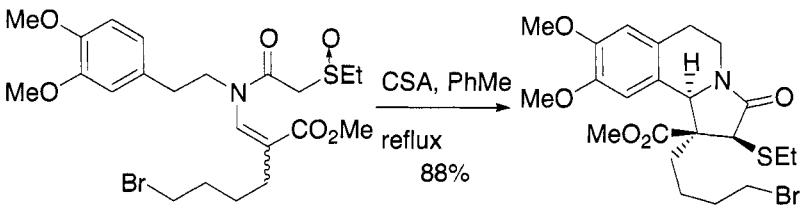
49 **51**

R	Configuration of reactant	Configuration of product	Product *ee*%	Yield %
CO_2Et	*R*	*R*	71	42
$CONMe_2$	*R*	*R*	84	39
Ph	*R*	*R*	20	64
$P(O)(OMe)_2$	*S*	*S*	69	38

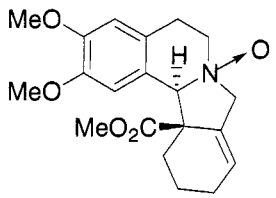


The mechanism of the Pummerer rearrangement whereby a planar sulfurane intermediate is formed makes it clear why the products tend to be racemic mixtures. Kita's proposed mechanism for the reaction involves ring transition states thus explaining the retention of configuration. They concluded that the cleavage of the *S–O* bond is inhibited when EVE bears a powerful electron-donating R group. The rearrangement is then accelerated and takes place through an intramolecular process.

The Pummerer rearrangement has been employed in tandem with other reactions to enable complex transformations to be carried out efficiently and in a one-pot manner. Studies of these have been reported mainly by Padwa who has utilized such transformations in the syntheses of natural products. A particularly intriguing cascade sequence involving the Pummerer rearrangement was employed in the synthesis of the alkaloid jamtine, **57**.[14] Padwa *et al.* synthesized the bromo-enamide **55** in a 4:1 (*Z*/*E*) mixture of isomers. Treatment of the isomeric mixture with camphorsulfonic acid caused the the sulfoxide to undergo a Pummerer/Mannich ion cyclization, which was then followed by a spontaneous Pictet-Spengler reaction to furnish the isoquinoline core. Although a 5:2:1:1 mixture of diastereoisomers was obtained, the desired diastereoisomer **56** was formed preferentially. This was attributed to a 4π-Nazarov-type conrotatory electrocyclisation which controls the direction of closure from the α-acylthionium ion intermediate.



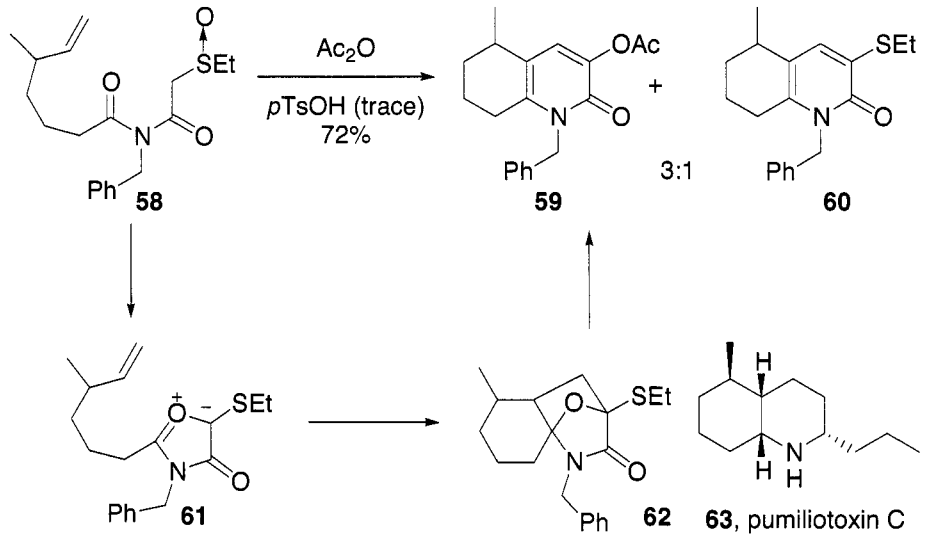
55 **56**



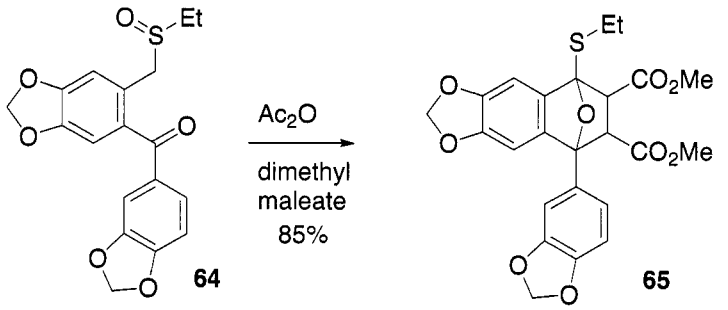
57, jamtine *N*-oxide

In a similar fashion, the Pummerer rearrangement has been used to generate mesoionic dipoles which can then undergo cycloaddition reactions to afford azapolycyclic ring systems.[29,30] This is illustrated in the reaction of imidosulfoxide **58** which, when treated under Pummerer reaction conditions, underwent a tandem Pummerer-induced cyclization–isomünchnone dipolar

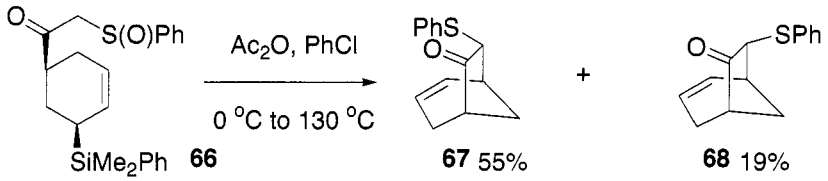
cycloaddition sequence.[31] This resulted in the desired pyridones **59** and **60**, eventually culminating in the formal synthesis of pumiliotoxin C, **63**.



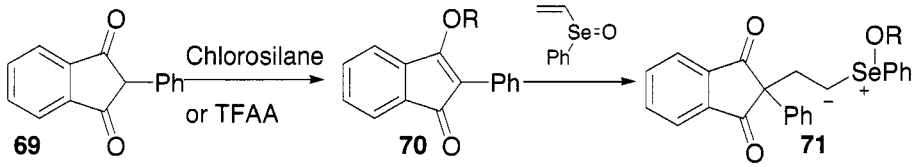
The Pummerer rearrangement can also be carried in tandem with a Diels–Alder reaction.[32] This sequence has been utilized in the syntheses of the arylnaphthalene lignan natural products.[33] Sulphoxide **64** in acetic anhydride was slowly added to a solution of dimethyl maleate in acetic anhydride under reflux, resulting in cycloadduct **65** in 85% yield.

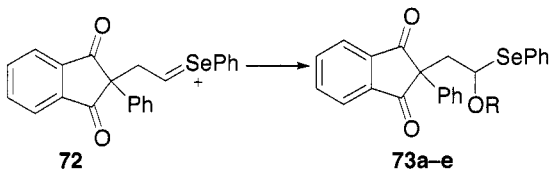


An important variant is the allylic silane directed Pummerer rearrangement. Magnus *et al.* utilized this in their studies towards complex diterpenoid natural products.[34] An added feature in this case was the formation of the bicyclo[1.2.1]octanone core.



Hagiwara *et al.* have described the first domino Michael–seleno additive Pummerer-type reaction, in which a selenoxide takes the place of the sulfoxide classically required for the Pummerer rearrangement.[35] The methodology allows for the introduction of formylmethyl units onto 1,3-dicarbonyl compounds.

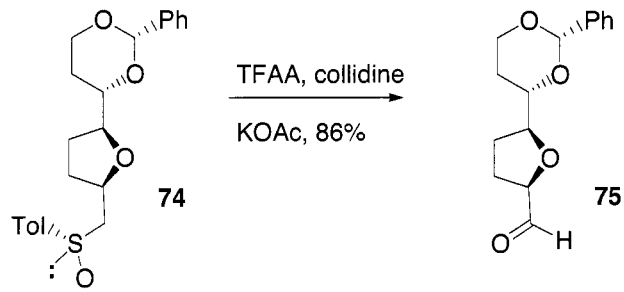




	R	Yield %
73a	TMS	70
73b	DMPS	27
73c	TES	36
73d	TBDPS	43
73e	$COCF_3$	18

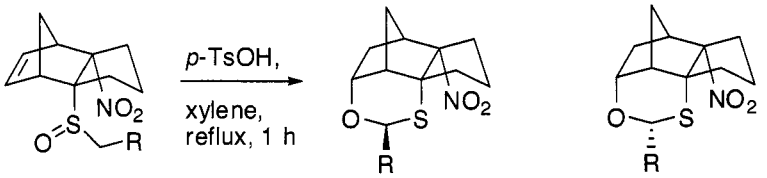
1.2.5.5 Synthetic Utility

Aldehydes and alcohols can be generated by the Pummerer rearrangement and many examples exist.[36] For example, Lee *et al.* employed this reaction in their synthesis of the natural product rolliniastatin 1, among others.[37] The reaction requires the addition of base and proceeds in good yield.



Abe *et al.* have reported methodology for the formation of 1,3-oxathiane rings by the Pummerer rearrangement of γ,δ-unsaturated sulfinyl

compounds.[38] 1,3-Oxathiane rings, mostly used as masked acyl anion equivalents,[39–41] are commonly formed from the hemiothioacetalization of carbonyl compounds with 2-mercaptoethanol. The structure of **77a** was determined by X-ray crystallography while the stereoselectivity was confirmed by nOe studies.

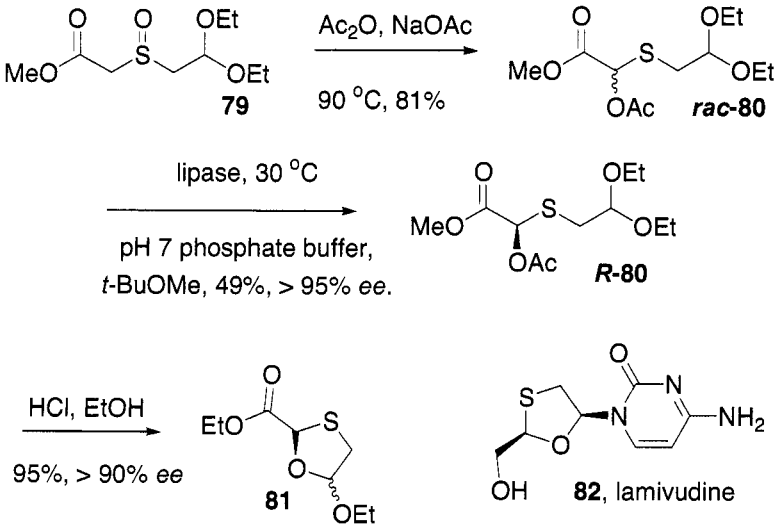


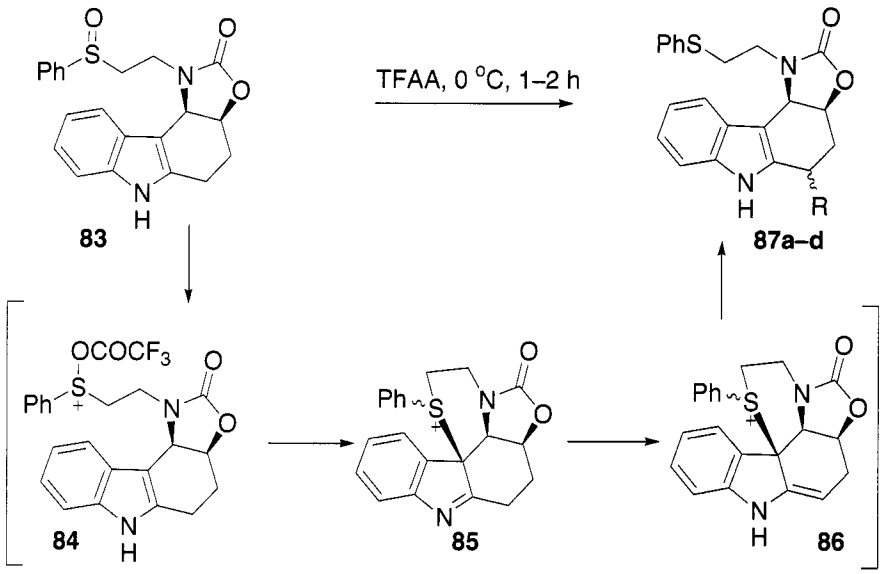
76a R = Me
76b R = Et
76c R = Ph

77a 73%
77c 77%
77c 82%

78a 4%
78b 6%
78c 1%

In their synthesis of the antiviral agent lamivudine **82**, Rayner *et al.* employed the Pummerer rearrangement to form the α-acetoxysulphide **80**.[42] Treating **80** with HCl in dry ethanol then instigated transesterification thus causing removal of the acetate and subsequent *in situ* cyclization to the oxathialane **81**. The authors note that heating the sulphoxide (120 °C) in the absence of NaOAc led to the formation of an enol ether by loss of ethanol.

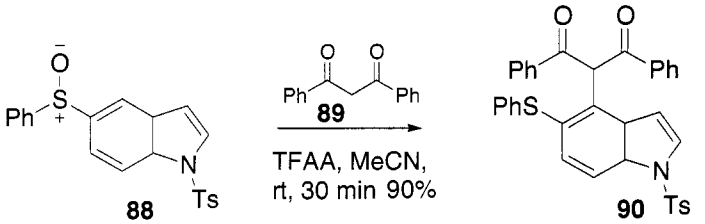




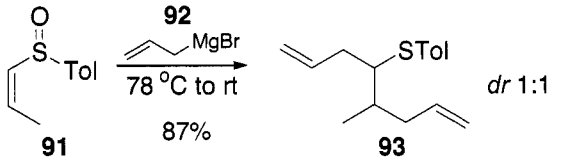
	RX	R	Yield % (α:β)
87a	EtOH	OEt	74 (2:1)
87b	Me_3SiN_3	N_3	72 (3:4)
87c	$HSCH_2Ph$	SCH_2Ph	80 (1:1)
87d	BrMgMe	Me	70 (6.5:1)

The synthesis of 1-substituted carbazole sulfides formed by an unusual Pummerer rearrangement has been reported.[43] The acyloxy group is displaced by an internal nucleophile, in this case, the indole **84**. Tautormerisation followed by the addition of a nucleophile then regenerated the indole and resulted in sulphides **87a–d**. A range of nucleophiles can be employed, giving good yields and moderate diastereoselectivity.

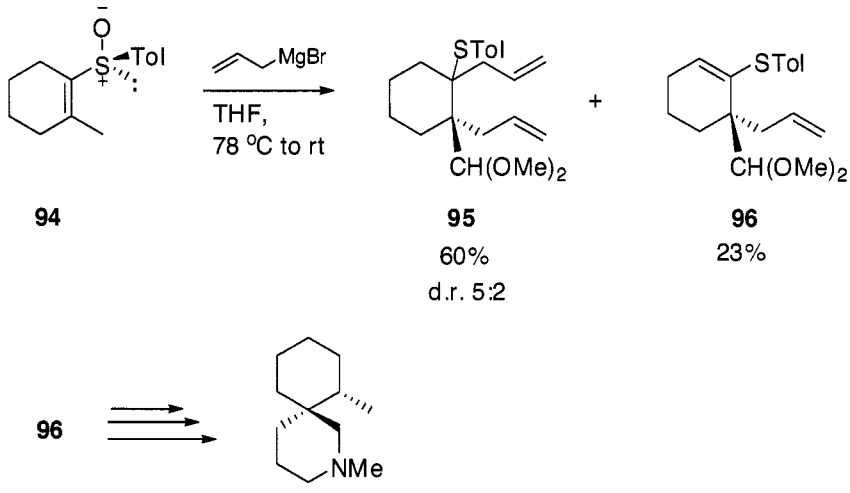
The Pummerer reaction has been utilized to initiate regioselective, nucleophilic carbon–carbon bond formation at the *C*-4 position of indoles.[44] 5-Sulfinylindoles were treated with trifluoroacetic anhydride in the presence of carbon nucleophiles to give *C*-4-substituted indoles in moderate to excellent yields.

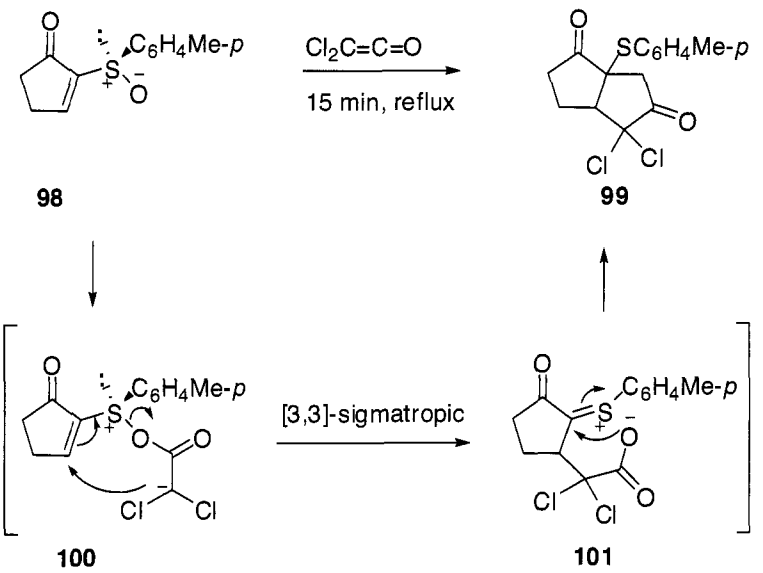


The formation of α- and β-allylated sulphides by the Pummerer-type reaction of vinylic sulphoxides with allylmagnesium bromide has been reported by Iwata *et al.*[16f] Monoallylation and diallylation can take place, depending on the bulkiness of the β-substituent, and both acyclic and cyclic vinyl sulphoxides undergo the reaction. This method offers applicability to asymmetric synthesis using sulfinyl chirality.



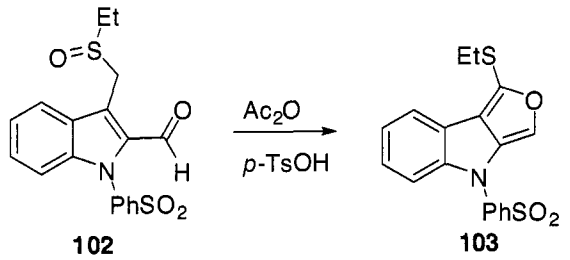
This methodology has been applied to the total synthesis of (–)-sibirine using chiral sufoxides.[45] The optical purity of the disubstituted sulfides **95** and **96** was determined through derivatisation with Mosher's ester. The high stereoselectivity was explained due to the chair-like transition state which forms when allylmagnesium bromide coordinates to the sulphoxide and acetal oxygen atoms.





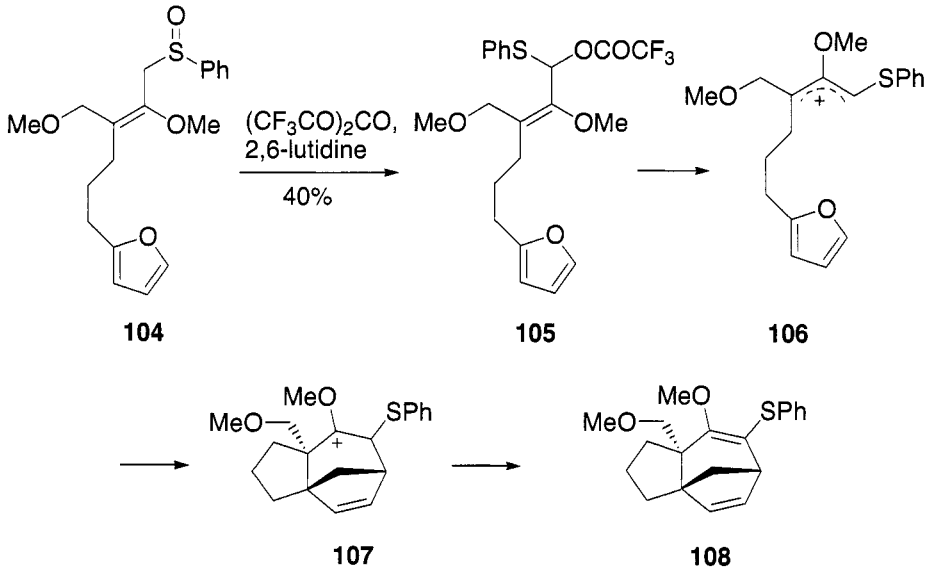
Posner *et al.* reported the first example of an asymmetric additive Pummerer rearrangement in their total synthesis of (–)-methyl jasmonate, a perfume essence.[16d] Enantiomerically pure sulfoxide **98** was treated with dichloroketene (generated *in situ* from dichloroacetyl chloride and triethylamine) to form α,β-disubstituted sulphide **99**. The mechanism is thought to involve a [3,3]-sigmatropic rearrangement of the doubly charged intermediate **100**.

The cyclisation of indole sulfoxides has been carried out to afford furo[3,4-*b*]indole **103**.[46] A catalytic quantity of *p*-toluenesulfonic acid added to the reaction mixture drove the reaction and prevented the formation of the usual Pummerer product, an acetoxy sulphide.



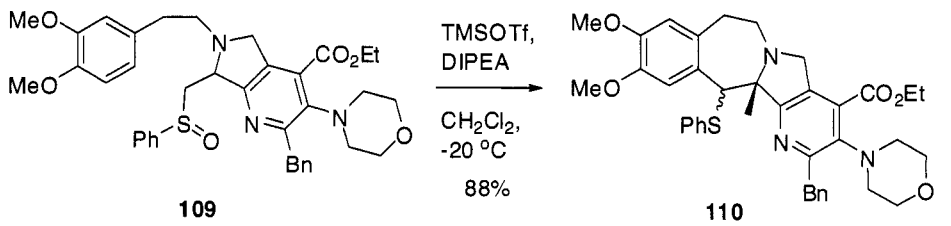
In their studies towards the synthesis of polycyclic natural products such as pseudolaric acid A, Bai *et al.* reported the tandem Pummerer rearrangement and intramolecular [4 + 3] cycloaddition of sulfoxide **104**.[47] The reaction constitutes the overall [4 + 3] cycloaddition of a fully

functionalised allylic cation and a diene. The 5,7-fused ring adduct **108** was obtained in 40% yield.



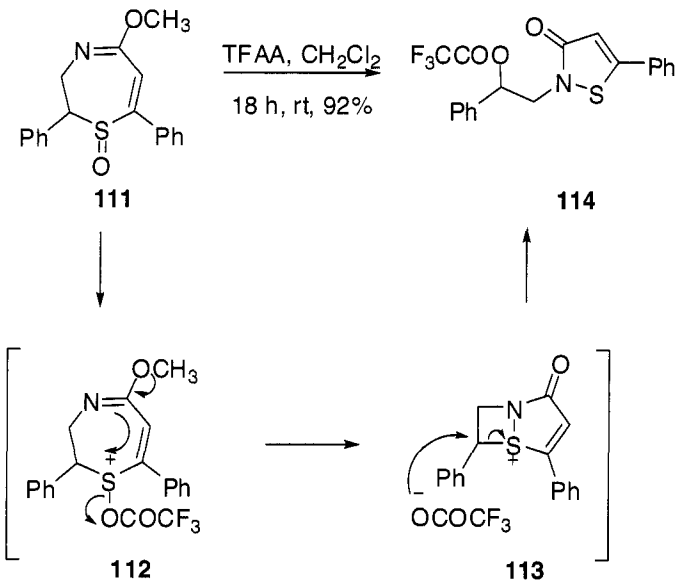
104 **105** **106** **107** **108**

Intramolecular cyclization to form tetracyclic ring systems has been reported wherein a 7-membered benzazepine ring was formed by the Pummerer cyclization of sulfoxide **109**.[48] Several reaction conditions were attempted, including the use of different electrophiles (trifluoroacetic anhydride, *p*-TsOH) and bases. Eventually, the desired reaction took place in good yield with the use of TMSOTf and an excess of Hunig's base.

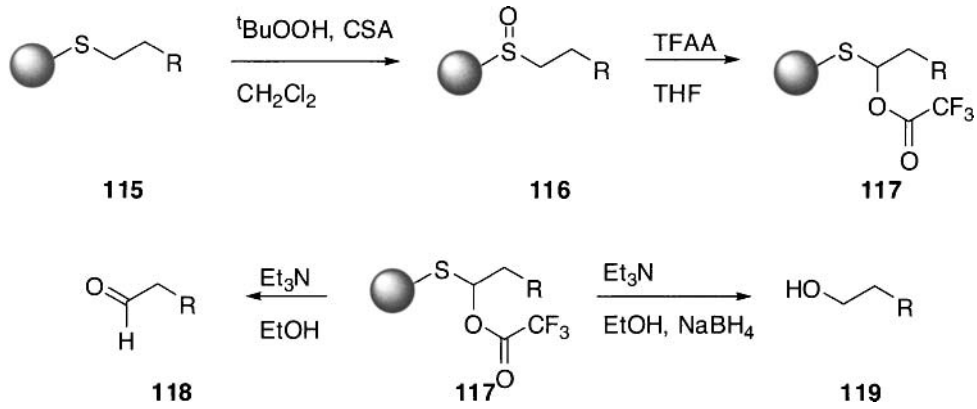


109 **110**

Ring contractions can also take place under Pummerer conditions.[49] Murata *et al.* have illustrated such contractions of dihydro- and tetrahydrothiazepins when treated with trifluoroacetic anhydride in dichloromethane.[49] The mechanism can be considered to involve the formation of a transannular bond between the *N* and *S* atoms to afford the bicyclic intermediate **113**. The benzylic carbon is then attacked by the trifluoroacetate ion resulting in isothiazole **114**.

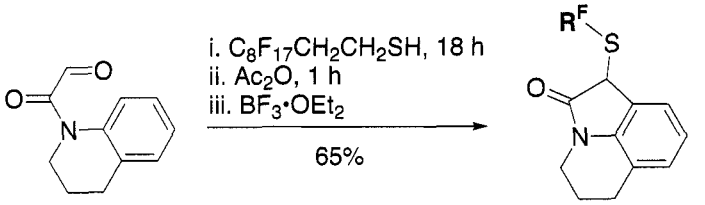


A novel use of the Pummerer rearrangement is as a method for cleavage of sulfide safety-catch linkers.[50–51] The sulfide safety-catch linker is oxidised to the sulfoxide, Pummerer rearrangement then takes place, followed by cleavage to give the desired alcohols and aldehydes.



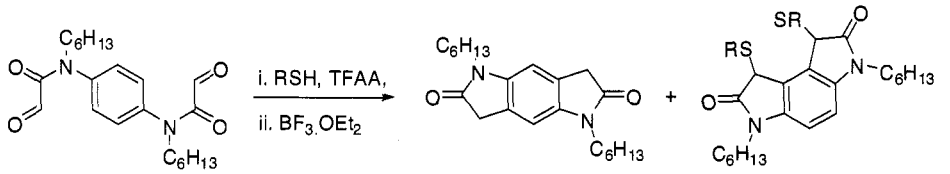
Milton *et al.* have demonstrated the preparation of substrates for the Pummerer reaction by the addition of thiols to glyoxalates.[42] Procter *et al.* have extended this methodology to include fluorous phase tag thiols which then led to Pummerer intramolecular cyclative capture under the appropriate reaction conditions.[52] The methodology efficiently resulted in tagged heterocyclic frameworks which could be further modified in a number of

ways. The resulting sulfides could be cleanly reduced with samarium iodide, SmI_2, regardless of the sulfur oxidation state. This was presumably due to the activated nature of the carbon-sulfur linkage to the fluorous phase tag.

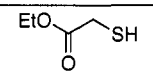
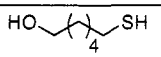
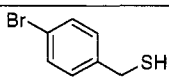
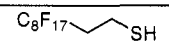


120 **121**

Procter *et al.* have followed up with the first reported two-dimensional connective Pummerer cyclisation.[53] A mixture of regioisomeric *bis*-oxindoles is formed, with the the linear regioisomer being the more prevalent. Each regioisomer was a 1:1 mixture of diastereoisomers. Yields were reported over the two steps as the glyoxamides were not purified. As before, the sulphides were cleaved with SmI_2.

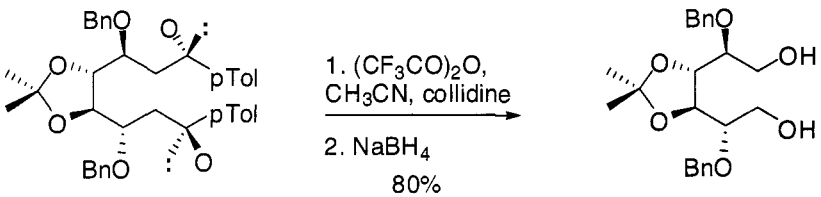


122 **123** (linear) **124** (bent)

RSH	Isolated yield %	Linear:bent
PhSH	55	>5:1
	54	5:1
	61	~3:1
	56	5:1
	50	2:1

1.2.5.6 Experimental

(+)-[2(*S*),2′(*S*),3(*R*)]-2,2′-Dibenzyloxy-3,3′-isopropylidenedioxy-1,1′-hexanediol 126[54]



125 **126**

To a solution of the bis-sulfoxide **125** (200 mg, 0.31 mmol, 1 eq.) in 3 mL of acetonitrile at 0 °C were added successively *sym*-collidine (0.239 mL, 1.81 mmol, 5.85 eq.) and trifluoroacetic anhydride (0.423 mL, 3.01 mmol, 9.71 eq.). The reaction was stirred for 30 min and then hydrolysed by addition of water (1 mL); the pH was adjusted to 7 by addition of K_2CO_3, and the reaction then allowed to warm to room temperature. After 30 min, the thioacetal intermediate was reduced by addition of $NaBH_4$ (71.65 mg, 1.86 mmol, 6 eq.) and stirring continued for 40 min. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed successively with HCl (10 mL, 1 N), saturated $NaHCO_3$ (10 mL) and saturated NaCl (20 mL). After being dried over $MgSO_4$, the solution was concentrated under vacuum, and the crude product purified by flash column chromatography (silica gel, EtOAc/hexane 1:1) to give compound **126** as a white solid (80%).

1.2.5.7 References

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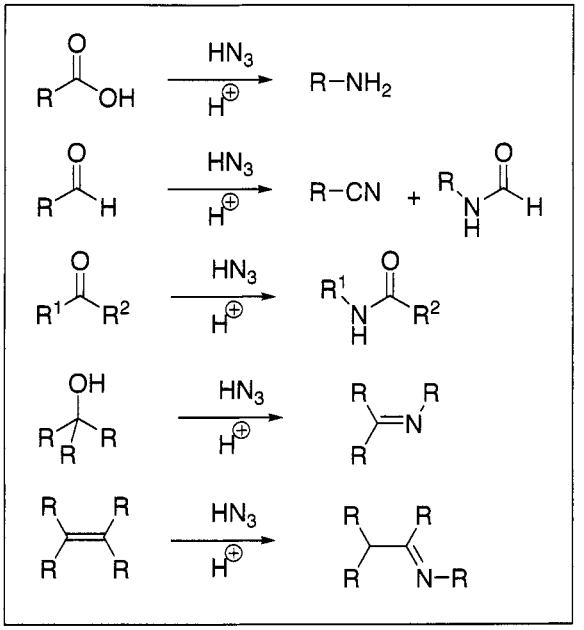
1.2.6 Schmidt reactions

Yong-Jin Wu

1.2.6.1 Description

The Schmidt reactions refer to the acid-catalyzed reactions of hydrazoic acid with electrophiles, such as carbonyl compounds, tertiary alcohols and alkenes. These substrates undergo rearrangement and extrusion of nitrogen to furnish amines, nitriles, amides or imines.



The Schmidt reaction of carboxylic acids with hydrazoic acid has the advantage over Curtius rearrangement that it is only one step from the acid to the amine, but the conditions are more drastic (usually sulphuric acid plus sodium azide). Under these harsh conditions, the isocyanate intermediate is rarely isolated. For these reasons, the Curtius rearrangement is frequently employed to convert acids to amines. The Schmidt reaction of ketones with hydrazoic acid is a powerful method for the synthesis of amides and lactams. This process is somewhat related to the Beckmann rearrangement of oximes; however, the Schmidt reaction is more succinct, allowing the conversion of ketones to amides in a single operation. Considering its widespread

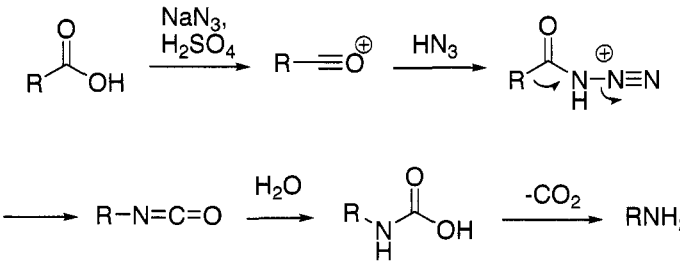
application in synthesis, the Schmidt reaction with ketones is the focus of this chapter.

1.2.6.2 Historical Perspective

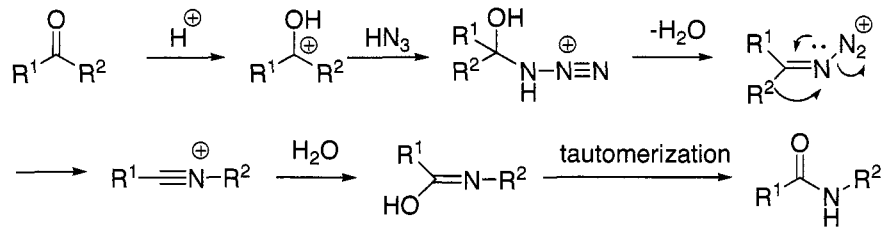
The Schmidt reaction was discovered in 1924 by Karl Friedrich Schmidt (1887–1971) who successfully converted benzophenone to benzanilide using hydrazoic acid.[1–6] Schmidt collaborated with Curtius at the University of Heidelberg, where Schmidt became a Professor of Chemistry in 1923.

1.2.6.3 Mechanism

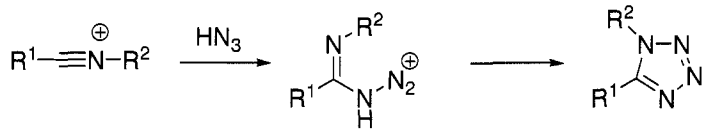
The Schmidt reaction of carboxylic acids proceeds via acylium ion, which undergoes addition with hydrazoic acid to generate acyl azide. This azide rearranges with loss of nitrogen to give isocyanate, which leads to an amine upon hydrolysis.[4]



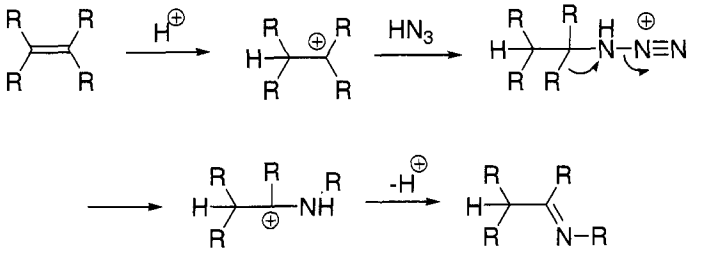
Reaction of ketones with hydrazoic acid gives azidohydrin intermediates, which undergo rearrangement to form amides.[5]



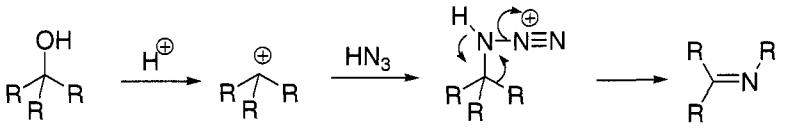
The iminocarbonium ions can further react with hydrazoic acid, thus resulting in tetrazoles as the common by-products. Tetrazole formation is favoured when a large excess of hydrazoic acid is employed.[7]



Addition of hydrogen azide to olefins results in alkyl azides, which rearranges to form imines.[8]

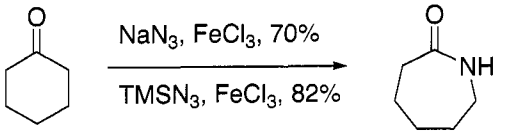


Tertiary alcohols are converted to azides via carbenium ions, and these azides rearrange to generate imines.[9]



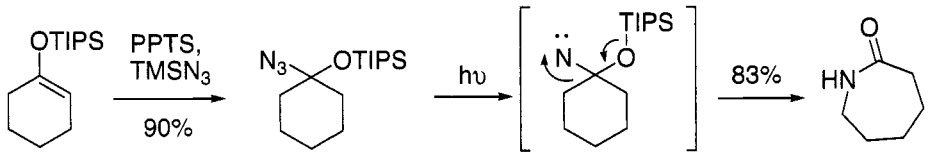
1.2.6.4 Variations and Improvements

The Schmidt reaction of ketones with hydrazoic acid requires the presence of an acid catalyst. Sulfuric acid is the most common catalyst, but Lewis acids have also been utilized. Hydrazoic acid is usually made in situ by treatment of sodium azide with sulphuric acid. The strongly acidic conditions can bring about decomposition of acid-sensitive substrates and result in undesired by-products. However, the Schmidt reaction can be conducted under mild conditions. For example, various ketones are converted to the corresponding amides or lactams using trimethylsilyl azide or sodium azide in the presence of $FeCl_3$ in dichloroethane at room temperature.[10]



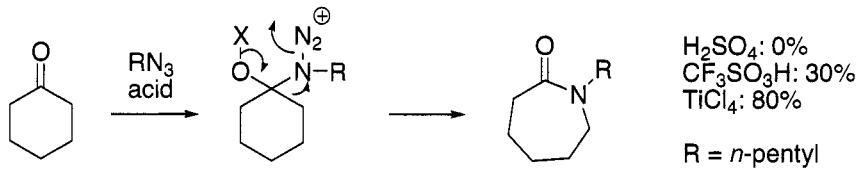
Variant 1: Photo-induced Schmidt Reaction of α-Azidohydrins (Evans[11,12])

The photo-induced ring expansion of α-azidohydrin represents a convenient and environmentally friendly Schmidt rearrangement. The starting azido-hydrin is prepared using an acid catalyst and $TMSN_3$, a non-explosive source of azide. The major limitation with this approach is that the ring expansion with unsymmetrical substrates is not regioselective. In addition, this process requires two more extra steps than the classic Schmidt rearrangement to convert ketones to lactams.



Variation 2: Intermolecular Reaction of Ketones with Alkyl Azides (Aubé [13,14])

Ketones generally fail to react with alkyl azides under standard Schmidt conditions. However, when these reactions are conducted in the presence of Lewis acid instead of the protic conditions used in the standard Schmidt reactions, the intermolecular Schmidt reactions can be carried out in moderate to good yields. Titanium(IV) chloride (> 1.0 equiv) in dichloromethane is the best reagent for effecting this type of reactions. The best substrates include the sterically unhindered ketones, especially cyclohexanones. This transformation is sensitive to steric effects, and even the α-substituted ketones may lead to poor yields and require long reaction time. The intermolecular Schmidt reaction with alkyl azides is still limited to a small range of cyclic ketones. For example, cyclopentanones do not react well with alkyl azides.

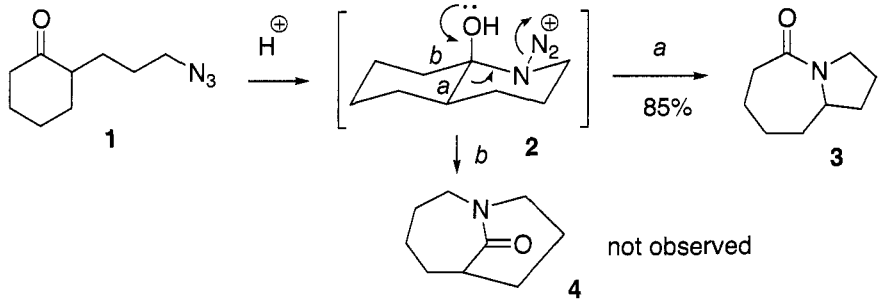


Variation 3: Intramolecular Reaction of Ketones with Alkyl Azides (Aube[15])

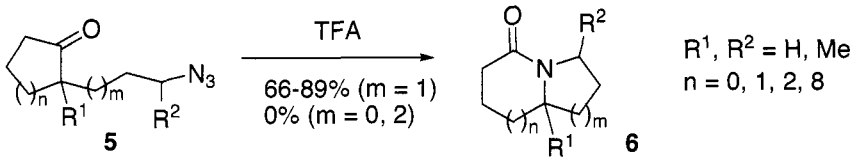
As compared with the intermolecular reaction of ketones with alkyl azides, the corresponding intramolecular version provides a reliable approach to

lactams. Both cyclic and acyclic ketones are good substrates for this transformation. The reaction can be promoted by a variety of protic or Lewis acids, most notably trifluoroacetic acid, trifluoromethanesulfonic acid, and titanium(IV) chloride.

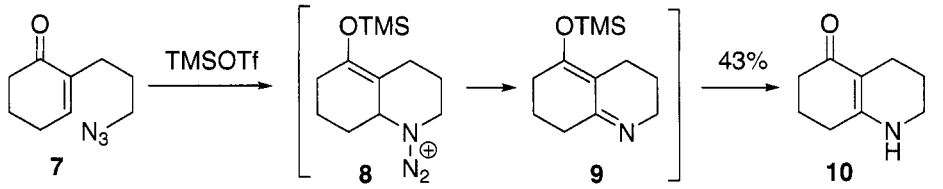
The mechanism of the intramolecular Schmidt reaction is the same as the intermolecular variant. Thus, nucleophilic attack of the azide on the activated ketone gives intermediate **2**, and rearrangement with concomitant loss of nitrogen leads to the fused lactam product via migration of bond *a*. The bridged bicyclic amide via migration of bond *b* is not observed presumably due to the instability of the amide linkage in that setting. However, the bridged lactams can be formed as minor products from some keto azides (*vide infra*).



The intramolecular reaction of ketones with alkyl azides is quite general in terms of the ketone moiety, but the distance between the carbonyl group and the azide moiety is critical. Thus, a good yield of lactam **6** is formed with a span of four carbons between the carbonyl and the azido group, and in contrast, no rearrangement occurs with a span of either three or five carbons.

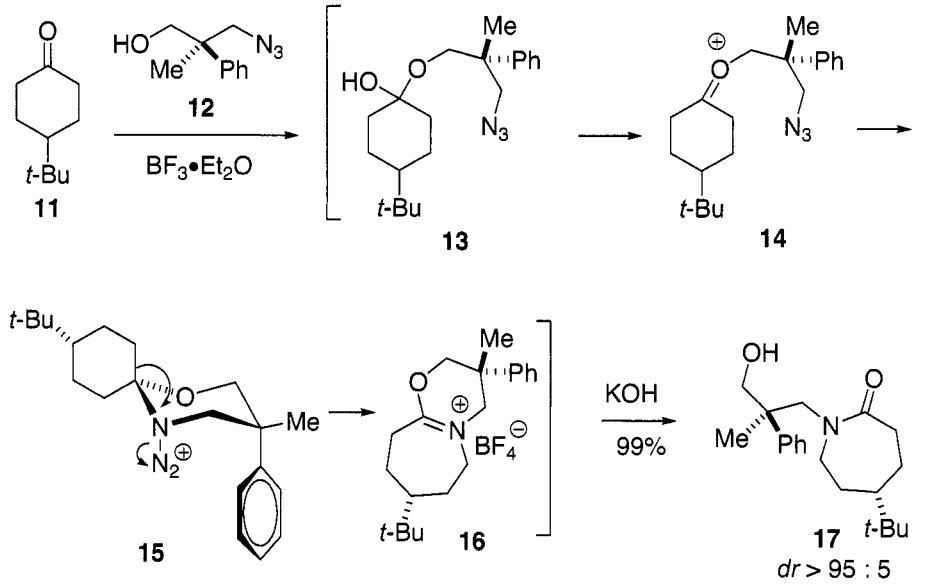


Enones are not useful substrates for intramolecular Schmidt reactions as azide addition to the olefin predominates over attack at the enone carbonyl. Thus, enone **7** undergoes Michael addition followed by loss of nitrogen to give the icyclic enone **10** in moderate yield.

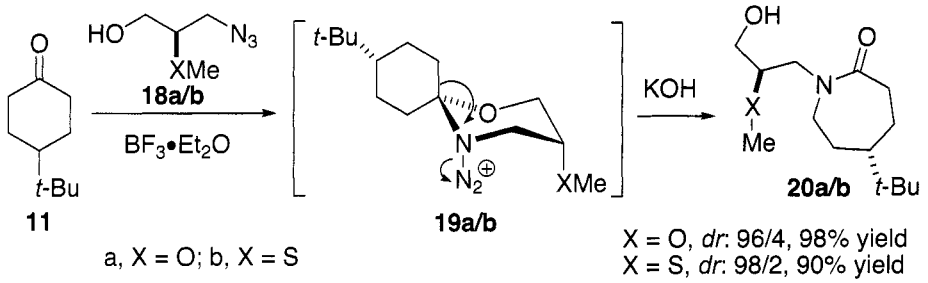


Variation 4: Asymmetric Schmidt Reaction of Ketones with Hydroxyalkyl Azides (Aubé[16–18])

Reaction of the disubstituted 3-carbon chain hydroxyalkyl azide **12** with 4-*tert*-butylcyclohexanone proceeds with high diastereoselectivity (*dr* > 95 : 5) to give lactam **17** in high yield. The overall process is formerly the same as the intermolecular reaction of ketones with alkyl azides, but the mechanism is quite different. Attack of the alcohol moiety of the hydroxyalkyl azide **12** onto the activated ketone generates hemiketal **13**, which undergoes dehydration to give the oxenium ion **14**. Addition of the azido group onto this ion leads to the chairlike heterocycle **15** where the phenyl group adopts a 1,3-diaxial relationship with the cationic N_2^+ leaving group, and the methyl is arranged equatorially. The 1,3-diaxial arrangement allows attractive, nonbonded interactions between the phenyl and the electron-deficient diazonium unit. Antiperiplannar migration of carbon to nitrogen from this intermediate yields an iminium ether **16**, which, upon hydrolytic workup, furnishes the *N*-hydroxyalkyl lactam **17.**

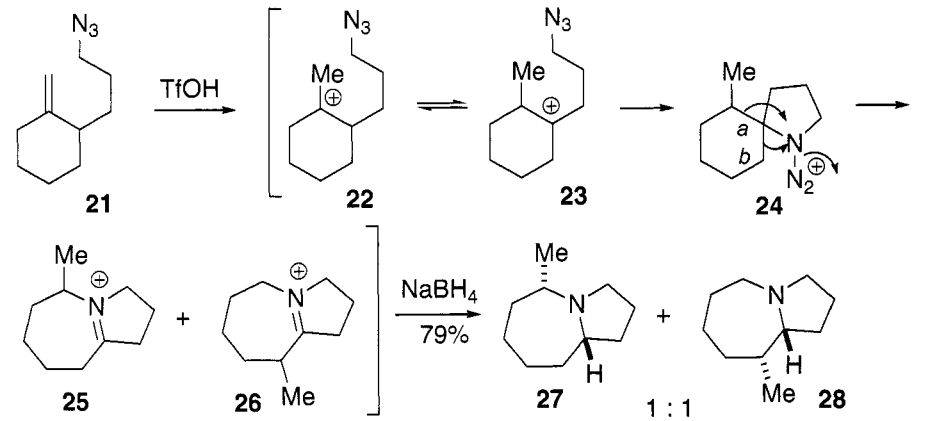


High diastereoselectivity is also obtained with azido alcohols **18a/b**. The major products are derived from intermediates **19a/b** which contain a diaxial relationship between the methoxy or methylthio group and the leaving N_2^+ leaving group. These intermediates are stabilized by an attractive cation-n interaction. In general, a two- to three-carbon span between the hydroxy moiety and the azide is optimal. The preferred acid reagent for this transformation is boron trifluoride etherate, which provides both high yield and convenience of workup. This asymmetric reaction also works well with cyclopentanones, which are poor substrates for intermolecular Schmidt reactions with simple alkyl azides.



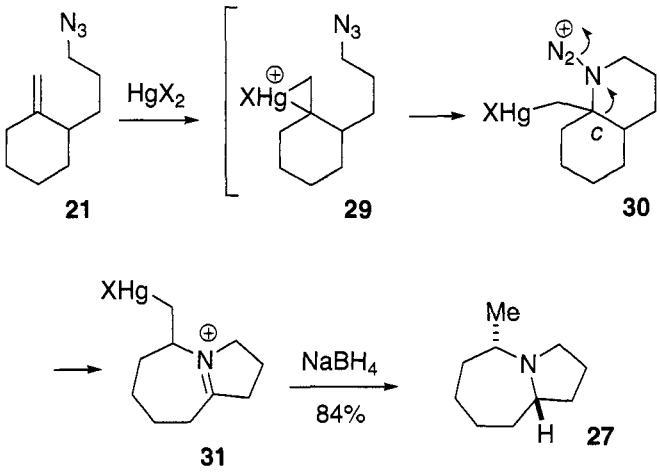
Variation 5: Intramolecular Schmidt Reaction of Olefins with Alkyl Azides (Pearson[8])

The proton-initiated intramolecular Schmidt reaction of the azidoalkene **21** produces a 1 : 1 mixture of two regioisomers **27** and **28** in 79% yield. According to the proposed mechanism, protonation of alkene **21** is followed by rearrangement of the resulting carbacation **22** to give another carbocation **23**, which cyclizes to the aminodiazonium ion **24**. A nonregioselective



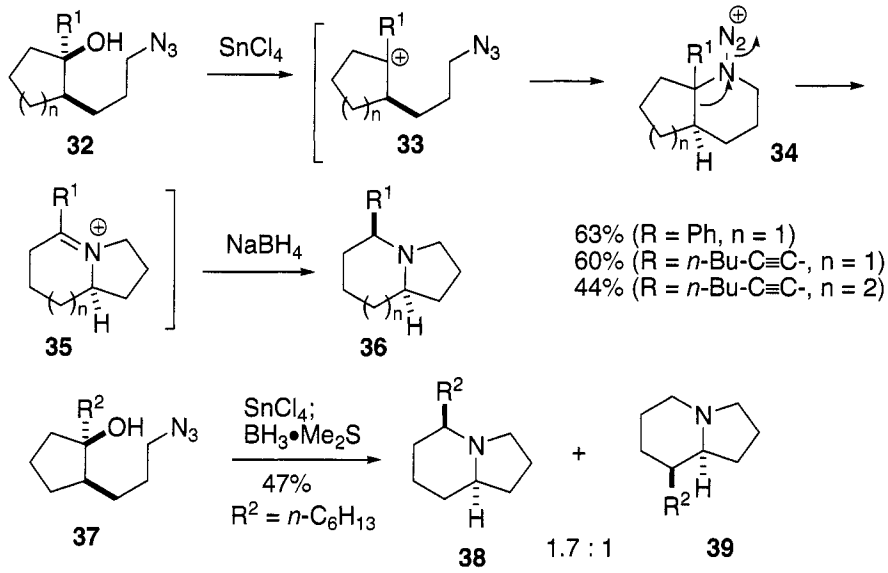
migration of bond *a* or bond *b* furnishes two regioisomeric iminium ions **25** and **26**, which are reduced to **27** and **28**, respectively.

The regioselectivity can be improved by using mercury(II) salts instead of strongly acidic conditions. Exposure of **21** with 1 equiv of mercuric perchlorate or mercuric trifluoromethanesulfonate followed reduction with sodium borohydride generates **27** in 84% yield as shown by LC/MS analysis. The mercury-promoted process begins with the formation of the mercuronium ion **29**, which is opened by the azide to generate the aminodiazonium ion **30** without rearrangement. Migration of bond *c* leads to the iminium ion **31**, which gives only **27** upon reduction. In addition to enhanced regioselectivity, the mercury-promoted Schmidt reaction also offers the advantage of mild reaction conditions, thus allowing the presence of acid-sensitive functionality in the substrate. The protic version, typically using trifluoromethanesulfonic acid, is limited in terms of functional group tolerance.



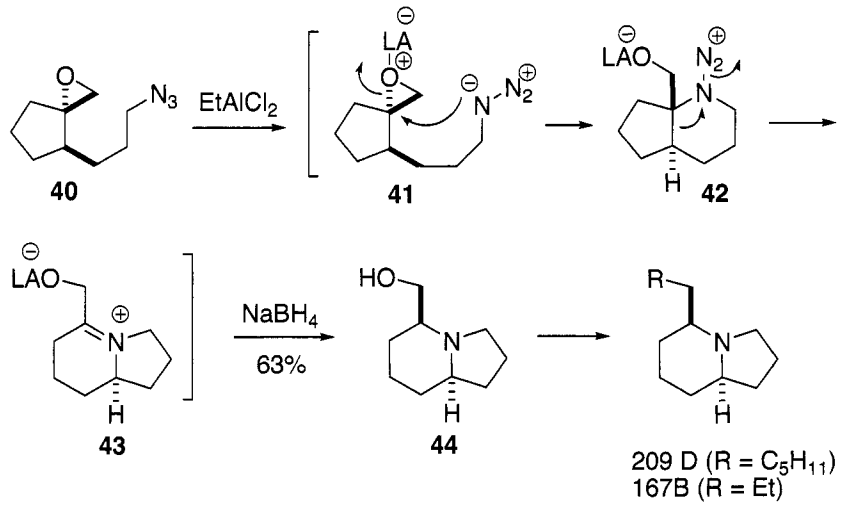
Variation 6: Intramolecular Schmidt Reaction of Alcohols with Alkyl Azides (Pearson[9])

The intramolecular Schmidt reactions of azido tertiary benzylic and propargylic alcohols **32** lead to 1-azabicyclo[5.3.0]decanes or 1-azabicyclo[4.3.0]decanes (indolizidines) **36** without formation of the products derived from cation rearrangement. However, simple tertiary alcohols such as **37** undergo cation rearrangement prior to cyclization to give a mixture of regioisomeric indolizidines.

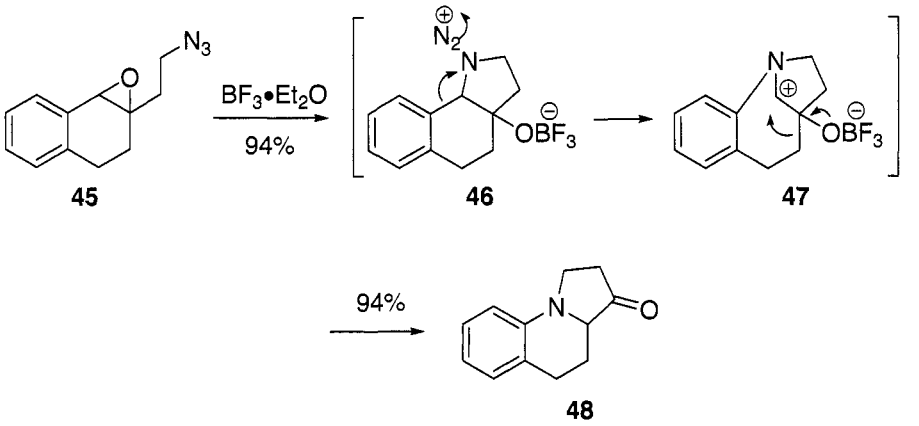


Variation 7: Intramolecular Schmidt Reaction of Epoxides with Alkyl Azides (Baskaran[19,20] and Murphy[21])

The epoxide-initiated Schmidt reaction proceeds in a similar fashion to the mercury-promoted version. Treatment of epoxyazide **40** with a Lewis acid brings about cyclization to give the aminodiazonium intermediate **42**, regioslective ring expansion results in the bicyclic iminium ion **43**, and in situ reduction of **43** affords 5-hydroxymethyl azabicyclic compound **44**. This alcohol has been converted to indolizidine alkaloids 167B and 209D.

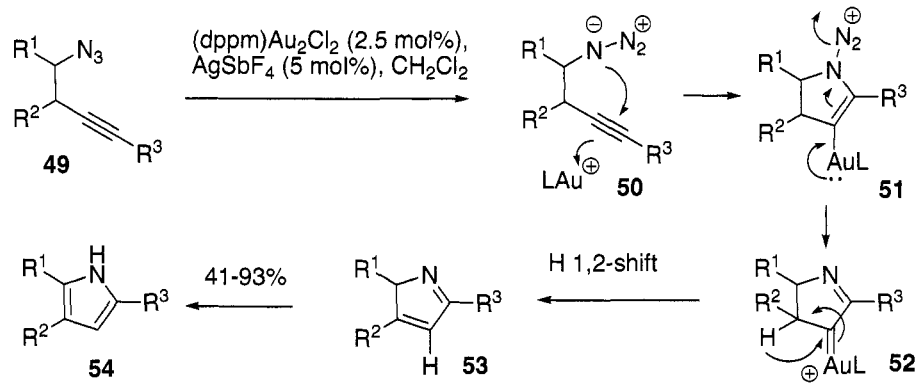


The Lewis acid induced reaction of aryl epoxyazide **45** leads to regiospecific amination of the aromatic ring to give the tricyclic ketone **48**. The reaction starts with epoxide opening, followed by regioselective migration of the aryl group to the electron-deficient nitrogen to give the bridged intermediate **47**, which undergoes a regiospecific ring contraction to generate ketone **48**.



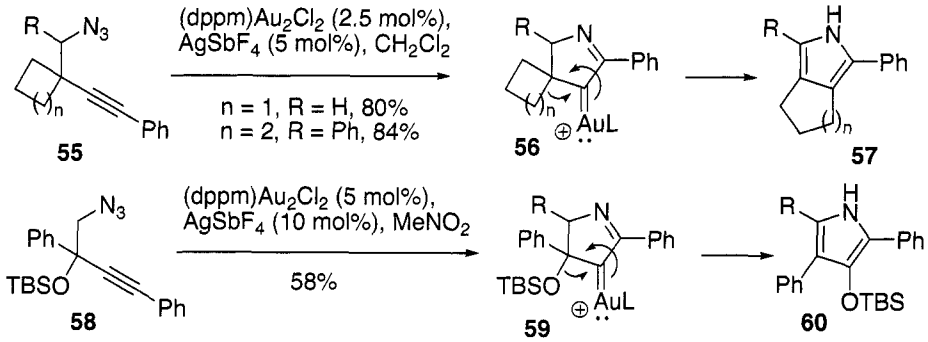
Variation 8: Gold(I)-catalyzed Intramolecular Acetylenic Schmidt Reaction (Toste[22])

The gold(I)-catalyzed intramolecular Schmidt reaction of azido alkynes **49** provides easy entry to a series of pyrroles **54** with a variety of substitution patterns. The proposed mechanism involves gold(I)-induced activation of the alkyne toward addition by the proximal nitrogen of the azide. Subsequent loss of nitrogen leads to cationic intermediate **52**, which is



stabilized by electron donation from gold(I). This intermediate undergoes formal hydrogen 1,2-shift to regenerate the cationic gold(I) catalyst and produce a 2*H*-pyrrole **53**, which tautomerizes to the 1*H*-pyrrole product **54**.

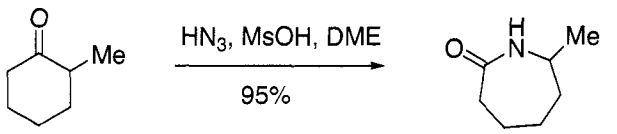
The 2,3-substituted pyrroles can also be prepared *via* gold(I)-induced Schmidt reaction. Thus, the gold(I)-catalyzed rearrangement of cyclobutyl azide and cyclopentyl azide **55** affords the trisubstituted and tetrasubstituted pyrroles **57** in good yields. In this case, the alkyl group in the intermediate **56** undergoes migration. The tandem cyclization-ring expansion of the TBS ether **58** proceeds with selective migration of the siloxy group to furnish pyrrole **60** in moderate yield.



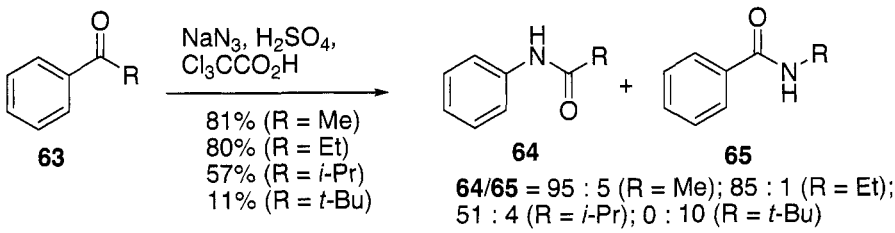
55 56 57 58 59 60

1.2.6.5 Synthetic Utility

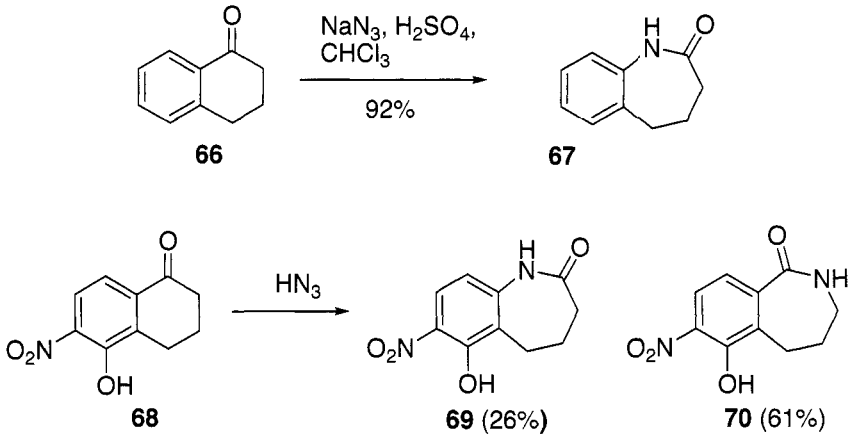
The Schmidt reaction of ketones with hydrazoic acid provides an effective approach for the synthesis of amides and lactams. In general, dialkyl ketones are the best substrates for the Schmidt reaction, followed by alkyl aryl ketones, and then diaryl ketones. When unsymmetrical dialkyl ketones are used, migration of the bulkier substituent usually predominates. Thus, 2-methylcyclohexanone **61** is converted to 7-methylazepan-2-one **62** in excellent yield.[23] The Schmidt reaction of methyl aryl ketones proceeds with nearly exclusive migration of the aryl group to give the *N*-aryl amides. However, when the alkyl group is bigger than methyl group, migration of the alkyl group is predominant over the aryl group.[24]



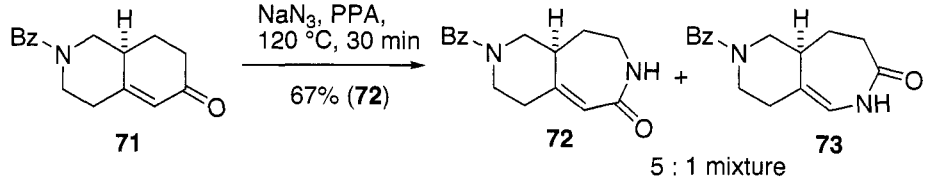
61 62



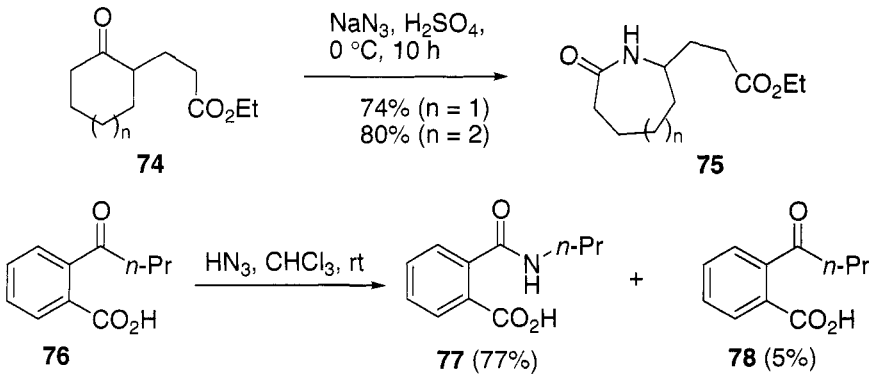
The unsubstituted tetralone **66** undergoes regioselective ring expansion,[25] but the regiospecificity can be compromised with substituted system as shown in the case of **68**.[26] Reaction of this compound with hydazoic acid gives lactam **70** as the major product due to alkyl migration.



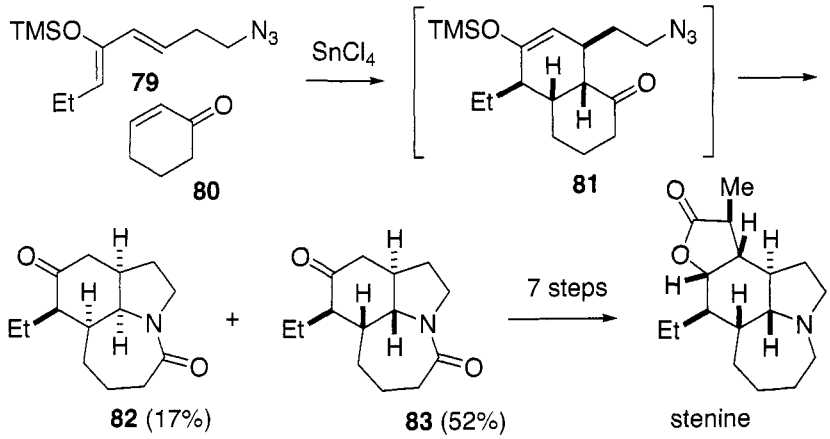
In general, simple enones are not suitable for the Schmidt reaction due to the Michael addition of hydrozoic acid onto the conjugated system. However, there are successful examples of substituted enones. For instance, the Schmidt reaction of enone **71** has been elegantly applied to the classic synthesis of quinine by a group of scientists from Hoffmann-La Roche.[27] Reaction of **71** with sodium azide in the presence of hot polyphosphoric acid furnishes **72** in 67% yield; only minor amounts of the regioisomeric product **73** result from the nitrogen insertion into the α,β-unsaturated system.

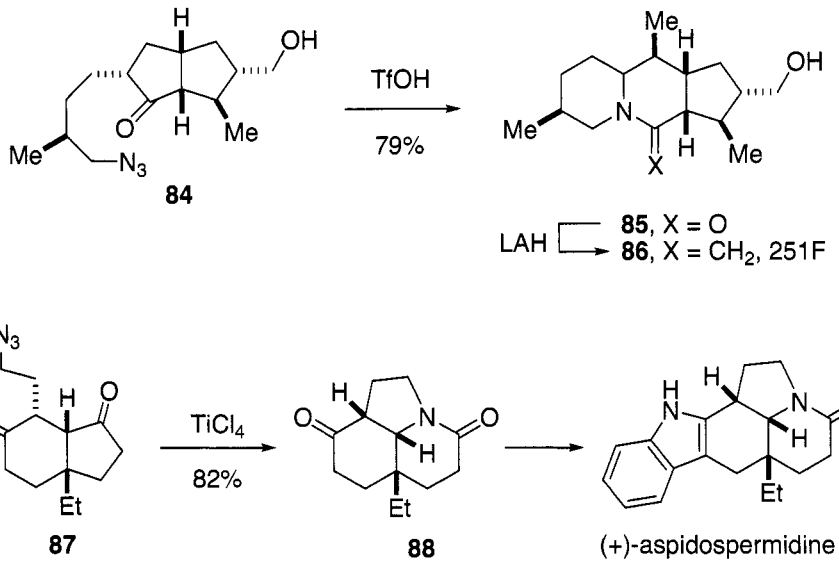


In general, ketones react with hydrozoic acid much faster than carboxylic acids or esters or lactones,[28–30] and therefore, ketones can be converted to amides or lactams in the presence of these functionalities. In comparison with ketones, aldehydes are not good substrates for Schmidt reactions with hydrazoic acid due to fragmentation to nitriles.

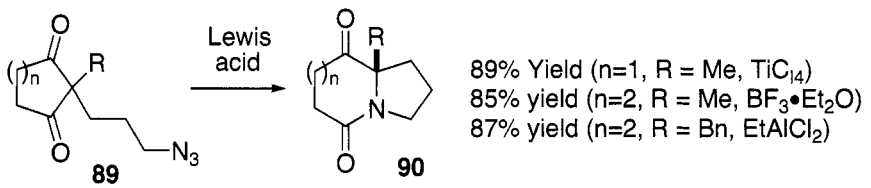


The power of the intramolecular Schmidt reaction is demonstrated in the concise synthesis of the Stemona alkaloid stenine.[31] Reaction of trimethylsilyloxy diene **79** with cyclohexenone **80** and tin(IV) tetrachloride brings about a tandem Diels–Alder/Schmidt reaction to give adducts **82** and **83** in 52% and 17% yields, respectively, with the *exo* addition product **83** predominating. Adduct **83** contains three rings and four stereocenters present in stenine. The intramolecular Schmidt reaction is also employed as a key step in the total syntheses of 251 F (**84** to **85**)[32] and (+)-aspidospermidine (**87** to **88**).[33]





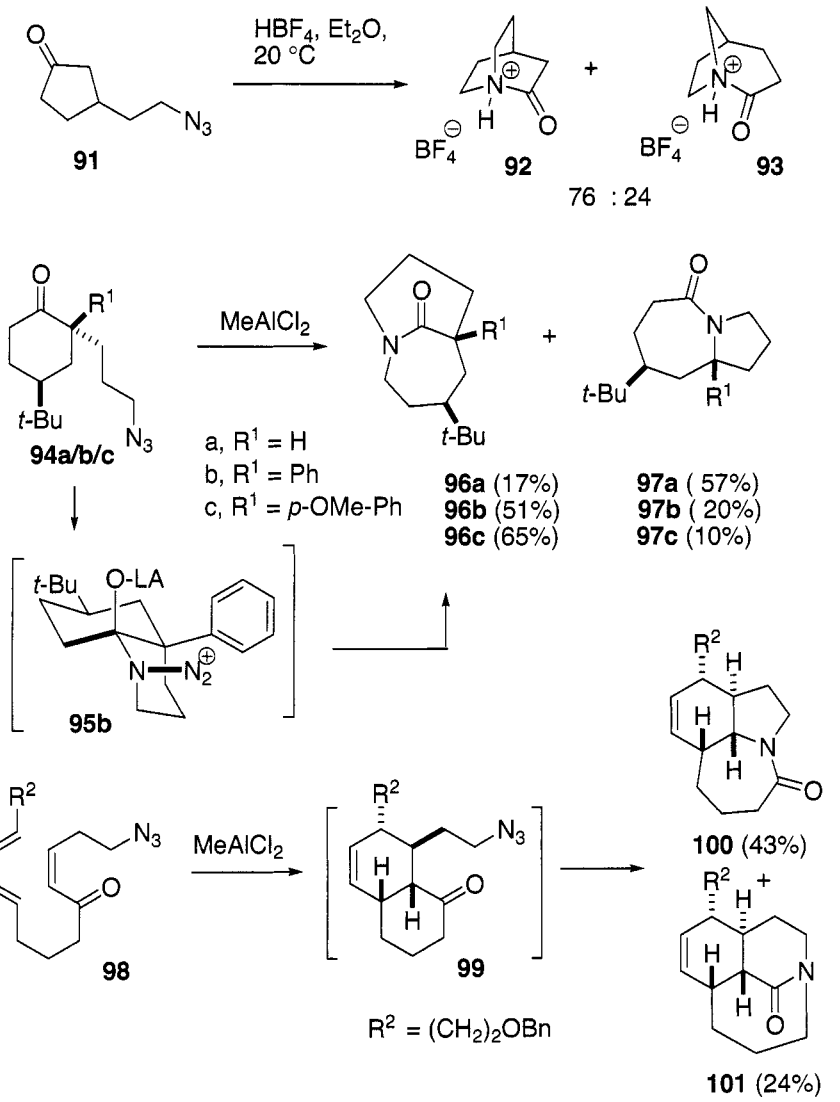
An efficient approach to indolizidinediones and pyrroloazepinediones **90** is based on the intramolecular Schmidt reaction of azidodiketones **89**.[34] In this case, the choice of Lewis acid appears critical to the yields.



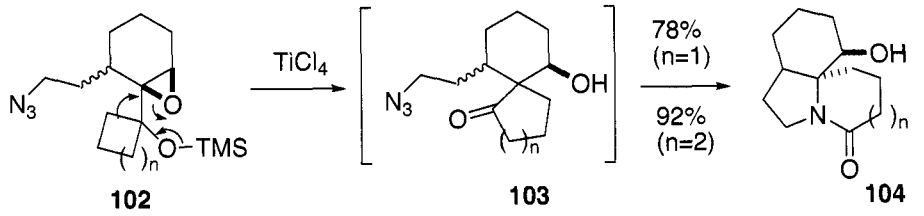
The intramolecular Schmidt reaction has provided a solution to the problem of bridgehead lactam synthesis. The bridged lactams incorporate a "twisted amide" unable to achieve standard planar geometry and can undergo rapid hydrolysis. Reaction of ketoazide with HBF_4 in ether results in a mixture of two latams from which the desired quinoclidone **92** is isolated in 38% yield after recrystalization.[35]

A similar strategy has been utilized for the synthesis of bridged bicyclic lactams **96a/b/c**.[36] The increased production of the bridged compounds vs. fused lactams when R is aromatic moiety presumably results from intermediate azidohydrin **95** where the leaving N_2^+ group and the phenyl are in a 1,3-diaxial relationship. This intermediate may be stabilized by an attractive through-space interaction between the positively charged leaving group (N_2^+) and the phenyl group. The tricyclic bridged lactam **101** is also

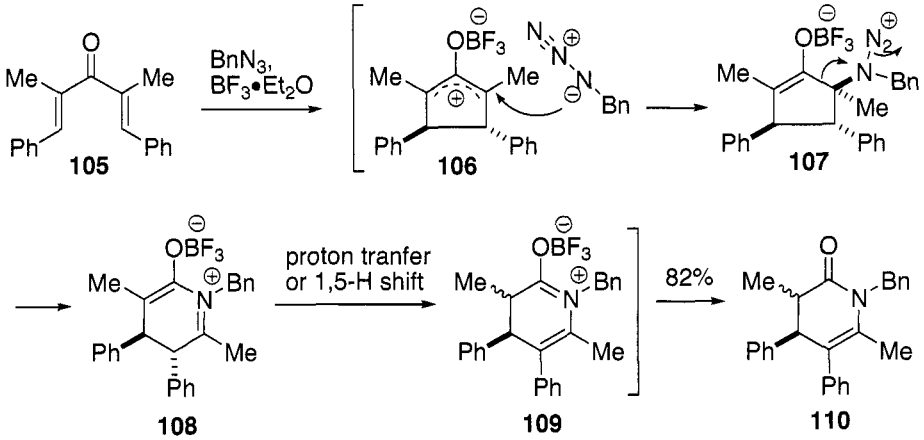
obtained as a minor product from the tandem Diels–Alder /Schmidt reaction of azido–triene **98**.



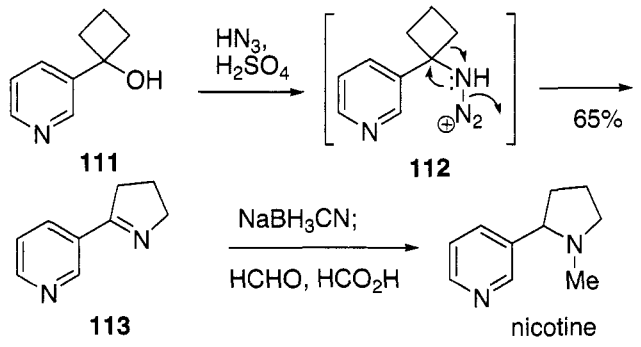
A novel approach to tricyclic azaquaternary alkaloids takes advantage of a tandem semipinacol rearrangement/Schmidt reaction.[37,38] Treatment of α-siloxy-epoxy azide **102** with $TiCl_4$ generates ketoazide **103** through a carbon-carbon 1,2-migration, and this intermediate undergoes Schmidt rearrangement to give the tricyclic lactam **104**.



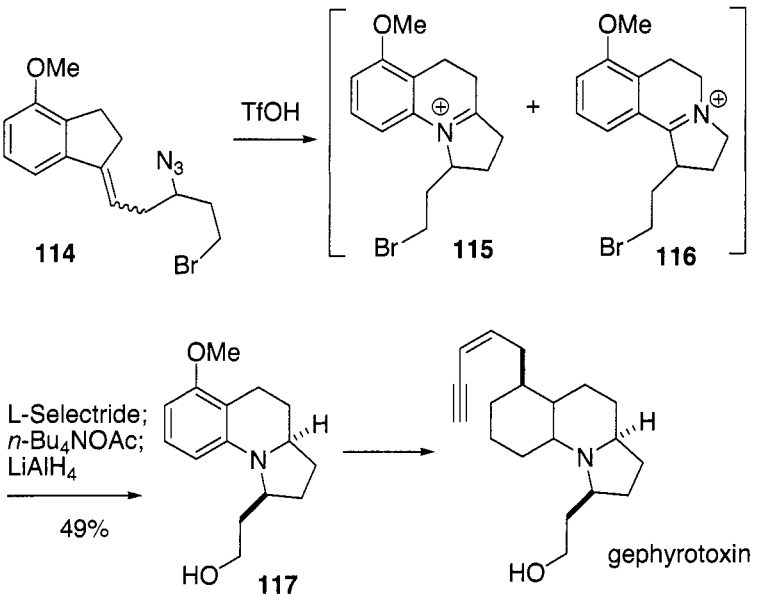
Dihydropyridones **110** are prepared from 1,4-dien-3-ones **105** by a combination of electrocyclization with Schmidt reaction.[39] Thus, enone **105** undergoes Lewis acid-catalyzed Nazarov electrocyclization, the resulting Nazarov intermediate **106** is trapped with benzyl azide, and ring expansion of the resulting azide **107** delivers zwitterion **108**. This intermediate rearranges to the dihydropyridone **110** via either proton transfer or 1,5-hydride shift.



The Schmidt reaction of the tertiary alcohol **111** is used as a key step in the synthesis of nicotine.[40] The reaction proceeds through **112**, which undergoes a regioselective ring expansion to give imine **113**.



The acid-promoted intramolecular Schmidt reaction of azido-alkene **114** is featured in the formal synthesis of gephyrotoxin.[41] Treatment of **114** with trifluoromethanesulfonic acid followed by *L*-Selectride reduction of the resultant iminium ions **115** and **116** generates a mixture of diastereomeric bromo-amines. The bromide is replaced with acetate ion, and the acetate is reduced to give alcohol **117**, a known intermediate in the synthesis of gephyrotoxin.



1.2.6.6 Experimental

Caution: Sodium azide is highly toxic can explode on heating. Contact of metal azides with acids generates the highly toxic and explosive hydrazoic acid. Although some literature procedures use chloroform or other halogenated solvents in the Schmidt reactions with hydrazoic acid, these conditions may lead to explosive mixtures of polyazides, generated *in situ* from the reaction of sodium azide (used in the formation of hydrazoic acid) with the halogenated solvent. For this reason, halogenated solvents should **never** be used in these reactions. DME has been proposed as a safer solvent than chloromethane or dichloromethane for performing reactions involving azides.[23] Using sodium azide and methanesulfonic acid in DME, ketones are converted to amides in high yields.

(*SR*)-5-*tert*-Butyl-1-((*RS*)-3-hydroxy-2-methyl-2-phenylpropyl)azepan-2-one [(±)-17][17]

A solution of 4-*tert*-butylcyclohexanone in anhydrous dichloromethane (0.04 M) was cooled to –78 °C and $BF_3 \cdot Et_2O$ (5.0 equiv) was added. After 30 min, a solution of hydroxyalkylazide (±)-**12** in anhydrous dichloromethane (0.04 M) was added to the cooled solution dropwise via a cannula. The reaction mixture was allowed to warm to room temperature slowly over 18–24 h at which time it was concentrated under reduced pressure and excess KOH was added slowly to the residual oil. The reaction mixture was stirred vigorously at room temperature for 30 min and then partioned between dichloromethane and water. The organic layer was washed with water, brine, and dried over sodium sulphate and concentrated to give only the single isomer **17** (99%) as determined through inspection of the crude ^{1}HNMR spectrum. The conservative estimation of the *dr* is ≥ 95:5.

7-Methylazepan-2-one (62):[23]

To a solution of 2-methylcyclohexanone (**61**) in DME (5 mL) at –30 °C was added MsOH (9 mL) at –30 °C. Sodium azide (49.9 mmol) was added portionwise while the temperature was maintained at –30 °C. The resulting solution was allowed to warm slowly to room temperature until the evolution of nitrogen ceased (*ca.* 3 h). Additional DME (15 mL) was added, followed by 30% ammonium hydroxide to adjust the pH to *ca.* 9. The solvent was removed *in vacuo*, and the aqueous solution was extracted with dichloromethane. The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*, and the residue was purified by silica gel chromatography to give the title compound (95% yield).

(5^1*S*,7a*R*,10*R*,10a*R*)-10-Ethyloctahydroazepino[3,2,1-hi]indole-4,9(1H,51H)-dione (83)[31]

To a cooled (–78 °C) solution of cyclohexen-1-one (95%, 500 mg, 5.0 mmol) in dichloromethane (20 mL) under argon was added $SnCl_4$ (1 equiv) followed by the addition of ((3*Z*,5*E*)-8-azidoocta-3,5-dien-4-yloxy)trimethylsilane (**79**) (1.8 equiv). The resulting reaction mixture was stirred at –78 °C and allowed to warm to –55 °C over 2 h. After slow addition of another portion of $SnCl_4$ 1.5 equiv), the mixture was stirred at room temperature for 12 hand quenched with aqueous NH_4Cl. The mixture was partioned between water and dichloromethane. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give an oil. Repeated chromatography afforded pure **82** (200 mg, 17%) and **83** (600 mg, 52%).

2-Quinuclidonium tetrafluoroborate (92):[35]

A 10 mL tube equipped with a stirbar and three-way stopcock was flame-dried under vacuum, backfilled with dry nitrogen, and charged with ketoazide **91** (306 mg, 2.00 mmol) and dry ether (4 mL). To this solution was added etheral HBF_4 (54 wt%, 0.55 mL, 4.00 mmol) at 0 °C, and the resulting mixture was stirred at room temperature until gas evolution ceased (3 h). The supernatant of the resulting suspension was removed by syringe and the remaining white solid was washed with dry ether and dried under vacuum. The resulting crude solid was then dissolved in 4 mL of dry acetonitrile and transferred to a 10 mL test tube, which was placed in a septum-sealed 200 mL Erlenmeyer flask. Dry ether (10 mL) was then added to the Erlenmeyer flask outside the tube, and the resulting flask was settled in a desiccator (P_2O_5) at room temperature until crystals formed (6 days). After the mother liquor was removed by syringe, the solid was washed with dry etherand dried under vacuum to yield 164 mg (38% yield) of the title compound (as its HBF_4 salt) as colourless crystals. Recrystallization from acetonitrile-ether provided crystals for X-ray analysis.

3.2.6.7 References

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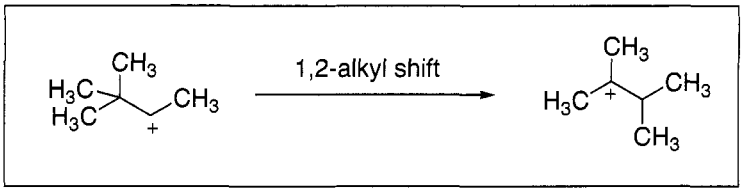
1.2.7 Wagner–Meerwein Rearrangement

Richard J. Mullins and Amy L. Grote

1.2.7.1 Description

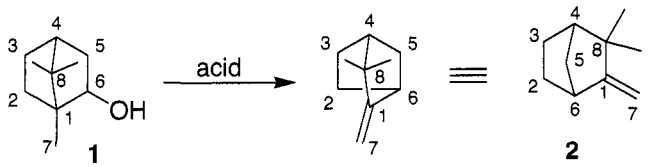
The Wagner–Meerwein rearrangement describes the 1,2-alkyl, aryl, or vinyl migration, predominantly from an alkyl group to a neighboring carbocation. The reaction usually proceeds to give greater cationic stability but can also occur to reduce the angle, steric, or torsional strain of the reactant.



1.2.7.2 Historical Perspective

Early Developments

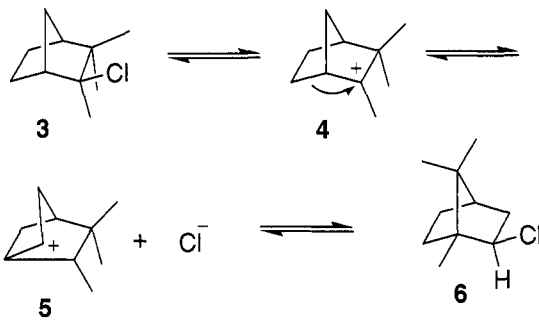
In 1899, Wagner published "The Structure of Camphene,"[1] in which he challenged the accepted structure of the bicyclic monoterpene camphene that had been proposed by his contemporaries. He stipulated that the acid-catalyzed dehydration of borneol (**1**) resulted from a skeletal rearrangement to give camphene (**2**), a structure unique from its precursor.



1 **2**

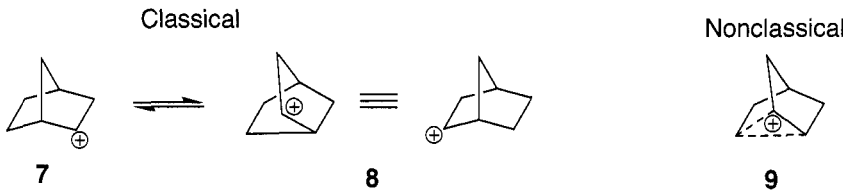
What followed were decades of investigation to determine the mechanism through which such a rearrangement would occur. Notably, the work of Meerwein and van Emster demonstrated the presence of a cationic intermediate that preceded the 1,2-alkyl migration.[2] Through his studies of equilibrium isomerism of bornyl chloride, camphene hydrochloride (**3**), and isobornyl chloride (**6**), Meerwein established that the rearrangement mechanism relied on ionization, and exhibited a heavily solvent-dependant kinetic profile. These studies, which laid the foundation for modern

carbocation chemistry,[3] heralded a period of increased mechanistic interest in, and development of, reactions involving the rearrangement. In a must-read for organic chemists, Birladeanu offers elegant insights on the Wagner–Meerwein rearrangement, specifically its place in the development of early mechanistic understanding, tracing its discovery and mechanistic studies to the early 1800s.[4]



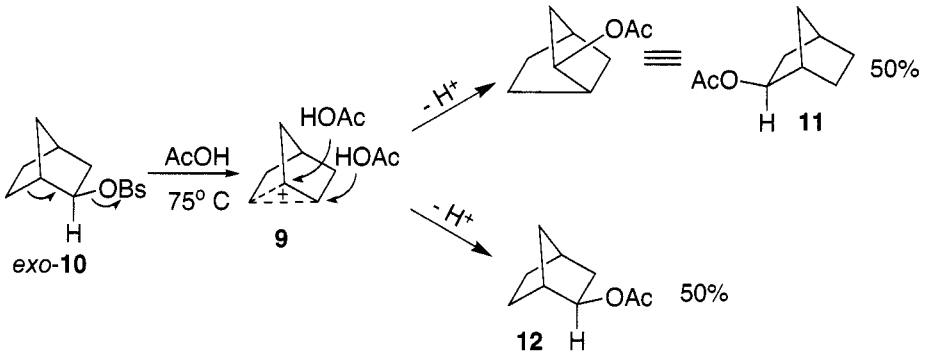
Classical-Nonclassical Ion Controversy:

While only an ancillary topic in this discussion, the nonclassical ion controversy, extensively reviewed elsewhere,[3,5–11] has a foundation in the historical context of the Wagner–Meerwein rearrangement. After completing a solvolytic study of structurally similar *exo*- and *endo*-2-norbornyl brosylates, Winstein and Trifan[12–14] suggested that the reaction's cationic intermediate was instead a σ-delocalized, symmetrically bridged norbornyl ion **9**. This concept deviated from the accepted classical cation structure proposed by Meerwein as the equilibrium between **7** and **8**, where the positive charge was considered to be localized on a single atom.



This intermediate was postulated as a result of several facts regarding the acetolysis of 2-norbornyl arenesulfonates. First, the *exo*-isomer reacts more rapidly than the corresponding *endo*-isomer, presumably from heightened levels of anchimeric assistance. Regardless of which isomer (*endo*/*exo*) is utilized as the reactant, the *exo*-acetate is produced exclusively. Finally, optically active *exo*-starting materials react to give complete

racemization, suggesting the intermediacy of a symmetrical and achiral structure, tentatively assigned to be **9**.[12–14]



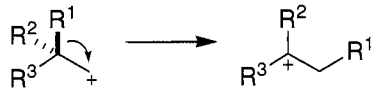
A major opponent of this "nonclassical" ion intermediate was Brown,[7,8] who published dissenting views throughout the latter half of the twentieth century. He insisted on the existence of a rapid equilibrium between the two classical carbocation forms facilitated via Wagner–Meerwein rearrangement. *Exo*- and *endo*-rate ratios were attributed to steric effects, as strain caused *endo*-isomers to exhibit more hindrance to ionization. Finally, Brown criticized the bridged intermediate model for not providing sufficient electrons for all bonds.[7,8]

Decades of extensive research followed, fueling controversy on the subject. In 1983, Olah, Saunders, and Schleyer were able to identify the intermediate as indeed the methylene-bridged nonclassical carbonium form of the norbornyl cation. This was demonstrated through extensive spectroscopic analysis, including ^{1}H- and ^{13}C-NMR, Raman, ESCA, and further physical and kinetic studies.[3] Molecular mechanics and thermodynamic cycles exhibited a stabilization energy of 6 ± 1 kcal/mol for the σ bridging feature of the nonclassical ion.

1.2.7.3 Mechanism

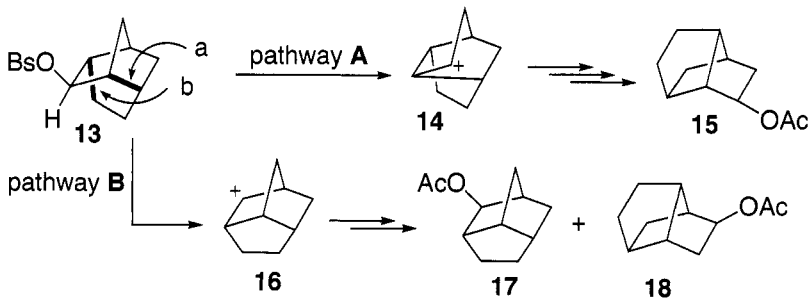
The Wagner–Meerwein rearrangement is quite versatile, allowing for the involvement of a variety of migrating groups, and its use in conjunction with a number of reactions. Rearrangement is typically preceded by formation of a carbocation, either through electrophilic addition to a π-bond, or by removal of a good leaving group. The mechanism of the Wagner–Meerwein rearrangement involves the intramolecular 1,2-shift of an alkyl group to a neighboring carbocation.[11] A hybrid transition state occurs, in which the positive charge is distributed between the migrating group, the migrating origin, and the migrating terminus. Following rearrangement, either

substitution or elimination reactions may occur. As a two-electron suprafacial process, stereochemistry of the migrating group is retained.[15]



Migration rates of alkyl groups tend to rise proportionally with the level of thermodynamic stability gained upon rearrangement. This can be due to heightened levels of cationic substitution, or the relief of steric, torsional, or angle strain. Groups that can more easily bear the positively-charged transition state also have a greater migration tendency. Reactions are often carried out in the presence of Lewis acids, which promote cation formation while minimizing the possibility for competing nucleophilic attack at the carbocation center.

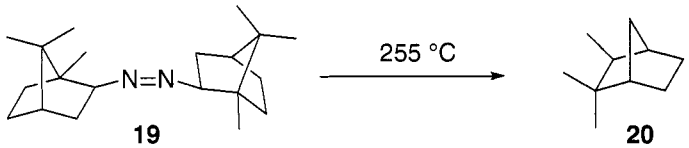
In addition, geometric considerations must be taken into account. The orbitals of the migrating group and the migrating terminus must be aligned properly for any rearrangement to occur. In a concerted ionization-migration process, the substituent is optimally located anti- and coplanar to the leaving group. Conversely, a non-concerted process will ideally have a coplanar terminus, ensuring maximum overlap between the migrating orbital and the empty p-orbital. Nickon made efforts to determine the relative importance of orbital geometry in his work with *exo*-twistbrendan-2-ol brosylate (**13**).[16] During acetolysis, this unique compound was able to follow two major mechanistic pathways during a concerted process, with pathway **A** favoring proper bond alignment and pathway **B** favoring product stability. In addition, the reaction could occur in a non-concerted manner, where both geometric optimization and product stability would favor pathway **B**. Thus, four possible situations could be conceived, with only one of them favoring pathway **A**. Solvolysis of **13** in acetic acid buffered with potassium acetate yielded a product mixture (**15**:**17** + **18**) corresponding to an **A**:**B** ratio of 2.2 to 1, demonstrating that proper orbital geometry held greater importance than product stability in predicting the outcome of the rearrangement.



1.1.7.4 Variations and Improvements

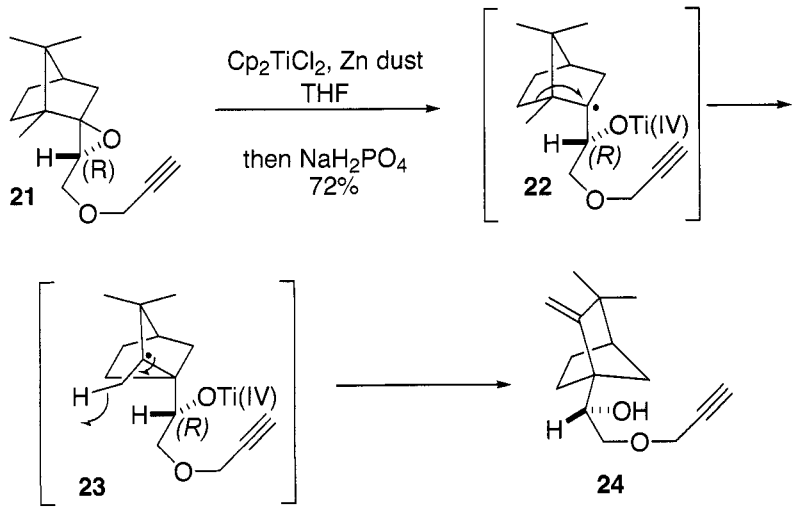
Radical-promoted Wagner–Meerwein rearrangement

In 1960, Berson reported the first formal Wagner–Meerwein rearrangement of an alkyl radical in the thermal decomposition of 2,2-bis-azocamphane (**19**). Isocamphane **20** was one of a number of products isolated in the reaction, but its identification implicates the occurrence of the free radical analog of the Wagner–Meerwein rearrangement.[17,18] Numerous reactions have been carried out which exploit the radical rearrangement scaffold demonstrated by Berson. In bicyclic terpenes, the Wagner–Meerwein rearrangement is often coupled with radical migration or hydrogen atom *exo*-migrations. This variation results in an inversion of the migration terminus.



19 **20**

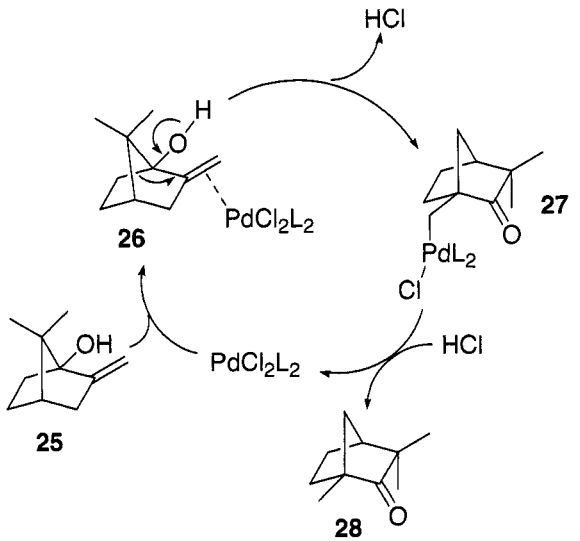
A more recent example of a radical-promoted Wagner–Meerwein rearrangement can be found in the rearrangement of camphor-derived epoxide **21**. Roy and co-workers demonstrated that upon addition of Cp_2TiCl_2 and Zn dust, epoxide **21** rearranges to produce **24** in 72% yield.[19] In this example, reductive epoxide-opening results in the formation of radical **23**, which undergoes a 1,2-alkyl shift to **24** and loss of a hydrogen atom through Ti(III) trapping of the radical and β-elimination.

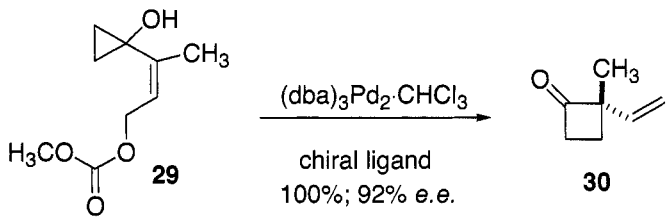


21 **22** **23** **24**

Palladium-promoted Wagner–Meerwein rearrangement

Palladium catalysts have been effective promoters of a formal Wagner–Meerwein rearrangement as demonstrated in the ring-expansion reaction of 1-alkenyl cyclopentanols.[20] Reaction of **25** with $PdCl_2(PPh_3)_2$ in refluxing *N*-methylpyrrolidin-2-one occurs as shown in the catalytic cycle below. Following the alkene–Pd(II) complexation to give **26**, a ring-opening Wagner–Meerwein rearrangement occurs providing ketone **28** following reductive elimination in **27**. This is just a single example of a well-known and widely used process,[21–37] although it is one of the first to feature the rearrangement of a non-strained ring system.[38,39]





Palladium catalysts have also proven effective in promoting an asymmetric Wagner–Meerwein rearrangement. Interestingly, the rearrangement may occur in an asymmetric manner if there is significant differentiation in the prochiral faces of the carbocation center. Trost has demonstrated that a chiral palladium catalyst can initiate ionization through preferentially reacting with one of the prochiral faces of alkene **29** to provide **30** with a high degree of enantioselectivity.[37] A similar rearrangement of

allenylcyclobutanols has been explored, providing a general synthesis of substituted cyclopentanones.[40]

Natural Triterpenoid rearrangement

Terpene synthesis in nature is a complex process involving successive electrophilic additions followed by a variety of skeletal rearrangements, including those of the Wagner–Meerwein variety. These reactions are typically catalyzed by enzymes and are responsible for the wide array of structural diversity in these compounds, including 6–6–6–5 tetracycles, 6–6–6–6–5 pentacycles, 6–6–6–6–6 pentacycles, and the less abundant acyclic, monocyclic, bicyclic, tricyclic, and hexacyclic triterpenoids.[41] Each of the more than 100 triterpene skeletons identified in nature are formed through the involvement of several multifunctional triterpene synthases.

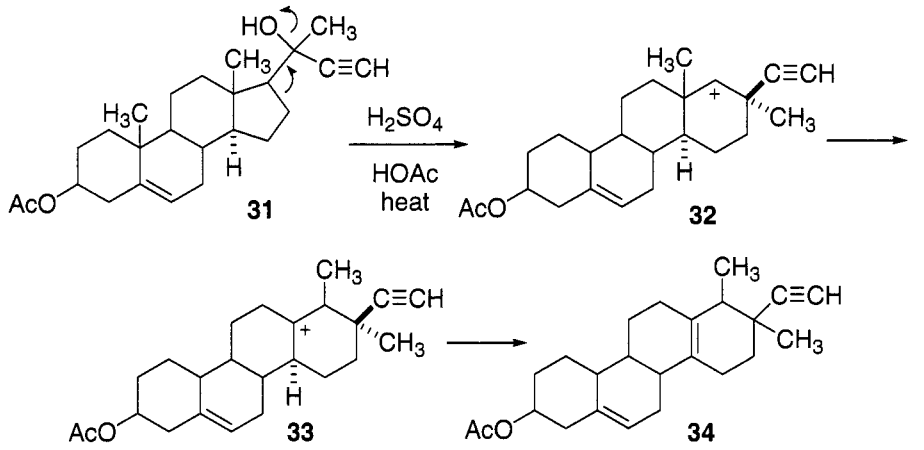
One such example is that of oxidosqualene, presumably the precursor for most 3β-OH-triterpenoids. This compound undergoes catalysis by oxidosqualene cyclase to bring about C–C bond formations, Wagner–Meerwein rearrangements, and other ring altering processes. Shibuya[42] demonstrated the varied triterpene structures that could be produced using oxidosqualene cyclase homologues through successive Wagner–Meerwein rearrangements and elimination steps.

Substantial efforts have been made to elucidate structure and mechanism of formation that results in such broad skeletal diversity. Single mutations in lupeol and β-amyrin synthases, for example, can substantially alter the structure of the triterpenoid product.[43] The extent of triterpenoid synthesis and analysis becomes apparent in the multitude of structures that result from rearrangements within just one terpenoid cation skeleton. One such structure, the lupyl cation, which is generated from 18β E-ring cyclization of a baccharenyl cation, will undergo a series of 1,2 shifts and deprotonation steps to form 18-lupen-3-ol,[44] 13(18)-lupen-3-ol,[45] neolupenol,[46] tarolupeol,[46] tylolupenol A,[47,48] tylolupenol B,[47, 48] cymbopogonol,[49] and cymopogonone.[49] Recent advances in technology have allowed for the study of biological processes at the enzymatic level, giving scientists more tools with which to carry out complex synthetic schemes.

1.2.7.5 Synthetic Utility

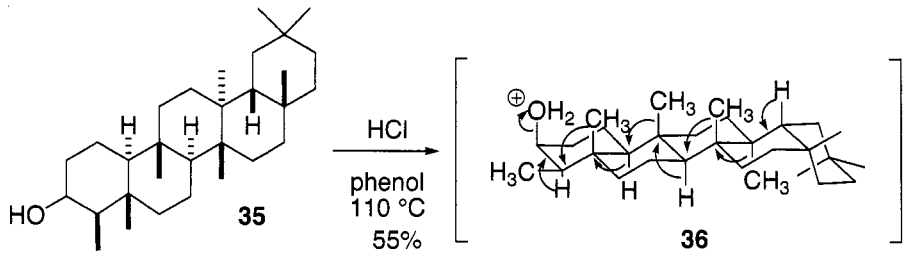
The Wagner–Meerwein rearrangement has been used in efforts towards the total synthesis of steroids and other terpenoids, molecules containing numerous fused rings with often-complex functionality. As an example of this strategy, Chaudhuri and Gut were able to form a *D*-homosteroid using propargylic alcohol **31**, prepared from the ethynylation of the corresponding methyl ketone.[50] This study was based on the work of Smissman,[51] who

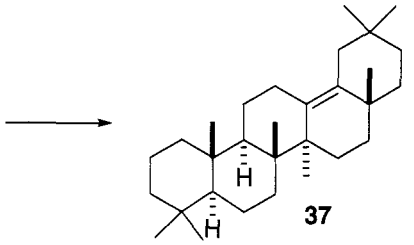
showed that the Wagner–Meerwein rearrangement could effectively compete with the undesired and irreversible Meyer-Schuster and Rupe rearrangements commonly observed for propargylic alcohols. In the formation of *D*-homosteroid **34**, removal of water from **31** results in a propargyl cation which undergoes a rapid Wagner–Meerwein rearrangement to give **33**. 1,2-Migration of the methyl group is then followed by elimination to form the desired **34** as the major product in an undisclosed yield.



Numerous synthetic studies have been carried out involving other Wagner–Meerwein rearrangements which mimic those that occur in biological systems.[52–56]

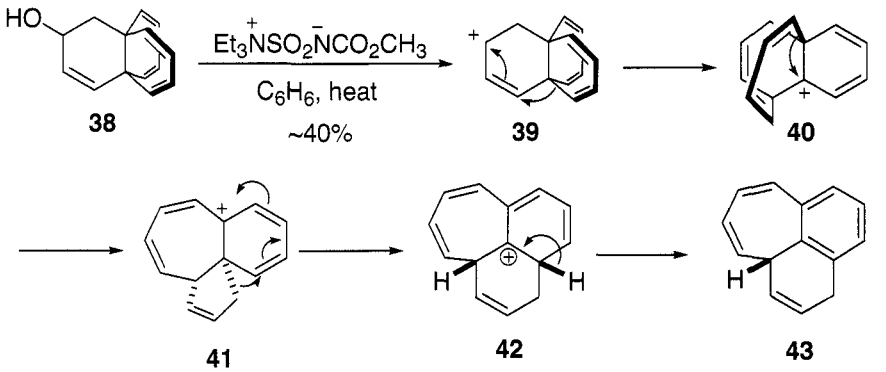
Successive Wagner–Meerwein rearrangements have been utilized in triterpenoid syntheses. A unique and fascinating example of this can be found in Corey's synthesis of the triterpenoid oleanene.[57] When 3β-friedelanol (**35**) is treated with acid, a total of seven 1,2-alkyl and 1,2-hydride migrations occur leading to the formation of **37**. The stereospecific shifts are driven by the apparent decrease in steric strain due to the original location of the axial substituents. Intermediate products have been isolated,[58] supporting the assertion that at least some of the steps are not concerted.





37

Paquette similarly observed a cascade of three Wagner–Meerwein rearrangements in the conversion of the carbocation **39** to **43**, significantly altering the backbone of the parent molecule.[59] The carbocation, formed upon treatment of **38** with the Burgess reagent, undergoes three consecutive Wagner–Meerwein rearrangements (**39** → **40** → **41** → **42**) followed by elimination to give **42** in moderate yield.

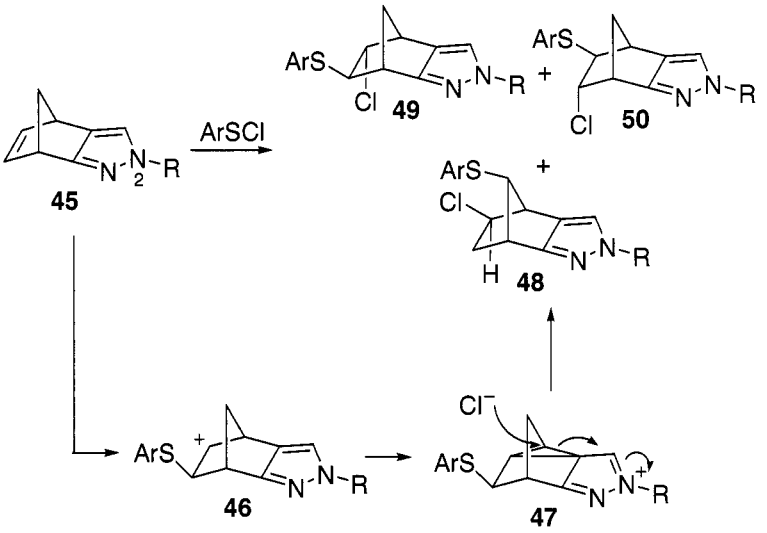


38 **39** **40** **41** **42** **43**

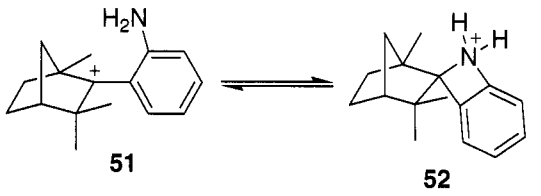
Adjacent substituents have often been exploited in organic reactions to gain kinetic control and influence stereoselectivity. A significant number of studies have been conducted that demonstrate the broad influence of neighboring groups and solvent choices on the outcome of Wagner–Meerwein rearrangements. For instance, the electron-deficient nature of an adjacent aldehyde substituent is known to further destabilize carbocations, frequently preventing them from Wagner–Meerwein rearrangement.[60] Numerous examples exist highlighting substituent effects on the Wagner–Meerwein rearrangement.[61–63]

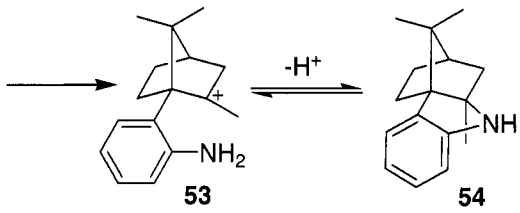
This concept has been nicely demonstrated in the electrophilic addition of norbornadiene-fused pyrazoles, the product distribution of which was dramatically effected by the electron donating ability of the substituent at *N*-2.[64] Electron withdrawing substituents inhibited the Wagner–Meerwein rearrangement by destabilizing **47** and therefore resulted in a predominance of alkene addition products **49** and **50**. Alternatively, in the absence of an

electron withdrawing substituent, **47** is stabilized and therefore the Wagner–Meerwein pathway predominates.

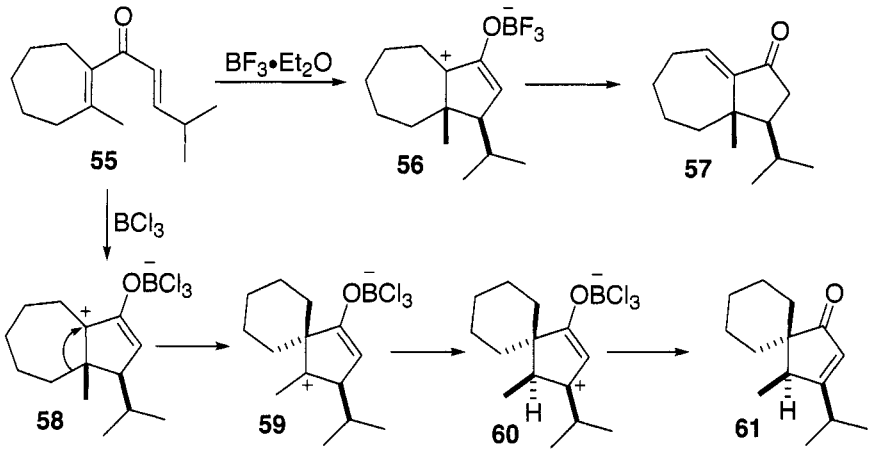


The manner in which the extensively studied fenchyl carbocation rearranges is also highly sensitive to attached functionality as demonstrated in studies of the effects of a 2-aryl substituent at C(2) of the fenchyl system. In a study conducted by Starling, it was found that *ortho*-substituted aryl groups inhibited Wagner–Meerwein migration except when substituted with amino or hydroxyl groups.[65] Presumably, anchimeric assistance facilitated formation of stabilized intermediate **52** allowing for rearrangement to **53** which is ultimately trapped by the nitrogen to afford **54**. In all other cases, *ortho*-substitution suppressed rearrangement by distorting the fenchyl-aryl bond angle, resulting in poor alignment with the empty p-orbital at the migrating terminus.



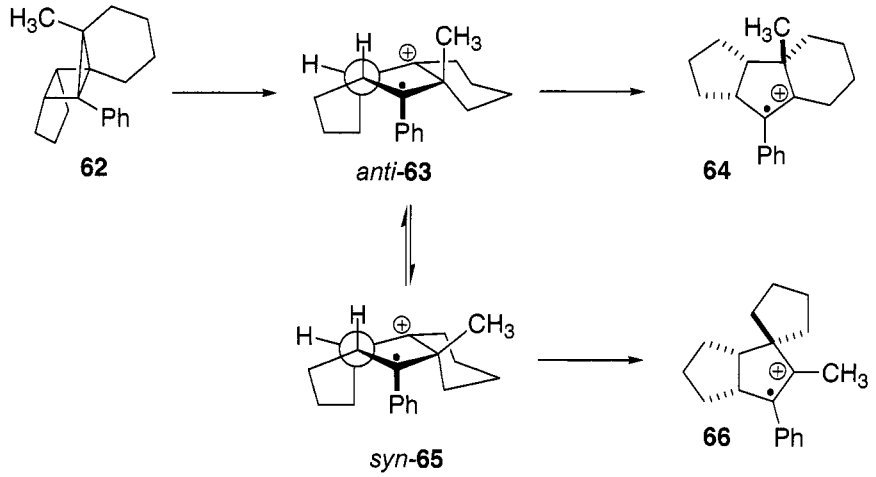


The relief of steric strain is often a driving force for the Wagner–Meerwein reaction. During a synthesis of the guanacastepene diterpenoid core, the fate of Nazarov cyclization products proved to be dependent on the steric bulk of the appended substituents, as well as the solvent in which the reaction was performed.[66] While the use of BF_3•OEt_2 effectively generated Nazarov product **57** upon reaction with divinyl ketone **55**, the use of BCl_3 generated predominantly the rearrangement product **61**. It was proposed that the use of coordinating solvents, such as Et_2O, EtOH and MeOH, results in either rapid deprotonation, or stabilization of **56** thus preventing the Wagner–Meerwein rearrangement. When the isopropyl substituent is replaced with a sterically less demanding methyl group, the Wagner–Meerwein is no longer a competitive process. This evidence suggests that the Wagner–Meerwein rearrangement occurs in order to relieve the steric strain created by the conrotatory cyclization which places the bulky substituents in a *cis*-orientation.

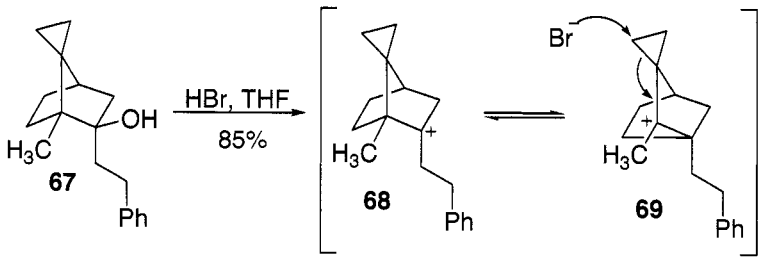


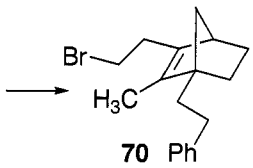
While the majority of Wagner–Meerwein rearrangements involve the retention of stereochemical memory,[67] there are examples where conformational equilibration has been shown to precede rearrangement. A notable instance of this was documented by Adam, in his viscosity-dependent studies of electron-transfer rearrangements of annulated housanes.[68] At low

viscosity, conformational changes from radical cations *anti*-**63** to *syn*-**65** were facilitated by an equilibration more rapid than the respective 1,2-alkyl migration. In the *anti*-conformation **63**, a methyl group occupies the requisite pseudo-axial position for migration, coplanar to the migration terminus. The *syn*-conformation **65** has a methylene fragment in this pseudoaxial position. When solvent viscosity increased, product formation favored **64** over **66** in a ratio of 2.33 to 1. This surprising trend was rationalized as a difference in "frictional impediments imposed by the solvent on ring contraction"[68] between the major structural change of methylene migration and minor structural change of methyl migration.

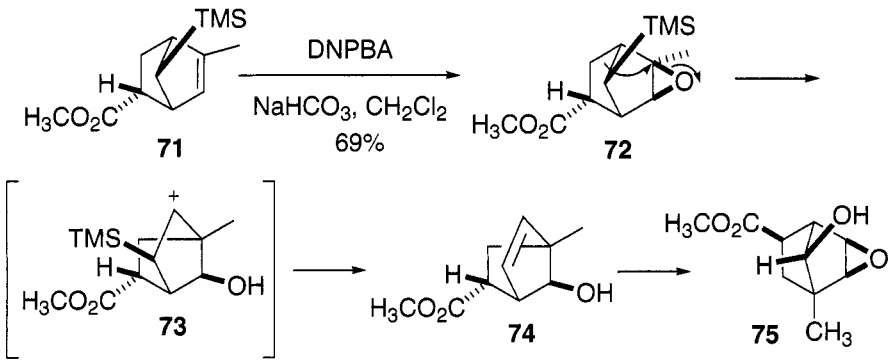


The Wagner–Meerwein rearrangement is often attractive as a result of its ability to stereoselectively form C–C bonds, especially in complex molecules where more traditional means often fail. However, the synthetic utility of this reaction is significantly increased when used in tandem with other reactions. A tandem Wagner–Meerwein rearrangement/cyclopropyl ring-opening sequence serves as a key step in the synthesis of cyclohexenes similar to **70**.[69] Depending on the acid employed, a variety of substituents (–OAc, –Cl, and –SPh) can be incorporated by nucleophilic attack on **69**.

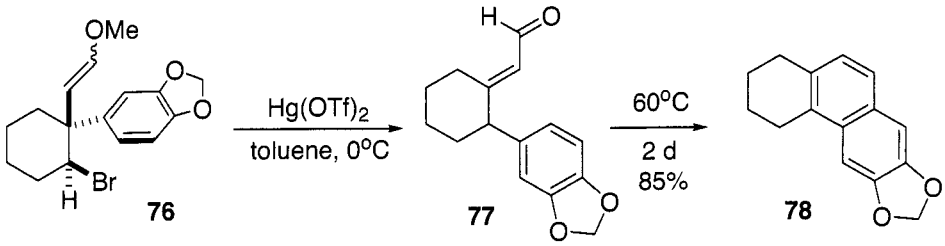




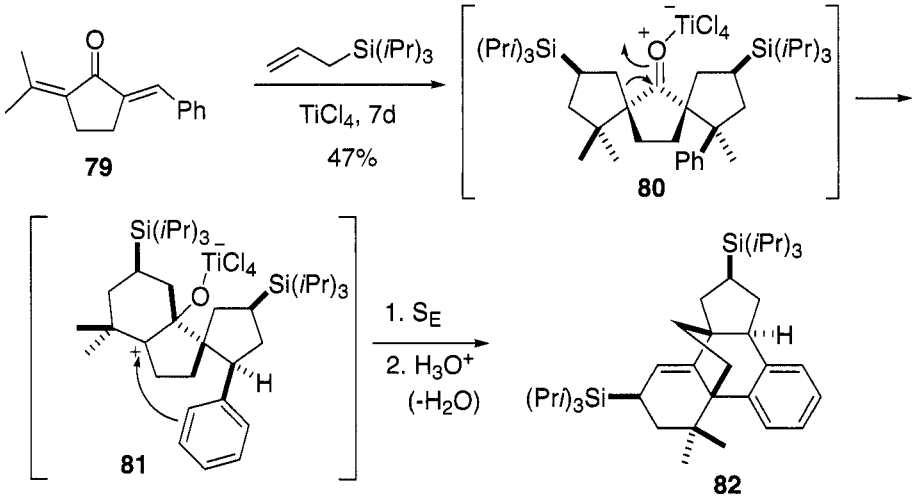
Roush and D'Ambra described a trimethylsilyl-controlled Wagner–Meerwein rearrangement as a key step in the synthesis of a bicyclic precursor of verrucarol.[70] Epoxidation of **71** using the highly reactive 3,5-dinitrophenylperbenzoic acid (DNPBA) resulted in **72** which immediately underwent Wagner–Meerwein rearrangement to yield β-silyl carbocation **73**. Silyl cleavage and epoxidation of the resulting alkene gives the highly oxygenated substrate **75**.



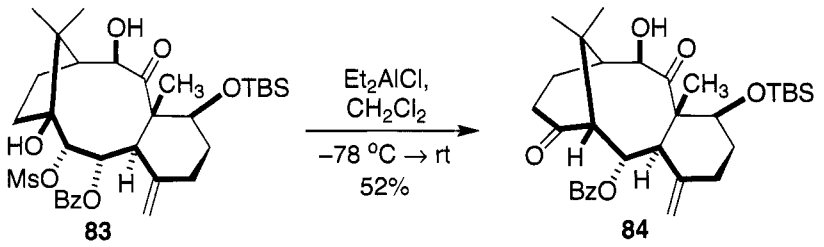
The tandem Wagner–Meerwein rearrangement/Friedel–Crafts alkylation sequence has been used recently for the synthesis of tricyclic aromatic ring systems. An appropriately functionalized aromatic migrating group attached to a α-quaternary β-bromo vinyl methyl ether as in **76** was found to rearrange in the presence of $Hg(OTf)_2$ to form a γ-aryl α,β-unsaturated aldehyde **77**.[60] Subsequent heating of the reaction mixture resulted in cyclization via the Friedel–Crafts alkylation to form the desired tricyclic compound **78** in high yield.



The synthesis of an unexpected pentacyclic ring system was executed by Knölker in his one-pot cascade reaction featuring a sequence of double allylsilane [3 + 2] cycloaddition, Wagner–Meerwein rearrangement, Friedel–Crafts alkylation and finally, elimination of water.[71] This multifaceted reaction involved no intermediate workup, and yielded **82** in an impressive 47% yield as a single diastereomer. Ring enlargement via Wagner–Meerwein rearrangement of **80** to **81** is likely prompted by coordination of the carbonyl with the Lewis acid and relief of steric strain caused by the geminal dimethyl substituent.

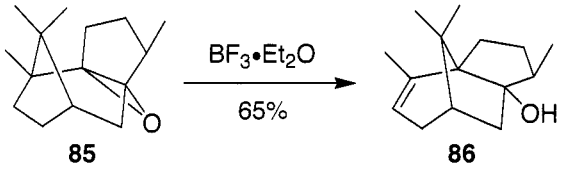


During the synthesis of an advanced precursor to 1-deoxypaclitaxel, Paquette and coworkers[93] employed a 1,2-shift of the *gem*-dimethyl-substituted carbon atom to form the target molecule **84**. Despite the inherent complexity of the molecule, there was sufficient structural flexibility to allow the necessary orbital geometry for the migration to occur.



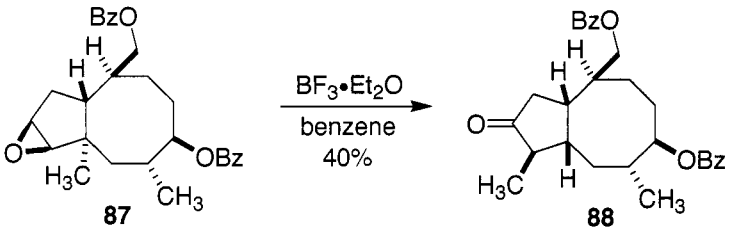
The Holton synthesis of the structurally-analogous taxane ring system involves acid-catalyzed rearrangement upon epoxide opening of β-

patchouline oxide (**85**). Finally, elimination affords tertiary alcohol **86** in good yield.[72]



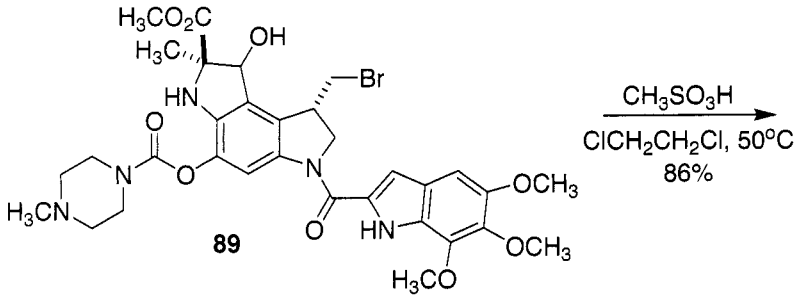
85 **86**

A similar protocol has been applied by Wicha and co-workers in efforts toward the synthesis of a cyclopenta[8]annulene ring precursor to ophiobolin metabolites.[73] Using BF_3•OEt_2 as a Lewis acid catalyst, epoxide ring opening of **87** resulted in the suprafacial 1,2-methyl shift followed by two consecutive hydride migrations to form ketone **88** in moderate yield.



87 **88**

In efforts toward an efficient synthesis of antitumor antibiotic KW-2189, Ogasa and coworkers utilized a Wagner–Meerwein rearrangement as the key step.[74] It was found that multiple Lewis and Brønsted acids were able to promote the migration, including $AlCl_3$, BF_3•OEt_2, CSA, and CH_3SO_3H. Ultimately, migration of the ester proceeded in high yield to provide the free base **90**.



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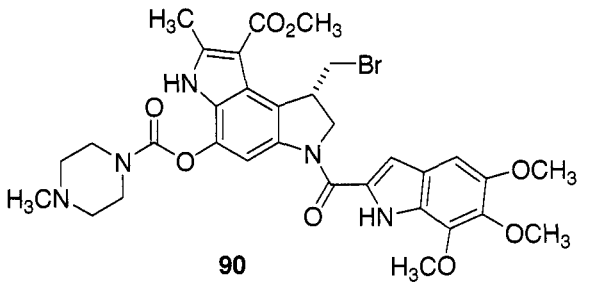
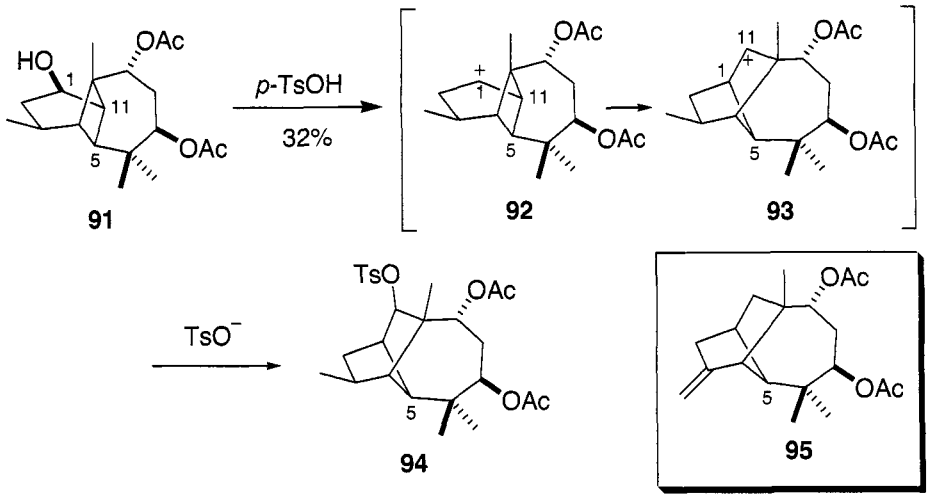


90

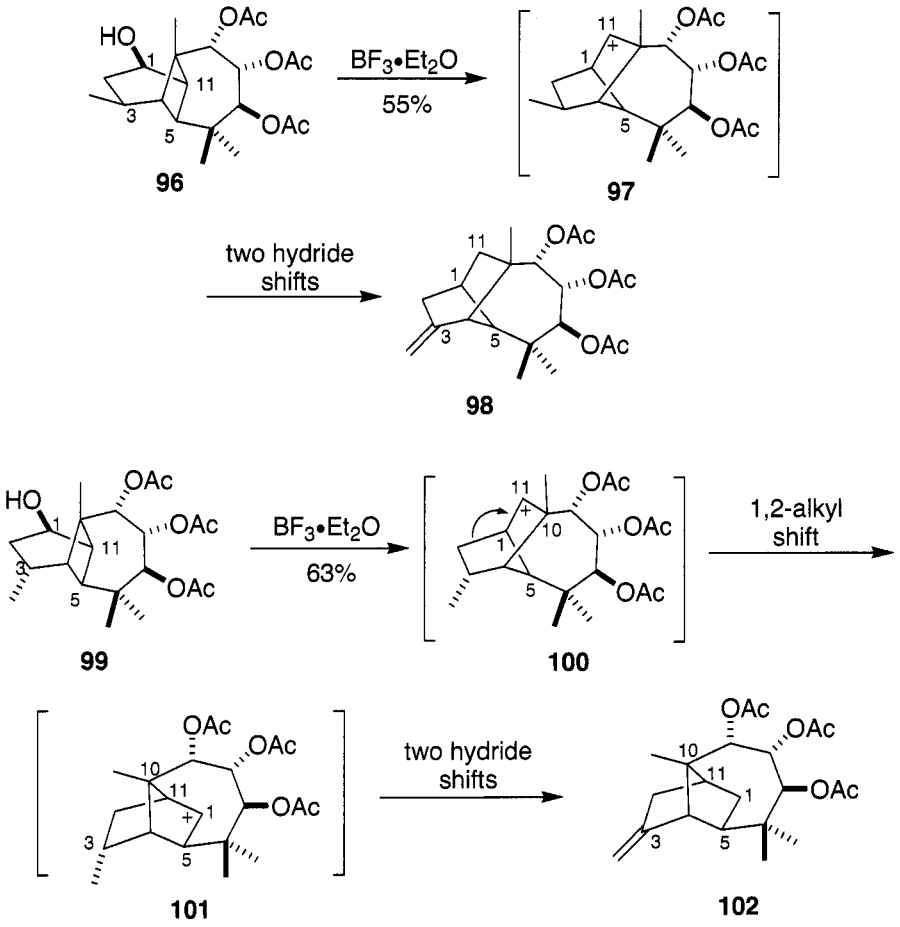
The isolation of various highly functionalized longipinane derivative skeletons has allowed investigations into the interplay of steric, electronic, and conformational influences on molecular rearrangement,[75–79] resulting in novel carbon skeletons whose chemical and pharmacological properties can be further examined.[80,81] Owing to the strain of the central 4-membered ring commonly found in this family of natural products, the Wagner–Meerwein rearrangement has been routinely observed in these systems. Notably, the carbonium ion **92** undergoes rearrangement to **93** upon protonation and dehydration of **91**.[82] Migration of the C_5–C_{11} bond is quite favorable as a result of its anticoplanarity with the leaving hydronium ion, suggesting an element of concertedness in the Wagner–Meerwein rearrangement. Utilizing *p*-toluenesulfonic acid to effect the rearrangement results in nucleophilic trapping of the carbonium ion to produce **94**. Alternatively, **95** is produced via a series of hydride migrations when **91** is treated with sulfuric acid.



91 **92** **93** **94** **95**

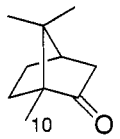
Further studies, conducted on similar longipinane derivatives examined the influence of stereochemistry in the molecular rearrangement.[83] By simply altering the stereochemistry of the C(3) substituent, the reaction

outcome was drastically altered. The Lewis-acid-catalyzed rearrangement of **96** is analogous to that of **91**, involving a Wagner–Meerwein rearrangement and two consecutive hydride shifts and elimination to form **98** in 55% yield. Compound **99** exhibits the analogous Wagner–Meerwein rearrangement to form **102**. The rearrangement which occurred in **97** is not possible as the necessary hydride shifts to form a compound like **98** are energetically disfavored. Instead, a second Wagner–Meerwein shift occurs to form **101**, with **102** finally resulting from consecutive hydride shifts and elimination.



The Martínez group has demonstrated the versatility of the Wagner–Meerwein rearrangement in the enantiospecific synthesis of C(10)-substituted camphors and fenchones from readily available (+)-camphor (**103**) and (–)-fenchone (**104**).[84] These derivatives represent a multitude of substitution types, including C(10)–O-,[85] C(10)–Br-,[86] C(10)–S-,[87] C(10)–Se-,[87] C(10)–N-,[88] C(10)–C–N-,[89,90] and C(9,10)-dihalocamphors.[91] They are of

particular synthetic interest as readily accessible chiral pool materials, which have found utility as chiral auxiliaries, precursors to complex natural products, chiral catalysts, and chiral resolving agents.[84]



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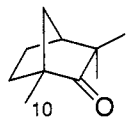
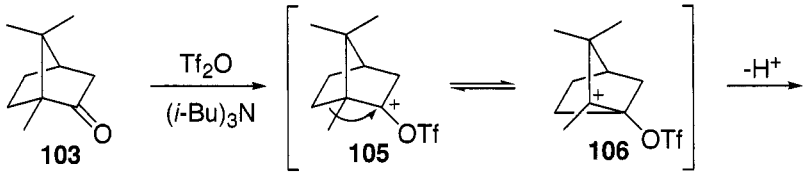
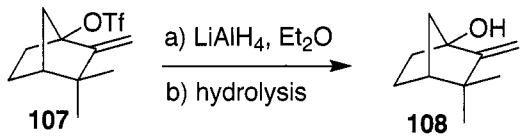


104

As demonstrated below, the general procedure begins by treatment of camphor with triflic anhydride and a non-nucleophilc base to give allyl triflate **107** via Wagner–Meerwein rearrangement of **105** followed by elimination. Reduction of **107** with $LiAlH_4$ then results in allylic alcohol **108**.[84–91]

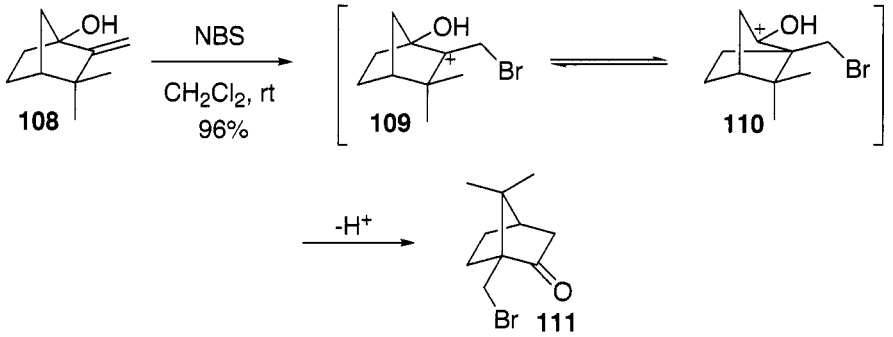


103 **105** **106**

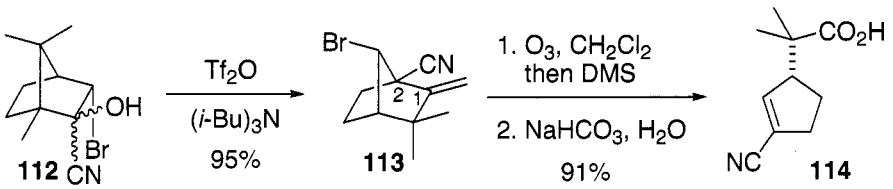


107 **108**

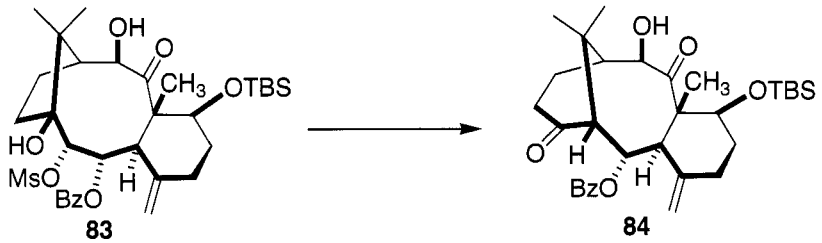
Allylic alcohol **108** is the key intermediate in the work of García Martinez and coworkers, as it sets the stage for the introduction of the C(10) substituent via a second Wagner–Meerwein rearrangement. Upon treatment of **108** with an electrophile, such as NBS,[84] the hydroxyl group stabilizes the incipient carbocation to exclusively promote Wagner–Meerwein rearrangement giving **110** instead of the competing Nametkin rearrangement.[92] Finally, deprotonation of **110** results in the formation of substituted C(10)-camphor derivative **111**. A large number of electrophilic reagents have been used to provide various C(10) substituents, including *m*-chloroperoxybenzoic acid (–OH), *p*-nitrobenzenesulfenyl chloride (–SAr), benzeneselenyl chloride (–SeAr), and *N,N*-dimethylmethaniminium iodide (-CH_2NR_2).[84–91] This reaction mechanism improves significantly on previous synthetic schemes, where tedious protection and deprotection of the carbonyl was necessary. Ultimately, reactions of the aforementioned type occur with high enantioselectivity and yield.



The power of this general methodology has been demonstrated as a means of preparing the enantiopure carboxylic acid **114**.[93] Exposure of alcohol **112** to the conditions above (Tf_2O/base) results in the expected Wagner–Meerwein rearrangement providing **113** in high yield. Ozonolysis of the resulting alkene in **113** is followed by mild basic hydrolysis to give cyclopentene carboxylic acid **114** upon C_1–C_2 bond scission promoted by the leaving bromide at C(7).



1.2.7.6 Experimental



Conversion of 83 to 84.[94]

To a solution of 740 mg (1.14 mmol) of **83** (azeotropically dried with benzene and evacuated for 2 h) in 114 mL of dry CH_2Cl_2 at –78 °C was added 11.4 mL (11.4 mmol) of 1.0 M Et_2AlCl solution in hexane. The reaction mixture was allowed to stir for 5 min at –78 °C, warmed to room temperature over a period of 1.5 h, quenched with 120 mL of 1.0 M tartaric acid aqueous solution, and stirred for 20 min. The separated aqueous layer

was extracted twice with 60 mL of CH_2Cl_2. The organic layers were combined, dried, and concentrated to leave the crude product. Purification by flash chromatography on silica gel (elution with 15% EtOAc/hexane) afforded 334 mg (52%) of **84** as a white foam:

1.2.7.7 References

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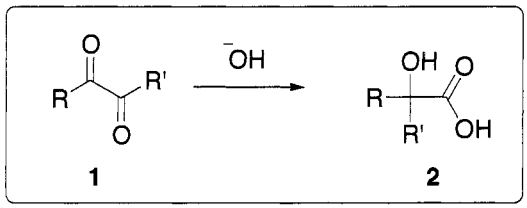
1.3.1 Benzilic Acid Rearrangement

Raju Ranjith Kumar and Marudai Balasubramanian

1.3.1.1 Description

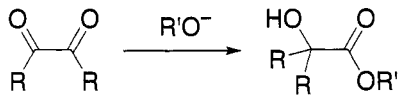
The rearrangement of 1,2-diketones to α-hydroxy carboxylic acids is referred to as Benzilic acid rearrangement. It is a base catalysed reaction whereby α-diketones are converted into α-hydroxy acids.

The 1,2-diketone **1** can be converted into the salt of an α-hydroxy carboxylic acid upon reaction with alkali hydroxide, which upon acidic workup affords α-hydroxy carboxylic acid **2**.[1–6] Semi-aromatic diketones,[7] aliphatic,[8] heterocyclic[9] and aromatic diketones[10] undergo this rearrangement. The substituents should not bear hydrogens α to the carbonyl group, to avoid competing reactions such as aldol condensation.



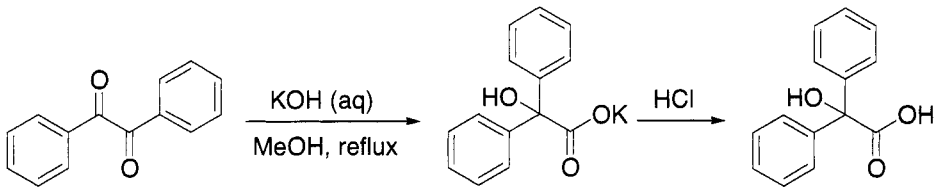
1 **2**

An alternate rearrangement known as benzilic ester rearrangement[2] occurs in presence of alkoxide as nucleophile. The rearrangement product is the corresponding benzilic ester.



1 **3**

1.1.1.2 Historical Perspective



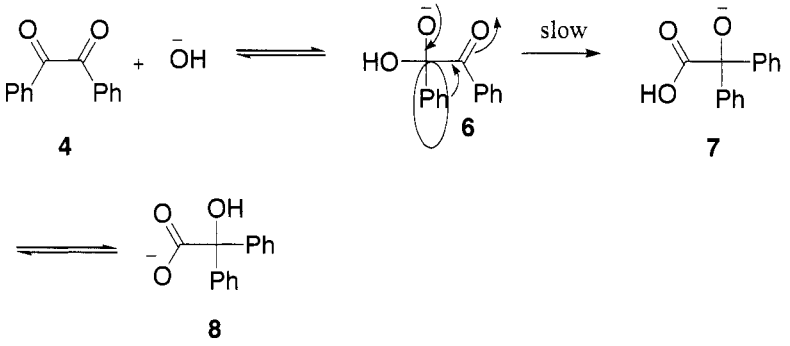
4 **5**

The reaction between benzil **4** with potassium hydroxide to afford benzilic acid **5** was first performed by Justus Liebig[10] in 1838 which is referred to as benzilic acid rearrangement.

Justus Liebig was born to a dealer of paint and common chemicals in Darmstadt, Germany, on May 12, 1803. He was appointed as an assistant professor at the University of Giessen in Germany on May 24, 1824. Another of Liebig's major accomplishments was in the field of applied chemistry. He published the following books: Organic Chemistry and its Application to Agriculture and Physiology, and Organic Chemistry and its Application to Physiology and Pathology, in 1840 and 1842 respectively, which revolutionized food production. Eventhough some of Liebig's ideas were later proved to be incorrect, he set in motion an application of chemical principles that had a profound effect on the future welfare of mankind. On April 18, 1873 Justus Liebig died leaving an extensive legacy to the chemical world.

1.1.1.3 Mechanism

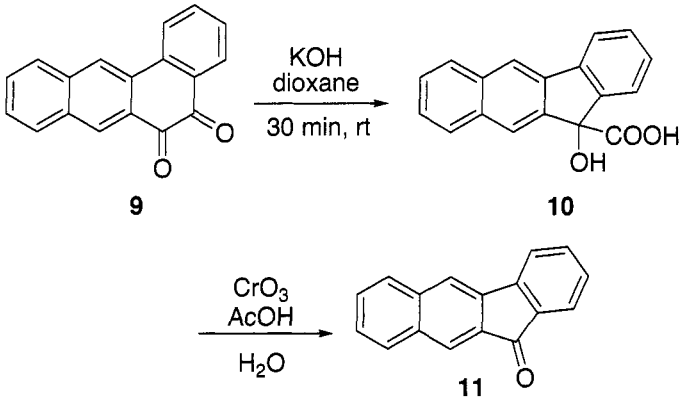
The mechanism for the benzilic acid rearrangement was first proposed by Ingold,[11] which involves three steps



In the first step the reversible addition of a hydroxide ion to a carbonyl group of the α-diketone, gives the anion intermediate **6**, which undergoes an intramolecular rearrangement, in a slow rate determining step affording another intermediate **7**, which upon proton transfer affords the salt of the corresponding α-hydroxy acid **8**. This rearrangement is a second order reaction, the rate being proportional to [benzil] and [base].[11]

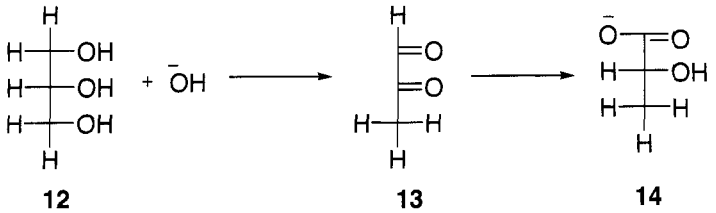
1.1.1.4 Variations and Improvements

Patra *et al.*[12] described the regiospecific synthesis of benz[*a*]anthracene-5,6-dione **9** and their efficient conversion to benzo[*b*]fluorenones **11** through the carboxylic acid **10**. The transformation of **9** to **10** has been effected by benzilic acid rearrangement employing the method of Toda *et al*[13] using powdered KOH in dioxane. Several other conditions such as NaOH in water, KOH in a mixture of ethanol and water, KOH in a mixture of dioxane and water and NaOEt in ethanol did not give satisfactory results.

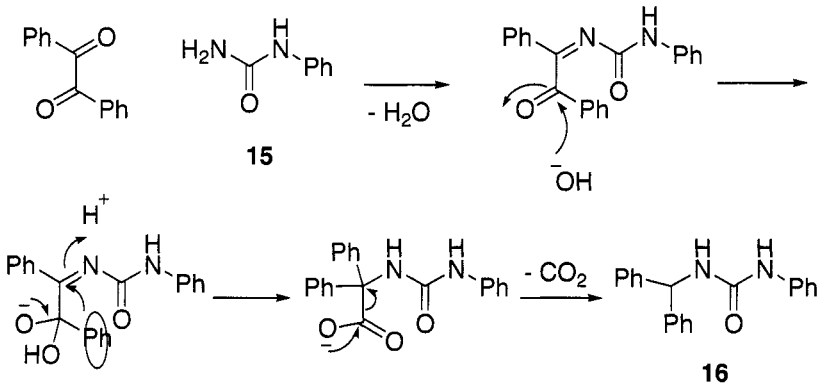


The rearrangement of benzil **4** in water at 300–380 °C proceeds under neutral conditions with no added catalyst. The yield of products shows little variation with pH at near neutral conditions, but it increases greatly under more strongly acidic or basic conditions. Hence, it has been shown that the rearrangement in high-temperature water is catalyzed not only by OH^- but also by H^+ and by water itself.[14]

The hydrothermal decomposition of glycerin **12** with an alkali was studied by Kishida *et al.*[15] He showed that glycerin is first decomposed to pyruvaldehyde **13** with elimination of hydrogen by a H^- shift to the adjacent hydrogen. Pyruvaldehyde formed is then converted into lactate ion **14** by the benzilic acid rearrangement.

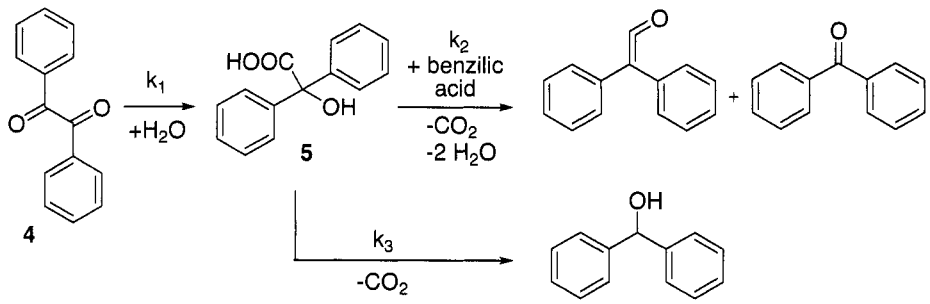


The condensation of benzil and phenylurea **15** followed by benzilic acid rearrangement and decarboxylation afforded 1-benzhydryl-3-phenylurea derivatives **16**.[16]



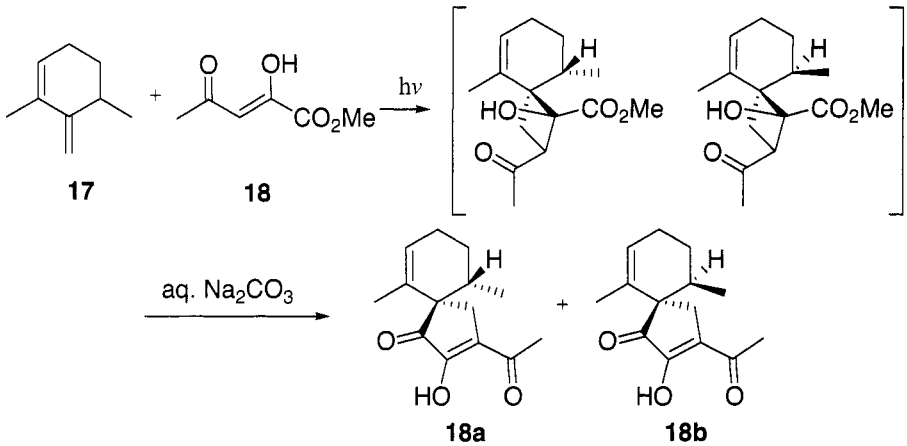
Polackova *et al.*[17] studied the benzilic acid rearrangement of **4** under phase-transfer conditions with the effect of ultrasound. No rearrangement was observed when 50% KOH solution–toluene and benzyltriethylammonium chloride (TEBA) was used as phase transfer catalyst. The yields increased considerably to 60% when a powdered KOH was used instead of pellets. Ultrasonic reactor with the horn immersed into the reaction mixture proved to be much more effective, and 84% of the benzilic acid **5** was isolated after 15 min sonication even when KOH pellets were used.

Comisar *et al.*[18] studied the kinetics and found that the benzilic acid rearrangement of **4** is rapid and the benzilic acid formed reacts in two parallel ways: (i) decarboxylation to form benzhydrol and (ii) self-reaction to form diphenylketene and benzophenone.



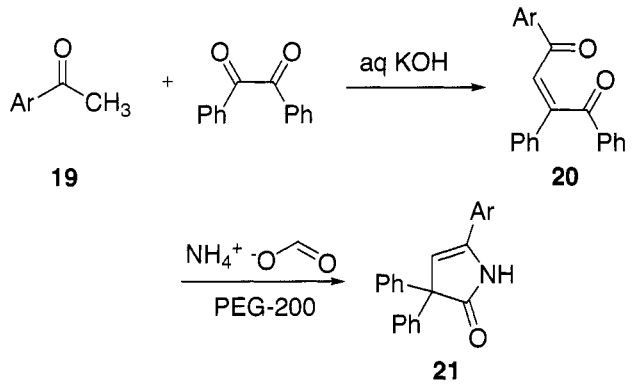
A *retro*-benzilic acid rearrangement was observed affording isomeric *proto*-[2+2]-photocycloadducts **18a** and **b** when a solution of **17** and **18** in

EtOAc was internally irradiated by means of a 400 W high-pressure mercury lamp through a Pyrex glass filter for 7 h.[19]



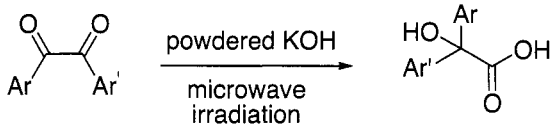
The reaction paths for the benzilic acid rearrangement of **4** along with its methyl analogue, biacetyl were investigated by Yamabe *et al.* using the density functional theory calculations.[20]

The diketone **20** was synthesized from the aldol condensation of aryl methyl ketones **19** and benzil. The benzilic acid type rearrangement of 4-aryl-1,2-diphenyl-2-butene-1,4-diones (**20**) to 5-aryl-3,3-diphenyl-2,3-dihydro-1*H*-2-pyrrolones (**21**) has been accomplished under microwave irradiation using ammonium formate in PEG-200.[21]



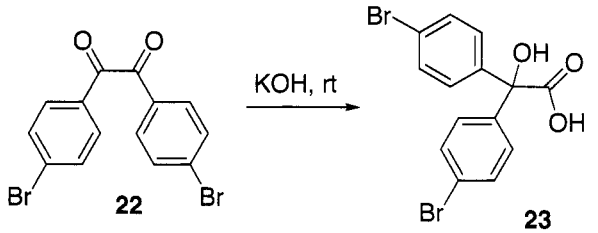
Microwave-assisted heterogeneous benzilic acid rearrangement in solid state has been reported by Yu *et al.*[22] The reported method provides a new route to the synthesis of interesting anticonvulsant dilantin. Powdered KOH and benzil were ground together along with two drops of water and

some Celite to absorb the milky material. The resulting solid was irradiated in a domestic microwave oven for 15 s initially and then at 10 s intervals until the reaction was completed. The rearrangement occurred safely, resulting in excellent yields of the acid. Without microwave irradiation, the benzils with electron-donating groups took a long time to complete.



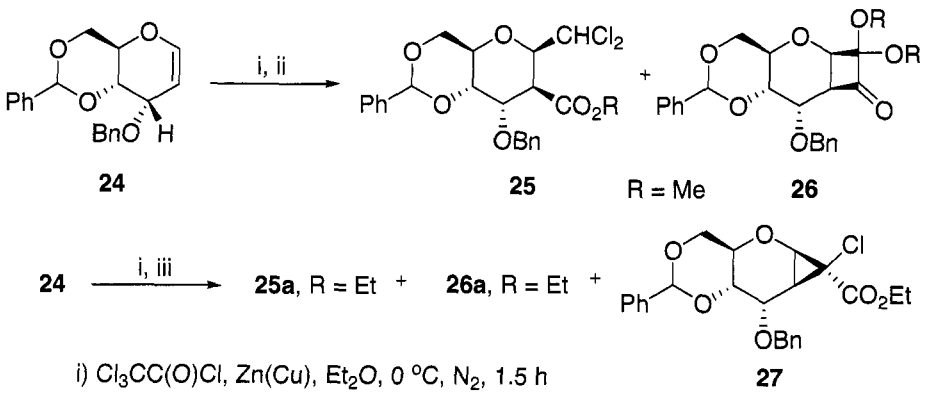
4 **4a** Ar = Ar' = *p*-MeC_6H_4 **5**
4b Ar = Ar' = *p*-$MeOC_6H_4$
4c Ar = Ar' = *o*-ClC_6H_4

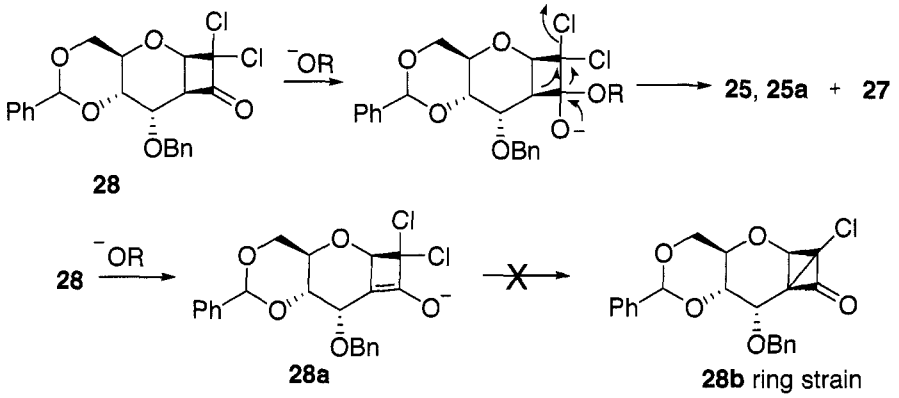
The synthesis of 4,4′-dibromobenzilic acid *via* the benzilic acid rearrangement of 4,4′-dibromobenzil (**22**) proceeded rapidly with high yields.[23] The use of KOH in benzene and methanol in the presence of hexadecyltrimethylammonium bromide as a phase-transfer catalyst afforded 96% yield of the pure acid **23** in 3 h at room temperature.



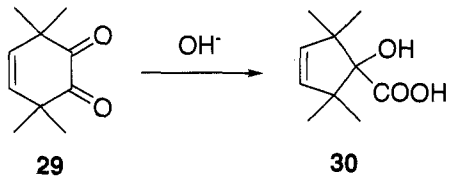
22 **23**

The cycloaddition of allal derivative **24** with dichloroketene followed by treatment of NaOMe in methanol afforded 1,2-dideoxy-β-*D*-altropyranoside **25** and dimethyl ketal **26** in 36 and 29% yields respectively.[24] In contrast to NaOMe, chlorocyclopropanated sugar **27** was also isolated in the case of NaOEt in ethanol. It has been suggested that the formation of ethyl ester **25a** and chlorocyclopropanated sugar **27** proceeds through the same intermediate **28**. Favorskii type reaction pathway has been ruled out due to ring strain in chlorocyclopropanone **28b**. Alternatively, benzilic acid rearrangement has been proposed as more probable reaction pathway through common intermediate for **25**, **25a** and **27**.



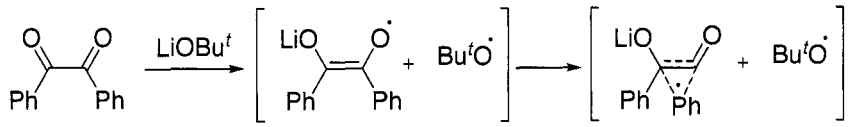


Schaltegger *et al.*[25] reported the base-catalysed benzilic acid rearrangement of cyclic diketone **29**, which, resulted in ring contraction affording the acid **30**.



Evidence for the existence of a single electron transfer mechanism for the benzilic ester rearrangement of benzil and 9,10-phenanthrenoquinone in the presence of lithium *t*-butoxide in tetrahydrofuran-benzene mixture was reported by Screttas *et al.*[26] They showed that the reaction with lithium *t*-butoxide occurred cleanly, while the usage of other alkoxides such as LiOEt

failed. Also the attempt to rearrange benzil with lithium dialkylamides, $LiNEt_2$ or LiN^iPr_2 were unsuccessful.



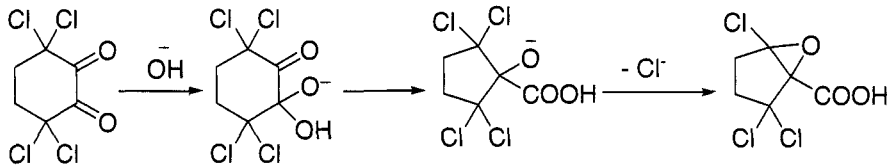
4

$\longrightarrow$ $Ph_2C(OLi)COOBu^t$

31

The mechanisms for benzilic acid and related rearrangements have been studied using the MNDO SCF-MO method to a great extent by Rajyaguru *et al.*[27]

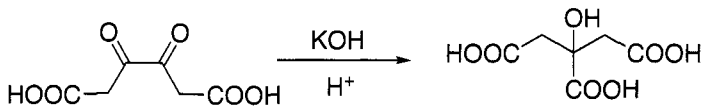
Guirado *et al.*[28] reported a one-pot preparative process involving a benzilic acid rearrangement step followed by a spontaneous epoxidation of the intermediates. Treatment of diketone **32** with sodium hydroxide at room temperature gave 2,5,5-trichloro-1,2-epoxycyclopentane-1-carboxylic acid **35** as a single product in quantitative yield. This transformation has been explained by sequential participation of intermediates **33** and **34**.



32 **33** **34** **35**

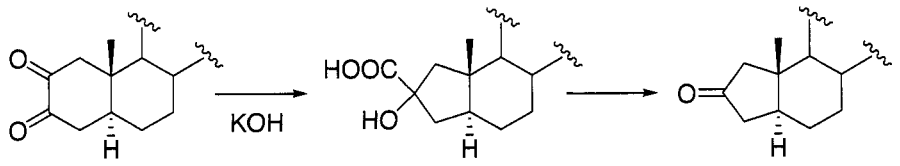
1.1.1.5 Synthetic Utility

Ketopinic acid (**36**), an aliphatic diketone, undergoes benzilic acid rearrangement in the presence of potassium hydroxide to give citric acid (**37**).[29]



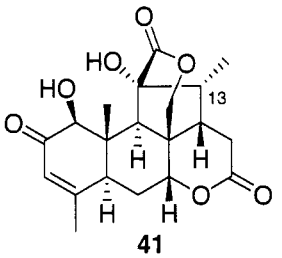
36 **37**

Benzilic acid rearrangement is used to obtain nor-steroids. Cholestan-2,3-dione **38** upon reaction with potassium hydroxide in refluxing propanol furnishes the α-hydroxy acid **39**, which upon oxidation results in the formation of the nor-ketone **40**.[30]



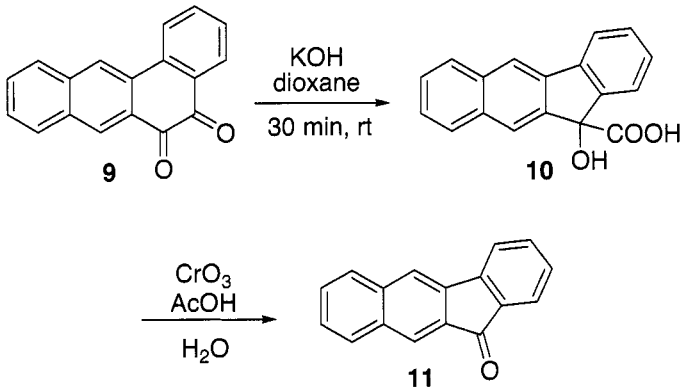
38 **39** **40**

The synthesis of (±)-shinjudilactone and (±)-13-*epi*-shinjudilactone (**41**) involves a benzilic acid type rearrangement.[31]



41

1.3.1.6 Experimental



9 **10** **11**

A mixture of a benz[*a*]anthracene-5,6-dione derivative **9** (500 mg, 1.5 mmol), powdered KOH (1.2 g, 21.4 mmol) and 10 drops of dioxane was stirred for 30 min at room temperature and the resulting mixture was diluted with water (50 mL). The aqueous phase was extracted with Et_2O (2 × 25 mL)

and acidified with dilute HCl and extracted with Et_2O (3 × 30 mL). The latter Et_2O extract were evaporated to dryness to furnish the corresponding hydroxycarboxylic acid **10** as a white residue.[12]

To solid KOH (0.56 g, 10 mmol) water (0.1 mL) was added and the resulting solution allowed stand for 2 min to dissolve the KOH. Powdered benzil (0.42 g, 2 mmol) was added to the KOH and the mixture was well ground with a pestle to form a milky material. Then Celite (5 mL) was added to this mixture and the resulting mixture was ground again. The final mixture was irradiated in a domestic microwave oven (70% of full power) for 15 s first and then three times for 10 s. Diethyl ether (5 mL) was added to the mixture, which was stirred for a while, filtered and the mixture acidified to pH 1.5 with 3 M HCl (25 mL) and then extracted with ethyl acetate (100 mL). The organic phase was dried over $MgSO_4$ and concentrated to give benzilic acid as a white solid.[22]

A solution of 0.065 m of sodium methoxide and 8.0 g (0.038 m) of benzil in 100 mL of methanol was refluxed for 2 h. Removal of solvent gave a purple residue which on treatment with water solidified to crude methyl benzilate. The alkaline aqueous wash liquid was extracted with ether. Concentration of the ether solution gave a small residue which was shaken with sodium bisulfite and ether. From the bisulfite solution about 10 mg of benzaldehyde was obtained, identified as the phenylhydrazone. Acidification of the alkaline aqueous wash liquid above gave 0.85 g of benzilic acid.[2]

1.1.1.7 References

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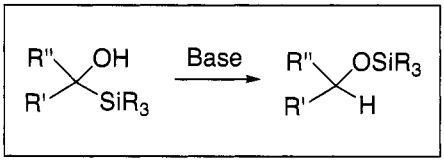
1.3.2 Brook Rearrangement

Christian M. Rojas

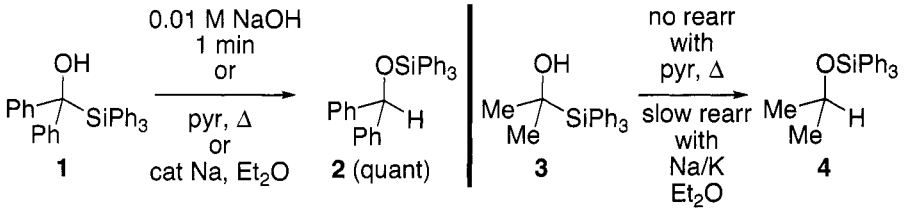
1.3.2.1 Description

The 1,2-migration of a silyl group from carbon to oxygen under basic conditions is known as the Brook rearrangement[1–8] and constitutes a mild, synthetically versatile way to generate carbanions. Mechanistic issues include stereochemistry at both the silicon and carbon centers involved in the rearrangement. Depending on the reaction conditions, the thermodynamics of carbon-to-oxygen silicon transfer may be quite evenly matched or even favor the reverse oxygen-to-carbon, or retro-Brook, process.[9–12] Longer-range silyl migrations, both in the Brook and retro-Brook senses, have also found wide application in organic synthesis.



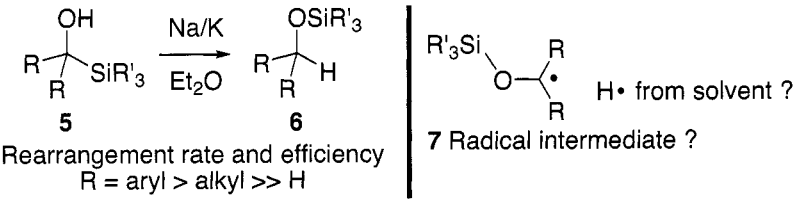
1.3.2.2 Historical Perspective

Two papers from Adrian G. Brook in the last two years of the 1950s established the rearrangement of α-hydroxysilanes to silyl ethers under a range of basic conditions. While Henry Gilman (Brook's Ph.D. advisor, whom Brook credited with his initial interest in organosilicon chemistry[1]) had earlier observed examples of silyl ether formation upon addition of silylmetallics to ketones,[13,14] he did not elucidate their exact origin. Brook, however, showed that triphenylsilyldiphenylcarbinol (**1**) provided nearly quantitative yields of benzhydryloxytriphenylsilane (**2**) upon very brief treatment with dilute hydroxide. Brook obtained similar results in refluxing pyridine, or by using a catalytic amount of alkali metal in ether, or with excess sodium hydride as the base.[15] A methyldiphenylsilyl group also migrated smoothly, but this initial report stipulated no rearrangement with triphenylsilyldimethylcarbinol (**3**) or triphenylsilylmethanol.



Base was required, as simply refluxing in xylene did not effect the rearrangement. When using alkali metals as promoters, only a catalytic amount of sodium or sodium-potassium alloy was required, hydrogen evolution was not observed, and the lump of metal was recovered unchanged after successful rearrangement. Under these conditions or using sodium hydride as base, hydrolysis was not required to isolate the final products. At this early stage, Brook proposed a mechanism showing participation of the base for removal of the alcohol proton and intramolecular silicon migration from carbon to oxygen. Protonation of the resulting carbanion would complete the reaction. In the case of the alkali metal-catalyzed reactions, protonation of the carbanion by the next molecule of carbinol would continue the process.

In the second paper,[16] Brook and co-workers extended the scope of the rearrangement to a series of α-hydroxysilanes **5**. As the carbinol substituents changed from aryl to alkyl or hydrogen, the qualitative rate of rearrangement to **6** was lower and the overall process became less efficient. Contrary to the previous report, triphenylsilyldimethylcarbinol did undergo the rearrangement (**3** → **4**), albeit in low yield. Triphenylsilylmethanol was, however, in fact inert. The reaction was more tolerant of the groups on silicon, as triphenylsilyl, trimethylsilyl, and methyldiphenylsilyl groups all transferred smoothly. The authors expressed doubts about their originally proposed mechanism, stating that it might not be consistent with new data. For example, they observed a deep blue color at the metal surface, perhaps attributable to a radical species such as **7**. In this scenario, hydrogen atom abstraction from the solvent would provide the C–H bond. Rearrangement products did not form in CCl_4 solvent.



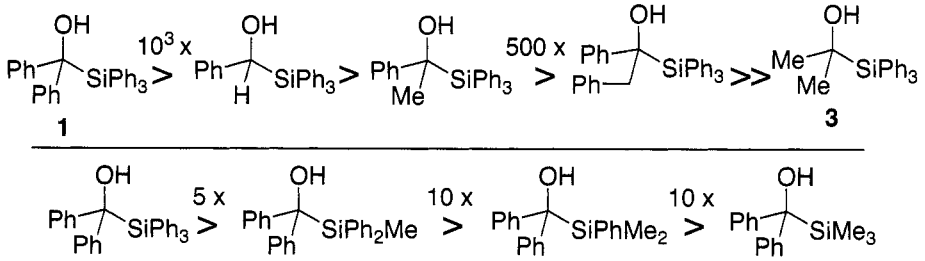
Brook had set the basis for developing the reaction that came to bear his name, but clearly many mechanistic details remained to be elucidated. In addition, Brook did not anticipate the potential utility of the rearrangement, in fact concluding the 1959 paper with what turned out to be wholly unwarranted self-deprecation: "It is doubtful whether the rearrangement reported here will have much synthetic application since in general silyl ethers are much more readily prepared than are the corresponding α-silylcarbinols."[16]

1.3.2.3 Mechanism

Kinetic evidence:

Brook found that the rearrangement was first order in silyl carbinol. The rate also depended in a first order way on the amount of added base, but this was not consumed and was used in substoichiometric amounts, so the reaction followed pseudo-first order kinetics overall. The groups at the carbinol carbon had a strong impact on the rate, with the α-diphenyl-substituted system **1** rearranging about a thousand times faster than when one of the phenyls was replaced with either hydrogen or methyl. Dialkyl substitution as in **3** rendered the rate too slow to measure (Figure 1, top). Substitution at silicon had a smaller effect on the rearrangement rate, though in DMSO the reaction slowed progressively as phenyl groups at silicon were replaced by methyls (Figure 1, bottom).[17]

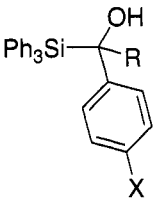
Figure 1. Relative rates of Brook rearrangement in DMSO



By examining rates at various temperatures, Brook and co-workers extracted the activation parameters for rearrangements of various silylcarbinols. The activation energies E_a were modest, in the range of 8–11 kcal/mol. More striking were the large negative entropies of activation, with $\Delta S^{\dagger}$ in the –35 to –45 cal/mol/K range.[17]

Hammett studies using a series of *p*-substituted phenyl groups at the carbinol carbon showed positive ρ values (Figure 2), indicating an

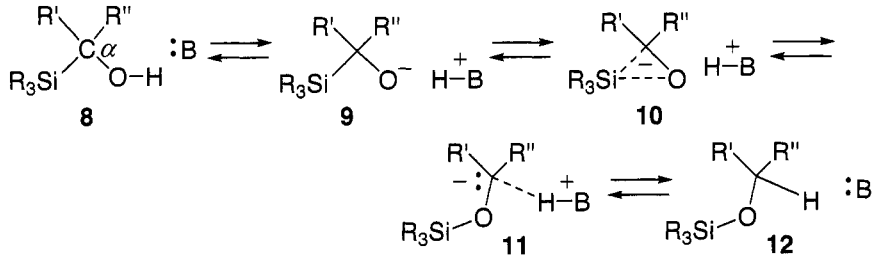
accumulation of negative charge at carbon in approaching the transition state.[17]



R	ρ	Solvent
Ph	+1.54	$CHCl_3$
Me	+4.63	DMSO
H	+3.66	DMSO

Figure 2. Hammett ρ values for Brook rearrangement of various α-triphenylsilyl carbinols

These careful studies supported the mechanism shown for **8** → **12**.[17,1] The first order kinetics in silylcarbinol were consistent with intramolecular C → O silyl migration. Reaction via **10** as a cyclic transition state, with the conjugate acid of the base remaining nearby, would account for the large negative entropy of activation. The Hammett studies indicated a transition state with buildup of carbanionic character in proceeding toward product.

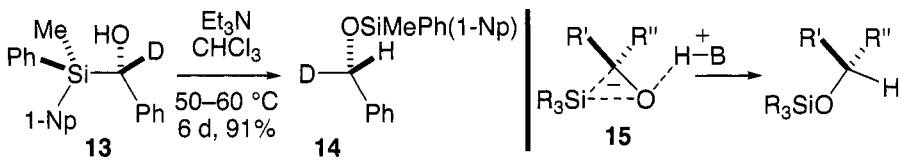


Stereochemistry at silicon:

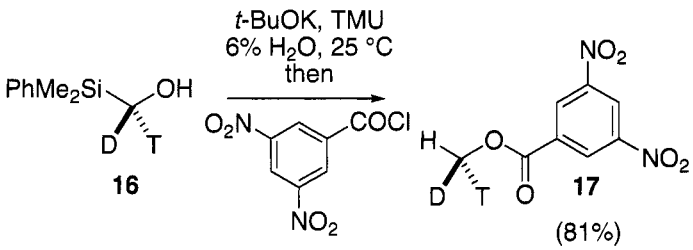
Brook addressed this important mechanistic issue early, developing evidence for retention of configuration at silicon in the rearrangement.[18,19] Based on the precedented assumption of inversion at asymmetric silicon in chloride displacement with either an organolithium or an alcohol, Brook and co-workers showed a stereochemical Walden cycle that implicated retention at silicon in the rearrangement step. Mechanistically, retention at silicon corresponds to a frontside-type displacement, consistent with the mechanism shown above. The displacement might implicate **10** as a pentacoordinate silicon intermediate rather than a transition state.

Stereochemistry at carbon:

Again, Brook was responsible for some of the earliest studies in this area. Initially, he reported retention of configuration at carbon in the rearrangement.[20] However, Brook's later studies on related systems, including **13**, showed that an assumption of a Cram-controlled carbonyl addition in the preparation of the substrate for the earlier study was flawed, reversing the required stereochemical course at carbon during the rearrangement to *inversion*.[21] Brook also found that the stereospecificity at carbon was higher using the conditions shown for the conversion of **13** to **14** than with sodium-potassium alloy in ether solvent and that, somewhat surprisingly, the stereospecificity was insensitive to solvent polarity. Contemporaneously, Mosher uncovered the flaw in Brook's earlier report and concluded that inversion occurred at carbon in the rearrangement.[22] Mosher proposed that inversion at carbon occurred by backside protonation of the three-membered-ring intermediate **15** by the nearby conjugate acid of the original base. Brook adopted this model in his 1974 summary article,[1] pointing out that the hydrogen-bonded complex **15** was consistent with the observed high negative entropy of activation for the rearrangement.

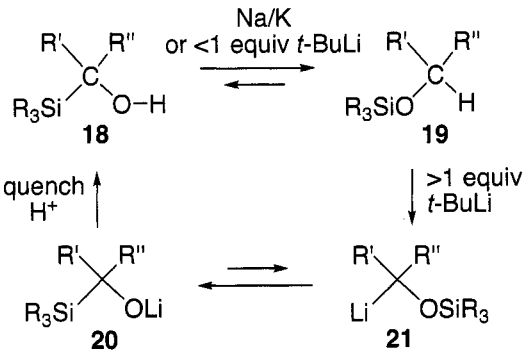


While inversion of configuration occurs during the Brook rearrangement of α-silyl-α-phenyl (i.e., benzyl) alcohols, the stereochemical course involves *retention* at carbon in systems having an alkyl substituent in place of the phenyl group at the α carbon.[23–25,79] This element of stereospecificity was confirmed and applied in a remarkable synthesis of chiral methanol. Brook rearrangement of highly enantiomerically enriched **16**, proceeded in *N*,*N*,*N'*,*N'*-tetramethylurea (TMU) solvent with a small amount of added water. Under these conditions, hydrolysis of the resulting silyl ether provided the alcohol, and this was esterified, providing **17**. The analogous conversion in the enantiomeric series was also carried out, leading to the preparation of either enantiomer of chiral methanol.[26]



Brook vs Retro-Brook Directionality:

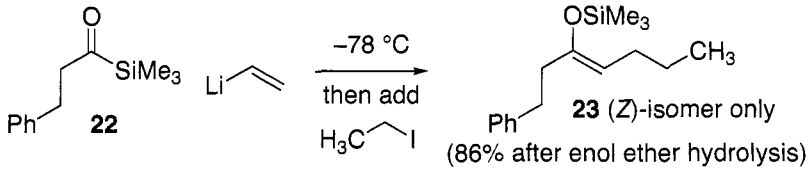
Silyl migrations in either the Brook (C → O) or retro-Brook (O → C) sense are feasible because the equilibria among the various neutral and anionic species **18**–**21** can be readily established and manipulated, depending upon the reaction conditions.[1,3,4,12] The protonation states of starting material and product are crucial. With catalytic amounts of base, the relevant equilibrium is that between the neutral species, and the stronger O–Si bond (120–130 kcal/mol) favors Brook rearrangement product **19** over the silyl carbinol **18**, with its weaker C–Si bond (75–85 kcal/mol). However, if the species are in their anionic forms (in the presence of an excess of powerful base, for example[27]), the oxyanion **20** may predominate over carbanion **21**, favoring the retro-Brook process. The tightly oxyanion-binding lithium cation is particularly effective in retro-Brook reactions, while looser binding Na^+ and K^+ can shift the balance in the Brook direction as can coordinating solvents (e.g., HMPA, THF) and chelating agents (e.g., crown ethers, TMEDA). Application of some of these parameters in synthesis and to extend the range of the Brook rearrangement concept are discussed in subsequent sections of this article.



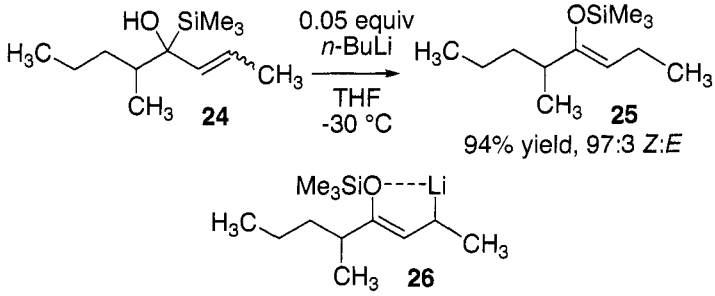
1.3.2.4 Synthetic Utility

Silyl enol ether formation:

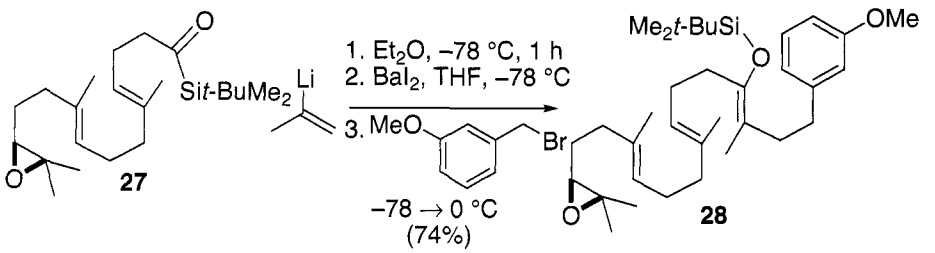
Reich employed the Brook rearrangement in a stereoselective synthesis of silyl enol ethers. Addition of vinyl lithium to acyl silane **22**, for example, was followed by the 1,2-carbon-to-oxygen silyl migration. The resulting resonance delocalized anion alkylated stereoselectively at the terminal end, efficiently providing (*Z*)-silyl enol ether **23**. The corresponding addition of terminal alkynyl organolithium reagents to silyl ketones provided silyl allenol ethers.[28]



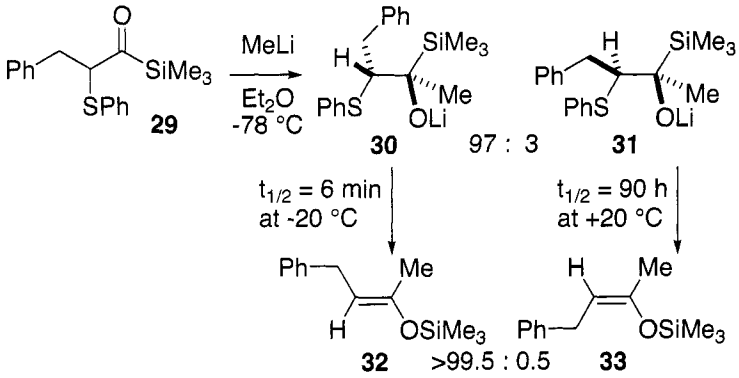
In contemporaneous studies by Kuwajima, the 1-silyloxy allyl anions were generated from 1-trimethylsilyl allylic alcohols such as **24**. Treatment with a catalytic amount of base led to silyl enol ether **25** in excellent yield and (*Z*)-selectivity. The alkene geometry was proposed to arise from chelate **26**, a structure consistent with Reich's results. Protonation of anionic intermediate **26** by alcohol **24**, would provide product **25** and the alkoxide of **24**, poised for Brook rearrangement.[29]



Corey has utilized the Brook-generated allyl anion alkylation in several syntheses.[30–33] A recent example was in the preparation of π-cation cyclization precursor **28**. Chemoselective addition of 2-propenyllithium to the acyl silane carbonyl of **27**, followed by transmetalation and alkylation provided the (*Z*)-silyl enol ether **28**.[34]

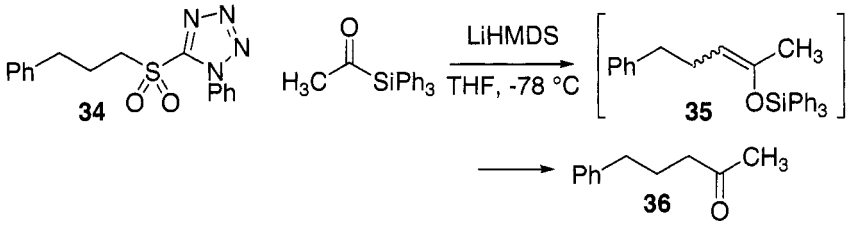


Another silyl enol ether synthesis developed by Reich utilized systems where the Brook rearrangement led to β-elimination from the resulting carbanion.[35] This approach was inspired by Brook's previous studies on the reaction of an acyl silane with a Wittig phosphorus ylide.[36] In that case, nucleophilic addition, Brook rearrangement, and elimination of triphenylphosphine led to a single geometrical isomer of silyl enol ether, although the stereochemistry was not determined. Reich employed addition of organolithium reagents to α-thiophenyl acyl silanes (e.g., **29**), generating (*E*)-silyl enol ether **32** after Brook rearrangement and thiophenoxide elimination. Careful mechanistic studies traced the high stereoselectivity to Felkin-Anh control in the initial carbonyl addition, leading to a preponderance of lithium alkoxide **30**. Moreover, this diastereomer was found to undergo silyl migration-elimination a great deal faster than **31**, further enriching the silyl enol product in the (*E*)-form **32**.

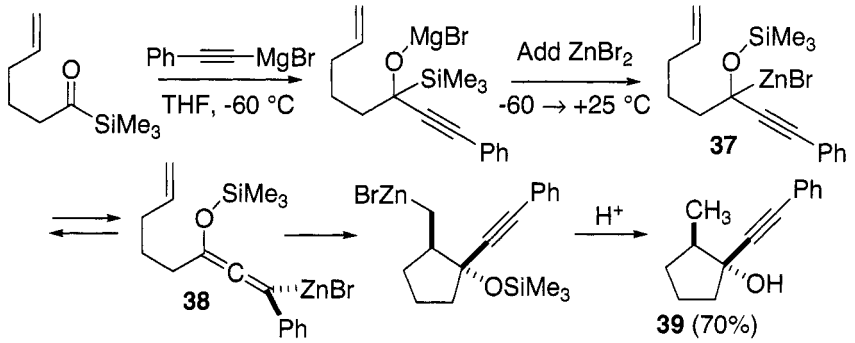


The concept of silyl enol ether synthesis via β-elimination from a Brook rearrangement-derived carbanion also appeared in Wicha's studies on additions of 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfonyl anions to acyl silanes. When PT sulfone **34** was deprotonated in the presence of acyl(triphenyl)silane, ketone **36** was isolated in good yield after hydrolysis of the silyl enol ether intermediate **35**. The mechanism involved addition of the

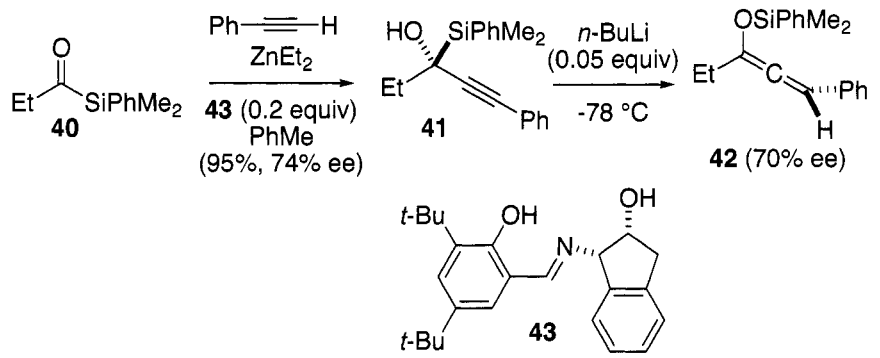
sulfonyl anion to the acyl silane, carbon-to-oxygen silyl migration, and elimination of the sulfinate. Wicha and co-workers also found that in other cases the sulfonyl anion addition to acyl silanes led to vinyl silanes by Smiles- rather than Brook rearrangement.[37]



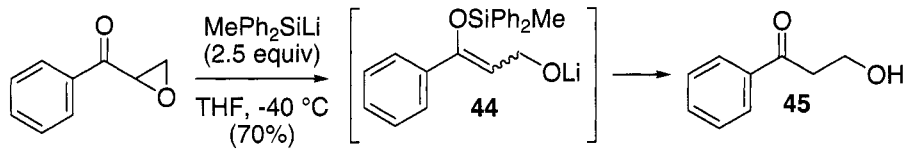
Marek and co-workers found that magnesium-to-zinc transmetalation of the alkoxides derived from addition of acetylenic Grignard reagents to acyl silanes promoted the 1,2-Brook rearrangement. The resulting propargyl zinc intermediates (e.g., **37**), in equilibrium with the silyl allenol ethers of type **38**, underwent diastereoselective carbocyclization in suitable systems, providing cyclopentanol **39**, for example, after acid quench and desilylation.[38]



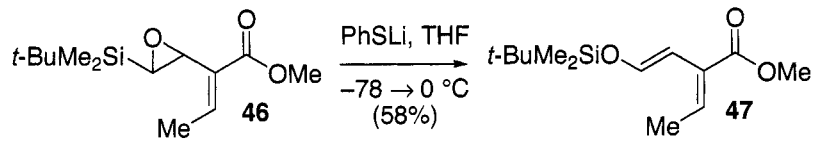
Interestingly, addition of a zinc acetylides to an acyl silane **40** having a bulkier silyl group did not lead to spontaneous Brook rearrangement. However, the 1,2-silyl migration from **41** was carried out with a catalytic amount of base, providing silyl allenol ether **42**. Asymmetric induction in the addition process utilized chiral ligand **43**, and the configuration of the α-silylcarbinol **41** was reflected nearly quantitatively in the 1,2-Brook rearrangement product **42**, formed by protonation at the γ-position of the propargylic carbanion.[39]

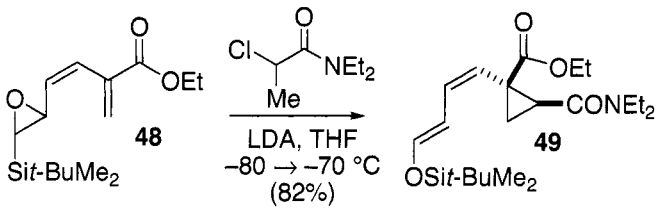


Silyl enol ethers were intermediates in the reduction of α,β-epoxy ketones by addition of methyldiphenylsilyllithium. The process involved addition to the carbonyl group, followed by 1,2-Brook rearrangement and epoxide opening. With excess of the silyllithium, the O–Si bond of the resulting silyl enol ether **44** was cleaved, providing the β-hydroxyketone product **45**.[40]

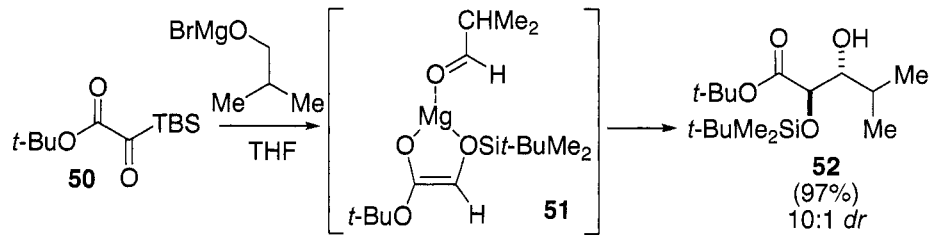


Addition of lithium thiophenoxide to epoxysilane **46** provided (*E*,*E*)-silyl enol ether **47**. Conjugate addition to the α,β-unsaturated ester moiety and β-elimination in the direction of the oxirane led to epoxide opening and 1,2-Brook rearrangement of the resulting α-silyl lithium alkoxide. The carbanion underwent 1,4-elimination of thiophenoxide, leading to diene **47**. Using the enolate of 2-chloro-*N*,*N*-diethylpropionamide as the nucleophile for Michael addition to **48**, led to a similar sequence, but with a final, diastereoselective cyclopropane-forming step, giving **49**.[41] Takeda and co-workers also used the epoxysilane rearrangement as part of a [3 + 4] annulation approach to seven-membered rings.[42]

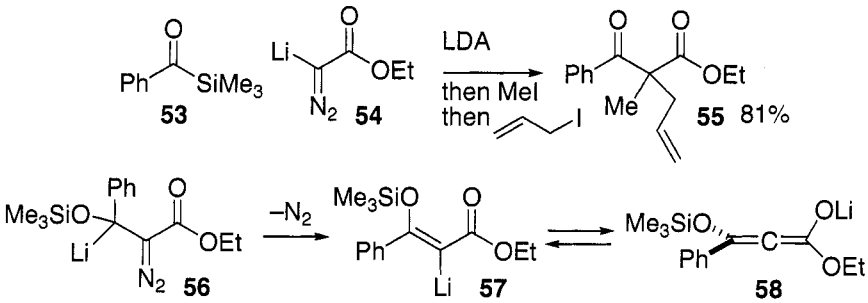




Meerwein–Ponndorf–Verley delivery of hydride to silylglyoxylate **50** from a primary or secondary magnesium alkoxide initiated 1,2-Brook rearrangement, with the resulting enediol silyl ether **51** ending up complexed to the aldehyde or ketone Oppenauer oxidation product. An aldol occurred directly, providing α-siloxy-β-hydroxy esters. Diastereoselectivity in the aldol step was variable in the examples studied, although the reaction using magnesium isobutoxide provided **52** with good diastereoselectivity and excellent yield.[43]

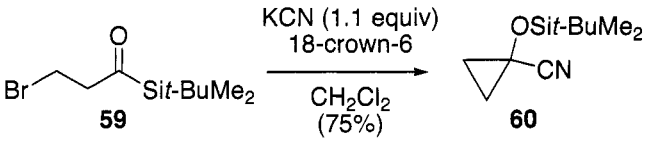


Addition of α-lithio ethyl diazoacetate **54** to acyl silanes such as **53** and subsequent 1,2-Brook rearrangement to carbanion **56** provided lithiated silyl enol ether **57**, apparently in equilibrium with the corresponding β-siloxy allenolate **58**. Sequential alkylation was possible, providing fully substituted β-ketoester product **55**.[44]



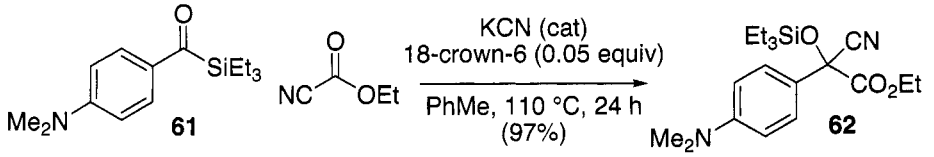
Cyanide-initiated rearrangement:

Explored initially by Reich,[35] cyanide addition to acyl silanes can produce Brook rearrangement, leading to an additional cascade of steps in appropriately designed systems. For example, Takeda, using a crown ether as a phase transfer agent but under non-aqueous conditions, showed that cyanide addition to acyl silanes and subsequent Brook rearrangement led, in the case of β-bromo acyl silane **59** to intramolecular alkylation and formation of cyclopropanone cyanohydrin derivative **60**.[45]



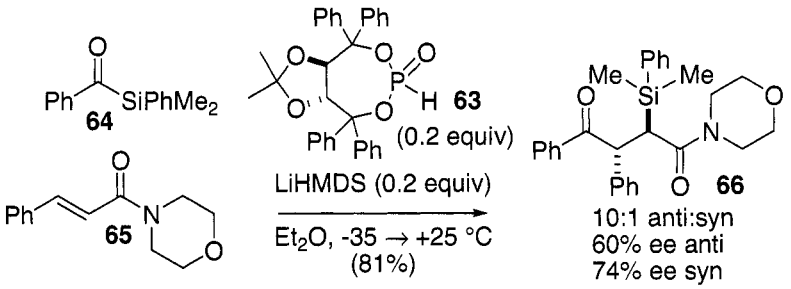
59 **60**

By using cyanoformate esters as electrophiles, Johnson and co-workers were able to employ catalytic amounts of the cyanide initiator in reactions with acyl silanes. This process led to carbon–carbon bond formation via *C*-acylation. For example, acyl silane **61** and ethylcyanoformate combined under these conditions to provide the tertiary alcohol silyl ether **62** in nearly quantitative yield.[46] Johnson's group has also developed an asymmetric version of this process, utilizing the Jacobsen (salen)aluminum system as a chiral carrier for the cyanide anion.[47,48]



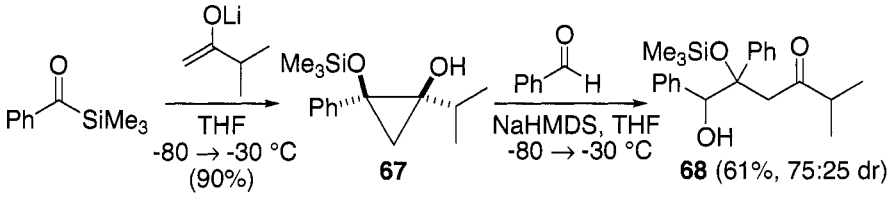
61 **62**

Instead of cyanide, metallophosphite catalysts can also be used in Brook rearrangement/carbon–carbon bond forming sequences. Work in this area has come from the laboratories of Reich[35] and Takeda.[49a] Additionally, Johnson reported that deprotonation of the Enders phosphite **63** provided an asymmetric catalyst for combination of acyl silane **64** and α,β-unsaturated amide **65**. The resulting 1,4-dicarbonyl product **66** was formed with good diastereoselectivity and moderate enantiocontrol. The proposed mechanism involved initial metallophosphite addition to the acyl silane, Brook rearrangement, and conjugate addition of the resulting carbanion to **65**. Interestingly, this was followed by retro-1,4-Brook transfer to install the C–Si bond of product **66**, also forming the ketone carbonyl and regenerating the metallophosphite catalyst.[49b]

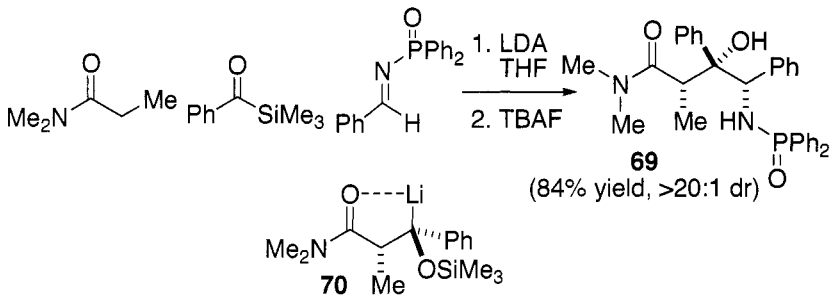


Homoenolate equivalents:

Addition of ketone enolates to acyl silanes, followed by Brook rearrangement and closure of the resulting carbanion onto the pendant ketone carbonyl leads to 1,2-cyclopropanediol products such as **67**. In the presence of an appropriate electrophile and using a sodium amide base, **67** serves as a homoenolate equivalent, generating β-siloxy-γ-hydroxyketone **68** as a mixture of diastereomers whose stereochemistry was not determined.[50]

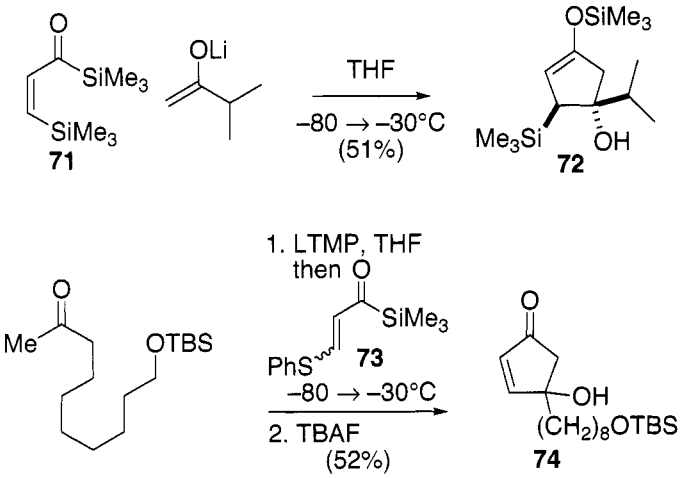


By using amide enolates, Scheidt found that cyclopropanediol formation was suppressed after addition of the enolate to an acyl silane. Instead, the carbanion resulting from the Brook rearrangement reacted in situ with *N*-diphenylphosphoryl aryl imines, enabling diastereoselective access to products such as **69**, bearing three contiguous stereogenic centers. The proposed mechanism involved formation of the configurationally stable, internally coordinated alkyllithium **70** after the Brook rearrangement step and subsequent stereocontrolled addition to the imine. Hydrolysis of the diphenylphosphoryl amides led to γ-lactam formation.[51] A similar process in which the Brook-derived carbanion was alkylated led to tertiary β-hydroxy amides.[52]



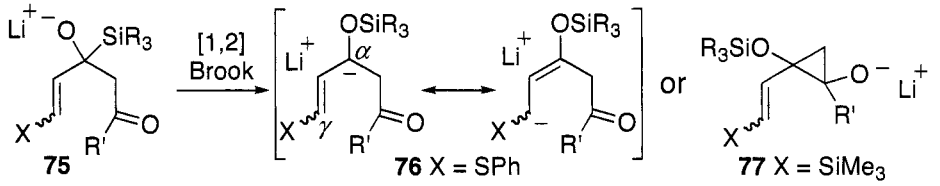
Five-membered ring synthesis:

Takeda and Yoshii found that upon addition of a ketone enolate to the carbonyl of an α,β-unsaturated acyl silane, Brook rearrangement produced an allyl anion that closed to the five-membered-ring silyl enol ether. In the case of acyl silane **71** and methyl isopropyl ketone enolate, the resulting annulation product **72** was formed as a single diastereomer. Incorporation of a β-thiophenyl group into the starting unsaturated acyl silane (e.g., **73**) led to elimination upon desilylation of the five-membered ring enol ether, providing access to 4-alkyl-4-hydroxy-2-cyclopenentones such as **74**, an intermediate en route to chromomoric acid D-II methyl ester.[53]



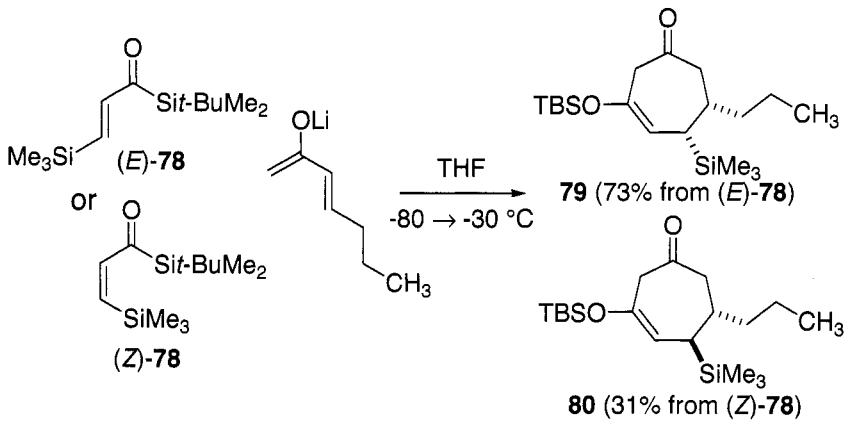
A detailed study from Takeda's group found that the exact mechanism for cyclopentene synthesis depended on the distal substituent of the unsaturated acyl silane (X in **75** below). With the thiophenyl group, after the Brook rearrangement, cyclization occurred via closure of the allyl anion **76** at the γ end. For the vinyl silane compounds, however, Takeda's studies

implicated an anion-accelerated vinyl cyclopropane to cyclopentene rearrangement of intermediate **77**.[54]



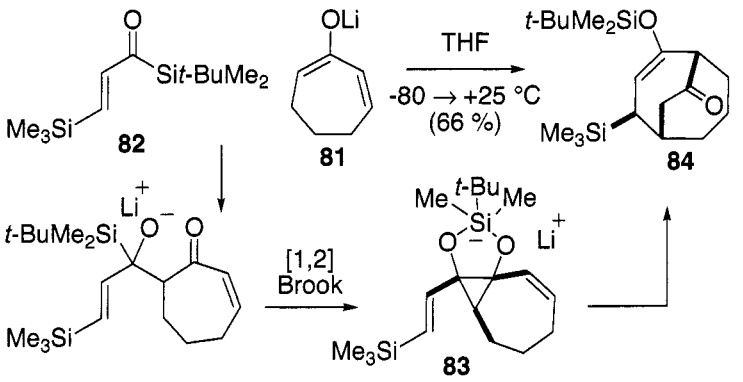
Seven-membered ring synthesis:

Takeda and Yoshii also developed a remarkable annulation using α,β-unsaturated ketone enolates for addition to β-silylacryloyl silane **78**. The reaction was stereospecific, with (*E*)-**78** providing **79** in good yield, but (*Z*)-**78** leading to the *trans*-product diastereomer **80** in a sluggish, lower-yielding reaction. The proposed mechanism involved an anion-accelerated Cope rearrangement of a 1,2-divinylcyclopropanediolate intermediate.[55]

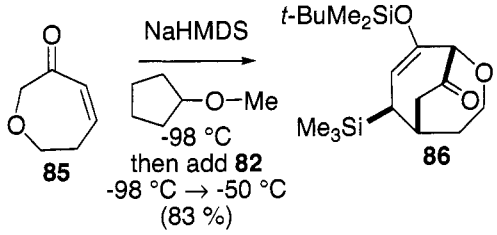


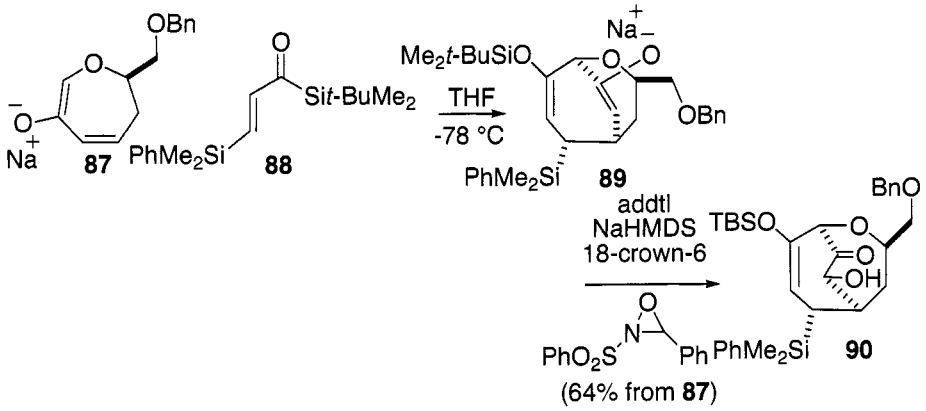
Eight-membered ring synthesis:

A divinylcyclopropanediolate was also involved in a Brook rearrangement-mediated synthetic approach to eight-membered-ring enol ethers. Addition of enolate **81** to α,β-unsaturated acyl silane **82**, for example, provoked carbon-to-oxygen silyl migration and addition of the resulting carbanion (or incipient carbanion) to the nearby ketone carbonyl. The proposed intermediate **83** underwent anionic Cope rearrangement to bridged product **84**.[56]



Eight-membered-ring oxacycles were available from an analogous route. Formation of the sodium enolate from oxacycloheptenone **85** and reaction with acyl silane **82** provided **86** in good yield and with high diastereoselectivity. The proper choice of enolate counterion and solvent were crucial in these systems.[57]

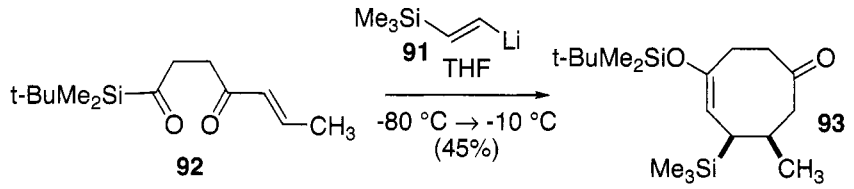




The ethanone bridge in products such as **84** and **86** could be oxidatively cleaved after hydroxylation α to the ketone. Conditions were found for *in situ* α-hydroxylation of the enolate resulting from the Brook-then-Cope sequence. For example, the union of sodium enolate **87** and α,β-

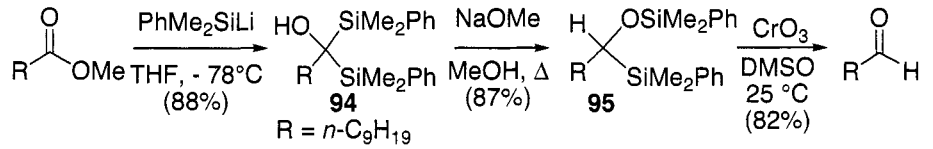
unsaturated acyl silane **88** led to the tandem rearrangement, giving enolate **89**. Direct hydroxylation using Davis's oxaziridine reagent permitted oxidative cleavage of the resulting α-hydroxyketone **90** using lead tetraacetate (not shown). The Brook rearrangement-initiated sequence occurred with high stereoselectivity relative to the pre-existing stereocenter in **87** and was the key step in the formal synthesis of (+)-laurallene, an α,α'-disubstituted oxacene natural product.[58]

Formation of an unbridged eight-membered ring was possible using a Brook-rearrangement-based [6 + 2] annulation strategy. Addition of β-(trimethylsilyl)vinyllithium (**91**) to β-alkenoylsilane **92** provided cyclooctenone **93**. This product formed by initial addition of the vinyllithium to the silane carbonyl, 1,2-Brook rearrangement, and four-membered ring closure. The resulting 1,2-divinyl cyclobutanediolate underwent anion-assisted Cope rearrangement to the final product **93**.[59]



Ester reduction without hydride:

An interesting reductive functional group interconversion employed the Brook rearrangement of the disilyl carbinol formed upon addition of two equivalents of a silyllithium to an ester. For example, **94** underwent Brook rearrangement to silyl ether **95**, and silicon–carbon bond oxidation provided the aldehyde in good overall yield.[60]

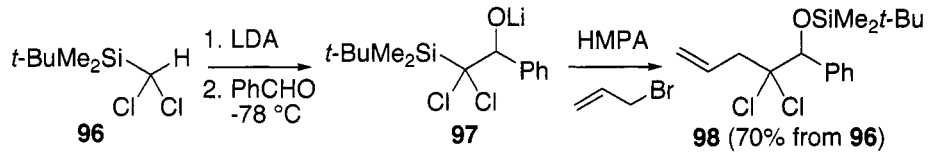


1.3.2.5 Variations and Improvements

Besides 1,2-carbon-to-oxygen migration, longer-range silyl-group transfers have been developed. Examples of these homo-Brook rearrangements are presented below. Transfer of the silyl group in the O → C direction can also occur intramolecularly over a range of tether lengths, and a variety of these retro-Brook rearrangements are also featured.

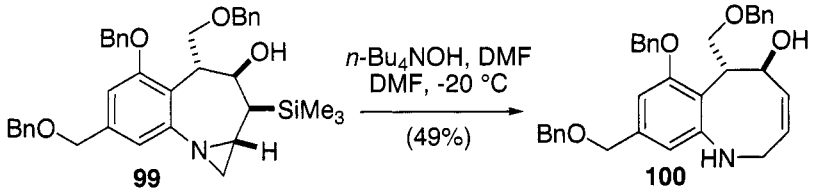
1,3-Rearrangement:

Adjacent alkoxy and silyl groups typically lead to the Peterson olefination, so 1,3-C-to-O silyl-group transfer without alkene formation is relatively uncommon. However, Oshima, Utimoto, and co-workers reported that metalation of dichloromethylsilane **96** and addition to aldehydes provided β-alkoxysilanes (e.g., **97**) that underwent 1,3-rearrangement and alkylation to **98**. Notably, the addition of HMPA promoted the 1,3-Brook rearrangement, presumably by increasing the reactivity of the lithium alkoxide intermediate. As the authors pointed out, this sequence demonstrated **96** as a methylene chloride dianion equivalent.[61]



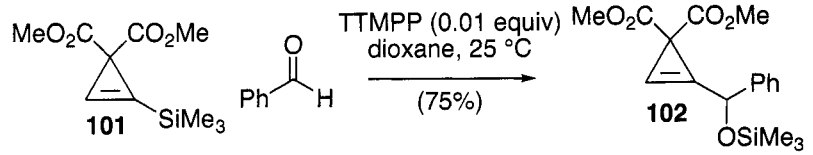
96 **97** **98** (70% from **96**)

Another instance of successful homo-Brook rearrangement occurred in a total synthesis of the antitumor agent FR66979. Here the tendency for Peterson elimination from β-hydroxysilane **99** was overcome by the countervailing aziridine-opening pathway, providing the ring-expanded product **100**.[62a]



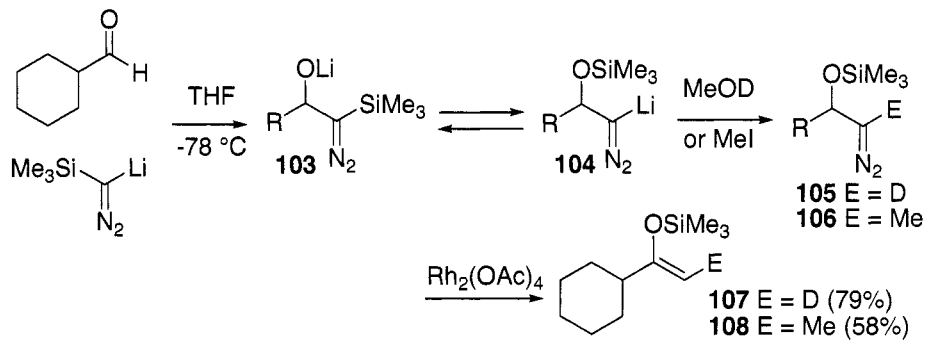
99 **100**

Contra-Peterson elimination also occurred in Morita–Baylis–Hillman-type reactions of 1-silylcyclopropene **101**. Addition of the nucleophilic catalyst tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) at the 2-position of the alkene and condensation of the anion with an aldehyde led to 1,3-Brook rearrangement, with expulsion of the catalyst to regenerate the cyclopropene double bond in product **102**.[62b]



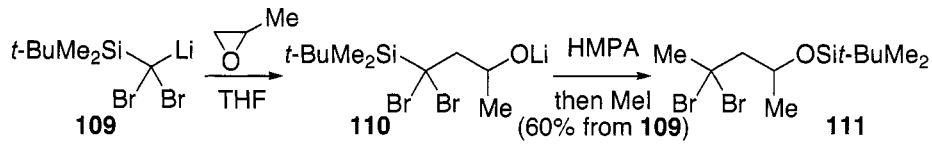
101 **102**

Addition of lithiated trimethylsilyldiazomethane to aldehydes provided adduct **103** which was shown through *in situ* IR measurements and quenching experiments to be in equilibrium with the 1,3-Brook-rearranged carbanion **104**. Addition of methanol or methyl iodide provided **105** and **106**, respectively. Stereocontrolled hydride shift upon formation of the rhodium-stabilized carbenoid provided (*Z*)-selective formation of silyl enol ethers **107** and **108**.[63]

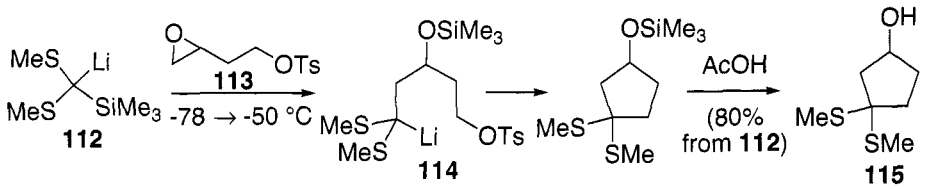


1,4-Rearrangement:

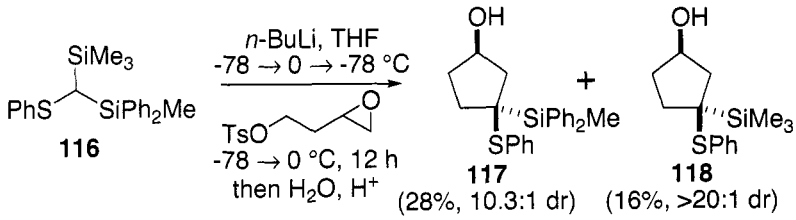
As part of their 1,3-Brook rearrangement study, Oshima and Utimoto also examined addition of silyl dihalomethyllithiums to epoxides, setting up the 1,4-carbon-to-oxygen silyl transfer. For example, γ-alkoxysilane **110** formed upon regioselective ring opening of propene oxide with **109**. The carbanion resulting from the subsequent 1,4 rearrangement was methylated, providing **111**. Again, HMPA was employed to facilitate the carbon-to-oxygen silyl migration. In addition, an experiment comparing 1,3- vs 1,4-rearrangement substrates in the same reaction mixture showed that in these systems the 1,3-rearrangement was faster than the 1,4-rearrangement.[61]



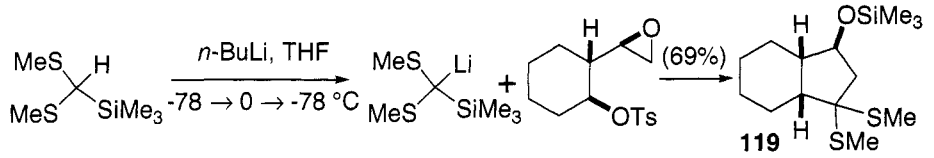
The Brook 1,4-rearrangement is useful in cyclopentanol synthesis. For example, Schaumann and co-workers demonstrated that lithiated α-silyl dithiane **112** was useful for construction of cyclopentanol **115**. Addition to epoxytosylate **113** followed by 1,4-silyl migration provided lithiodithiane **114** for closure of the five-membered ring.[64]



A variation of this strategy used lithiation of bis-silyl thiophenyl methane **116**. After the 1,4-silyl migration and cyclization, hydrolysis of the resulting silyl ethers provided cyclopentanols **117** and **118**. There was a preference for migration of the -$SiMe_3$ group versus the -$SiPh_2Me$ in this case. Generally, ease of silyl group migration is a balance between electronic effects which favor transfer of phenyl-substituted silicon and the steric preference for transfer of the smaller silyl group.[65]

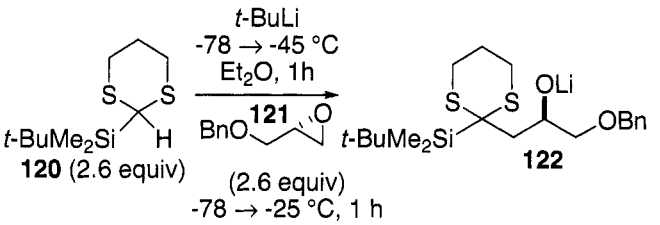


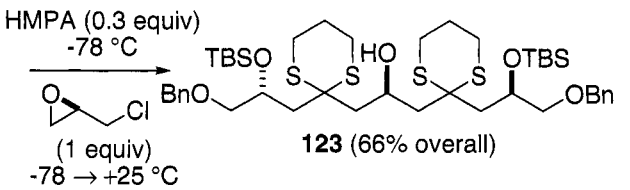
The Schaumann process was also amenable to construction of the cis-fused 5,6-ring system **119** by epoxide opening, 1,4-rearrangement, and stereospecific displacement of the secondary tosylate.[66]



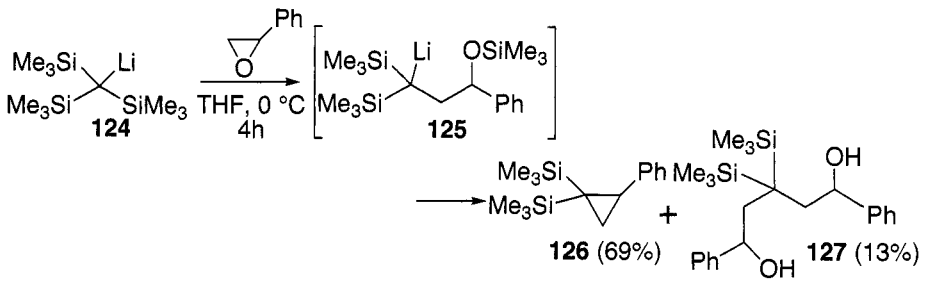
A remarkable set of examples from Amos Smith's laboratory capitalized on the 1,4-Brook rearrangement by using the concept of solvent control. As presaged in the work of Oshima and Utimoto (see **97** and **110** above), in some cases, rearrangement in the Brook (C → O) sense is not favored until addition of a counterion-chelating agent. In Smith's study, this permitted the "linchpin coupling" of epoxide building blocks, where the linchpin derives from silyldithiane **120**. In the example shown below, addition of lithiated **120** to scalemic epoxide **121** produced the γ-alkoxysilane **122**, which resisted 1,4-Brook rearrangement until addition of HMPA. This permitted introduction of the bis electrophile (–)-epichlorohydrin

(approximately half an equivalent relative to **122**), resulting in **123**, comprising five building block components and presenting a rapid synthetic entry to an extended 1,3-polyol motif.[67] Smith has further applied this general strategy for controlled generation of anions to diversity oriented synthesis[68] and in preparation of natural products.[69]



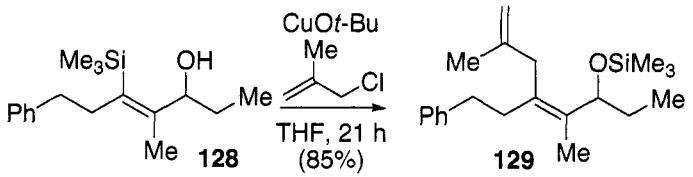


A homo-Peterson process intervened upon 1,4-rearrangement of the alkoxide formed by addition of tris(trimethylsilyl)methyllithium **124** to styrene oxide. The resulting carbanion **125** led mainly to the homo-Peterson product **126**, with some of the adduct **127** from addition to a second equivalent of the epoxide. In their report, Fleming and co-workers noted that the homo-Peterson reaction is probably favored in this case by the benzylic positioning of the silyloxy group in **125**, and they discussed the parallel between the Peterson olefination and a 1,3-Brook rearrangement process.[70]

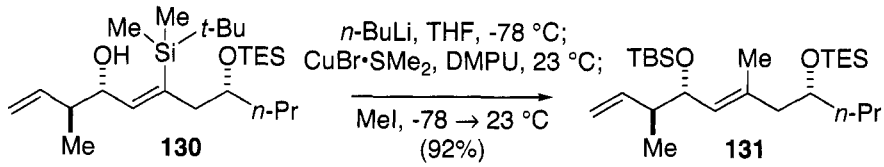


Brook 1,4-rearrangement is feasible starting from vinyl silanes as in (*Z*)-γ-trimethylsilyl allylic alcohol **128**. Takeda found a synthetically useful process using copper *tert*-butoxide in which the 1,4-silyl migration from sp^2-hybridized carbon to oxygen produced a vinylcopper intermediate that could

be coupled with allyl- and alkyl halides. The tetrasubstituted alkene of product **129** was thereby established with complete stereocontrol.[71,72]

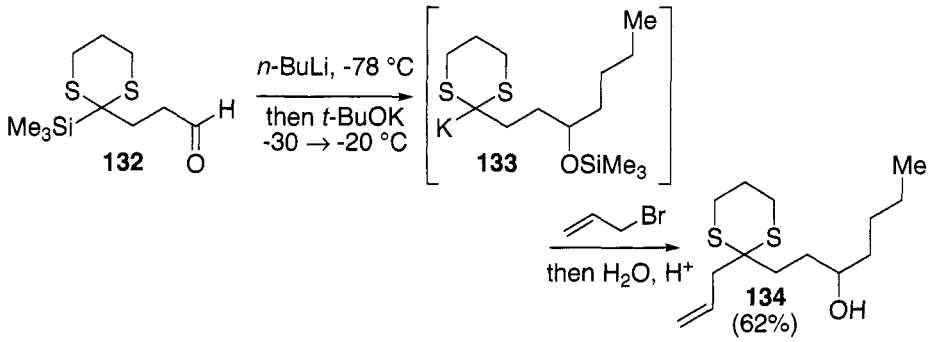


Leighton and co-workers used the 1,4-Brook rearrangement of a vinyl *tert*-butyldimethylsilane **130** in their total synthesis of dolabelide D. Deprotonation of the allylic alcohol at low temperature, followed by the addition of copper(I) and DMPU, enabled the silyl transfer, and methylation of the vinylcopper provided (*E*)-trisubstituted olefin **131** in excellent yield.[73,74]



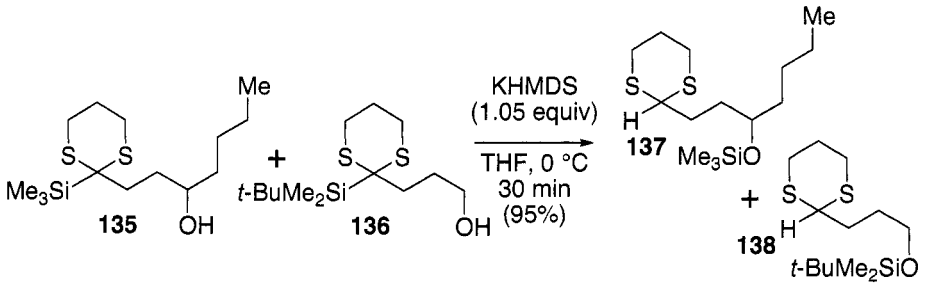
1,5-Rearrangement:

Addition of an alkyllithium to the aldehyde of **132**, followed by cation exchange to the potassium alkoxide, led to 1,5-Brook rearrangement. The resulting potassium dithiane **133** was allylated, providing masked γ-hydroxyketone **134** in good overall yield.[75]



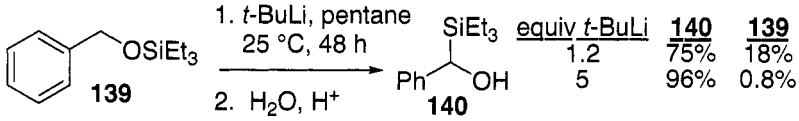
Given the long range of the silyl transfer, the intramolecularity of the process was verified by a crossover experiment with δ-hydroxy-α-silyl

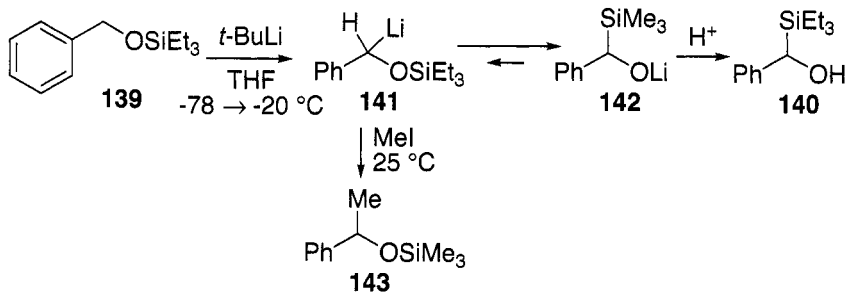
dithianes **135** and **136**. Upon treatment with a potassium amide base, smooth 1,5-rearrangement occurred, providing products **137** and **138** in high yield without any sign of intermolecular crossover.



Retro-1,2-rearrangement:

As discussed earlier in the mechanism section, when Brook-type processes are conducted with excess base, the retro-Brook (O → C silyl migration) is often favored. The first example, reported by West's group, demonstrated the retro-1,2-Brook scenario (now known as the West rearrangement) for benzyloxytriethylsilane (**139**). By using over one equivalent of base, *α*-silylcarbinol **140** was isolated in high conversion after protic quench. The preference for the oxygen-to-carbon rearrangement was magnified with a larger excess of the base. Additionally, West found that with catalytic amounts of *tert*-butyllithium the alcohol **140** underwent Brook rearrangement to the silyl ether.[27]



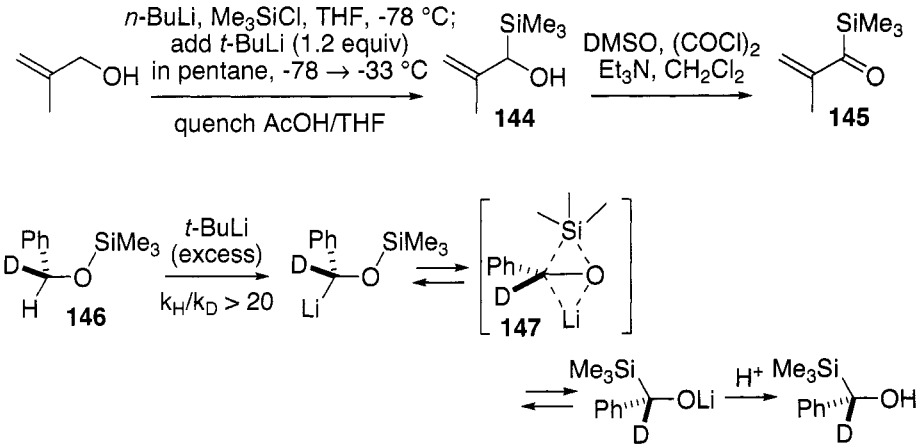


West proposed that under these conditions the relevant equilibrium is between the carbanion and alkoxide (e.g., **141** and **142**). The advantage of

having negative charge localized at oxygen rather than carbon then outweighs the greater strength of the O–Si bond compared to C–Si. West put it succinctly: "...[the retro-Brook rearrangement product] is the preferred product when anions are equilibrated, and [the Brook product] the preferred product when neutral species are equilibrated."[27]

In further studies, West and Wright used a crossover experiment to establish the intramolecularity of the retro-1,2-process and also found that while rapid protic quench traps **142** as the favored side of the anionic equilibrium, alkylation proceeds slowly and occurs preferentially at carbon, shown above for conversion to **143**.[76]

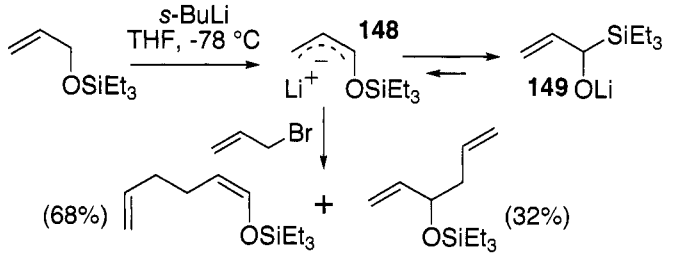
Danheiser used retro-1,2-Brook rearrangement of allyl silyl ethers in a convenient route to α,β-unsaturated acyl silanes. For example, 2-methyl-2-propen-1-ol was converted to the trimethylsilyl ether and, in a single-pot process, deprotonated by addition of 1.2 equiv *tert*-butyllithium. Protonation with a solution of acetic acid in tetrahydrofuran gave the α-hydroxyallylsilane **144**. Removal of volatiles from the thermally sensitive product provided 95-percent-pure material that was oxidized to the α,β-unsaturated acyl silane **145** under Swern conditions.[77]



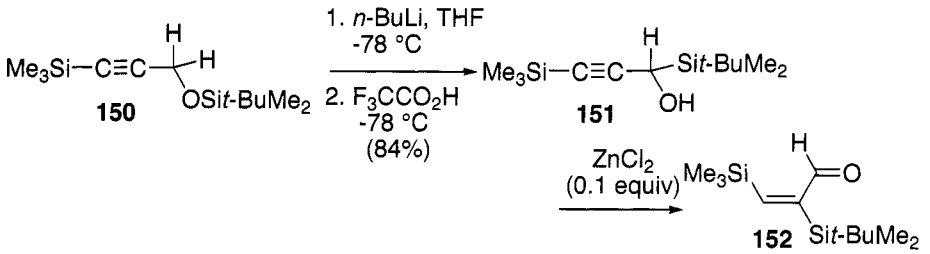
A stereochemical investigation established that West rearrangement of deuteriobenzylsilyl ether **146** occurred with inversion of configuration at carbon. There was a remarkably large kinetic isotope effect in the deprotonation, and the inversion was rationalized by transition structure (or possibly pentacoordinate silicon intermediate) **147**. The proposed transition state is similar to that surmised for the Brook rearrangement (cf. **15**), with the difference that this is a fully anionic variant: the proton transferred from the alcohol oxygen to carbon in the course of the 1,2-Brook process is not present under retro-Brook conditions. The rearrangement was expected to be

nearly concerted with removal of the benzylic proton.[78] While inversion is observed in benzylic systems, retention of configuration was reported in the retro-1,2-Brook rearrangement of α-silyloxyalklyllithiums derived by transmetalation of the corresponding stannanes.[79]

Allyl-stabilized carbanion **148** underwent allylation mainly at the terminal carbon, without interference from the retro-1,2-Brook rearrangement to **149**. However, the existence of an equilibrium that actually favored the retro-Brook direction was demonstrated by low temperature protic quench, which trapped alkoxide **149**.[80] These results were consistent with West's earlier results with alkylation of **141**.



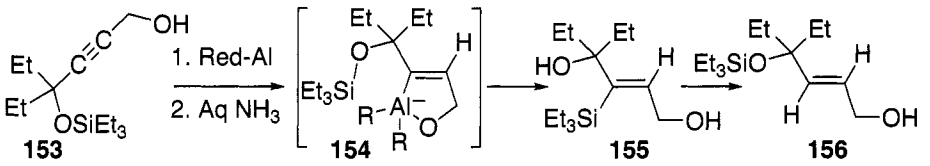
The retro-1,2-Brook rearrangement was used in a stereocontrolled synthesis of bis-silylated enals and enones (e.g., **152**). Deprotonation of propargyl silyl ether **150** led to α-silylcarbinol **151** via the West rearrangement. The product was best isolated upon cold quench with trifluoroacetic acid. The bis *C*-silylated propargyl alcohol **151** was the substrate for a stereoselective Lewis acid-catalyzed conversion to enal **152**.[81]



Retro-1,3-rearrangement:

An aluminum hydride reduction of propargylic alcohol **153** to trans alkene **156** was found to proceed through retro-1,3-Brook rearrangement to vinyl silane diol **155**, followed by 1,3-Brook rearrangement back again. While the final product **156** was isolated directly after longer reaction times, immediate workup following the aqueous ammonia quench revealed the formation of

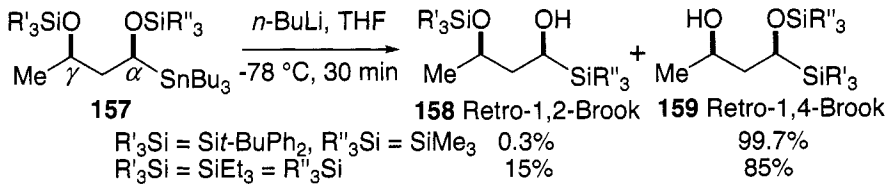
155, which could be rearranged to **156** by treatment with a catalytic amount of Red-Al and aqueous ammonia. Formation of **155** presumably occurred by retro-1,3-Brook rearrangement of vinyl aluminate intermediate **154**. This is an example of retro-Brook migration of the silyl group to an sp^2-hybridized carbon.[82]



153 **154** **155** **156**

Retro-1,4-rearrangement:

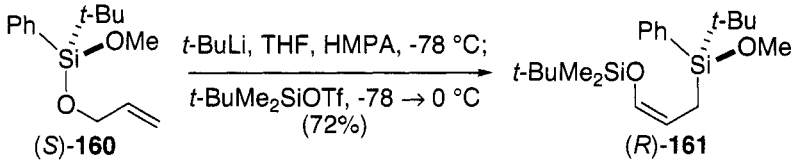
On the grounds that longer-range silyl transfer should be more difficult, it might have been assumed that the rates of retro-1,4-Brook rearrangements would be slower than for the retro-1,2-process. But Mori found that retro-1,4-Brook rearrangement was favored in internal competition experiments with substrates such as *syn*-1,3-disilyloxystannane **157**. In all cases, the retro-1,4-Brook product **159** was preferred. Interestingly, the most selective reaction in the *syn* series involved transfer of the largest silicon group (–Si*t*-BuPh$_2$) from the γ-oxygen. Transmetalation of the stannane to the alkyllithium and the retro-Brook rearrangements occurred with overall retention of configuration at the α position, as reflected in products **158** and **159**.[83]



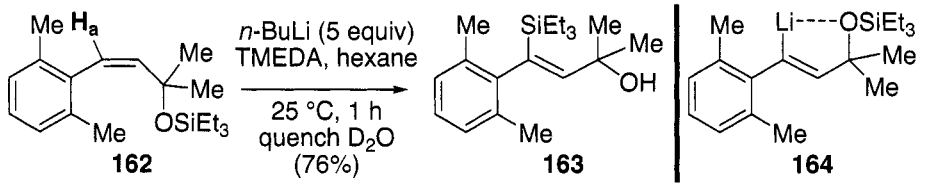
157 **158** Retro-1,2-Brook **159** Retro-1,4-Brook

R'_3Si = Si*t*-BuPh$_2$, R''_3Si = $SiMe_3$	0.3%	99.7%
R'_3Si = $SiEt_3$ = R''_3Si	15%	85%

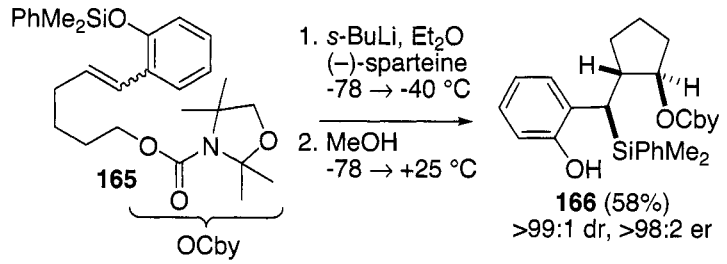
Under carefully optimized conditions, including addition of HMPA to the reaction mixture, deprotonation of allyloxysilanes favored the retro-1,4-Brook rearrangement. The method was applied to systems having an asymmetric center at silicon (e.g., **160**), and it was shown that the rearrangement occurred with retention of configuration at silicon.[84]



The π axes of the alkene and benzene ring in (*Z*)-styrenyl derivative **162** approach orthogonality, aligning the C–H_a σ bond with the empty benzene π^* system. Mori and co-workers found that this stereoelectronic arrangement enabled deprotonation at H_a and that the resulting vinyl anion underwent an oxygen-to-sp^2-carbon retro-1,4-Brook rearrangement, providing **163**. This intramolecular process required isomerization of the initially formed vinyl anion to the chelated structure **164** prior to the silyl shift.[85]

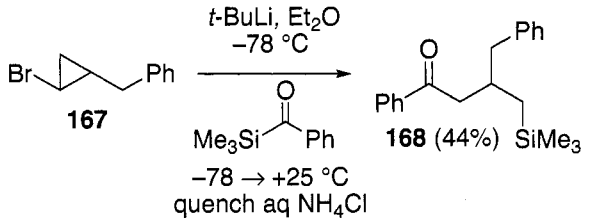


Hoppe's group demonstrated enantioselective deprotonation and alkene carbolithiation of carbamate **165**. The resulting configurationally stable benzyllithium intermediate participated in a retro-1,4-Brook rearrangement, providing phenol **166** with excellent diastereo- and enantiocontrol. Based in part on stereochemical comparison to an analogous *intermolecular* silyl-transfer reaction, Hoppe proposed a mechanism involving retention of configuration at carbon during the retro-1,4-Brook process.[86]

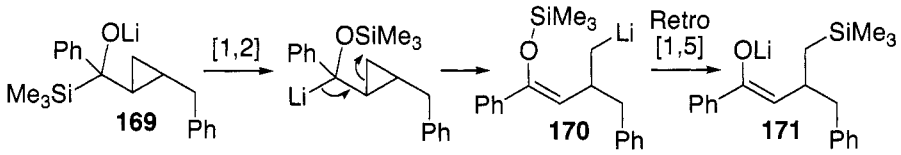


Retro-1,5-rearrangement:

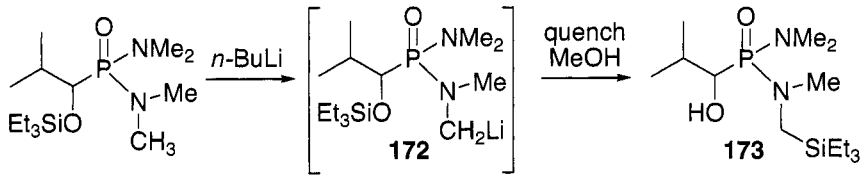
Jonathan Clayden's group at Oxford reported that addition of the cyclopropyllithium derived from bromide **167** to trimethylbenzoylsilane provided γ-silylketone **168** in moderate yield.[87]



This silyl-transfer cascade involved initial cyclopropane-opening-assisted 1,2-Brook rearrangement of lithium alkoxide **169**. The resulting primary alkyllithium **170** underwent retro-1,5-Brook silyl migration to the ketone enolate **171**.

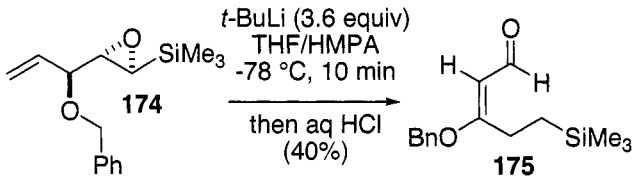


A retro-1,5-Brook rearrangement may have been the source of the unusual silane **173**, formed unexpectedly in the course of Evans's studies on phosphonamide-stabilized carbanions. Metalation at the *N*-methyl position would lead to the rearrangement of **172** across a unique heteroatom-containing tether.[88]

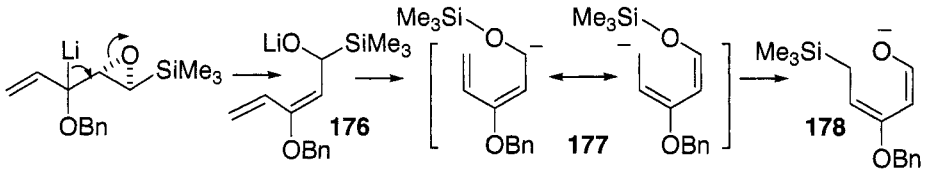


Retro-1,6-rearrangement:

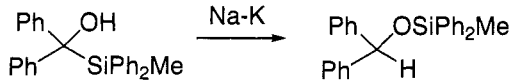
When epoxysilane **174** was treated with an excess of *tert*-butyllithium, enal **175** was isolated as a single double-bond isomer after an acidic workup.[89]



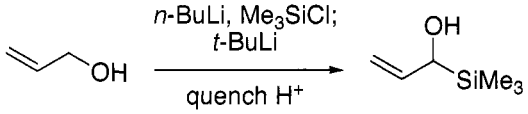
In their study, Jung and co-workers proposed that metalation at the allylic position, followed by epoxide opening led to α-silylalkoxide **176**. A 1,2-Brook rearrangement provided resonance-stabilized dienyl anion **177**, which underwent retro-1,6-Brook rearrangement to enolate **178**. The thermodynamically favored (*E*)-α,β-unsaturated enal **175** was formed during the aqueous workup.



1.3.2.6 *Experimental*



Benzhydryloxymethyldiphenylsilane.[16]
To 1.0 g (0.0026 mole) of methyldiphenylsilyldiphenylcarbinol in 20 mL dry ether was added 4 drops of 1:5 sodium-potassium alloy. The surface of the metal soon became blue but no hydrogen evolution was observed. When the mixture was swirled the blue color momentarily disappeared. After 1 h the mixture was slightly cloudy and yellow. The ether solution was decanted off the alloy into dilute hydrochloric acid and the material was ether extracted and then dried over anhydrous sodium sulfate. The ether solution was evaporated under reduced pressure to yield an oil which completely crystallized when seeded with authentic benzhydryloxymethyldiphenylsilane. This 0.91 g (91%) of material was recrystallized from petroleum ether (b.p. 60–70 °C) to yield 0.86 g (86%) of the ether, m.p. 71–72 °C, identified by mixed melting point with an authentic specimen.



(1-Hydroxy-2-propenyl)trimethylsilane[77]*—via retro-1,2-Brook (West) rearrangement.*

A 1-L three-necked, round-bottomed flask was equipped with two 150-mL pressure-equalizing dropping funnels and an argon inlet adapter. The flask was charged with allyl alcohol (10.00 g, 172.2 mmol) and 220 mL of tetrahydrofuran and then cooled at –78 °C while *n*-butyllithium solution (78.3 mL of a 2.31 M solution in hexane, 180.8 mmol, 1.05 equiv) was added dropwise over 40 min. After 1 h, a solution of chlorotrimethylsilane (19.64 g, 180.8 mmol, 1.05 equiv) in 20 mL tetrahydrofuran was added dropwise over 20 min, and the resulting colorless solution was stirred at –78 °C for 1.25 h and then treated dropwise over 40 min with 129.1 mL of a 1.60 M solution of *tert*-butyllithium in pentane (206.6 mmol, 1.20 equiv). After 2 h, the cold bath was removed, and 50 mL satd aq NH_4Cl was added to the yellow reaction mixture. The resulting solution was stirred for 5 min and then diluted with 50 mL of water and 300 mL of pentane. The organic phase was separated and washed with four 100-mL portions of water and three 50-mL portions of brine, dried over Na_2SO_4, filtered, and concentrated by carefully distilling off the solvents at atmospheric pressure through a 10-cm Vigreux column. The residual pale yellow liquid was transferred to a 50-mL round-bottomed flask, and the remaining volatile impurities were removed by distillation at 15 mmHg through a 4-cm column packed with glass helices, leaving 19.75 g of the product as a pale yellow oil. The purity of this material was determined to be 95% by gas chromatographic analysis (10% OV-101 on 100–120 mesh Chromosorb W, 6 ft × 1/8 in, program: 50 °C for 2 min and then 50–250 °C at 32 °C/min).

1.3.2.7 References

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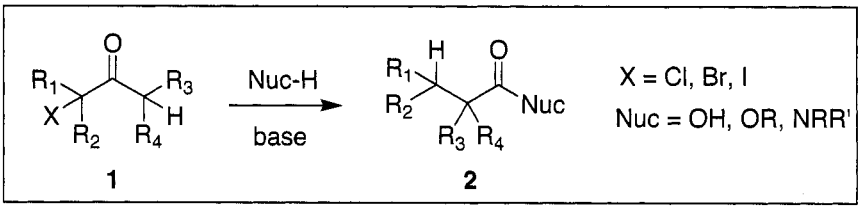
1.3.3 Favorskii Rearrangement

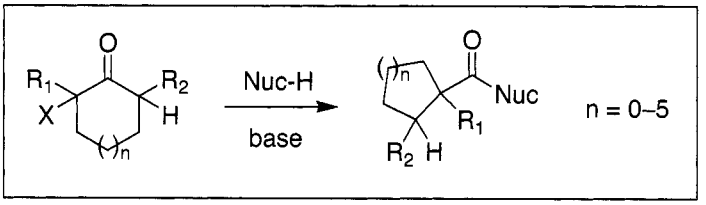
Kevin J. Filipski and Jeffrey A. Pfefferkorn

1.3.3.1 Description

The Favorskii rearrangement is a base-mediated carbon skeletal rearrangement that occurs when a nucleophile adds to an α′-halo ketone possessing an α-hydrogen. This transformation converts an α-halo ketone **1** to a carboxylic acid derivative **2**. There is also an intramolecular variant of this transformation in which the resulting ring size contracts by one-carbon atom.



The Intramolecular Favorskii Rearrangement:



The halogen (X) can either be chloro, bromo, or iodo while the nucleophile (Nuc-H) can be water, alcohol, or amine resulting in the formation of a carboxylic acid, ester, or amide, respectively.[1] The choice of base and solvent plays a key role in the success of the reaction.[2] This rearrangement finds utility in the synthesis of branched carboxylic acids and their derivatives,[3,4] in particular, molecules possessing a tertiary carbon next to the carboxyl group are readily accessible.[5] Also, *cis*-α,β-unsaturated acids can be prepared using either α,α- or α,α′-dihaloketones. Trihaloketones can be converted to mono-halo-α,β-unsaturated acids as well.[4]

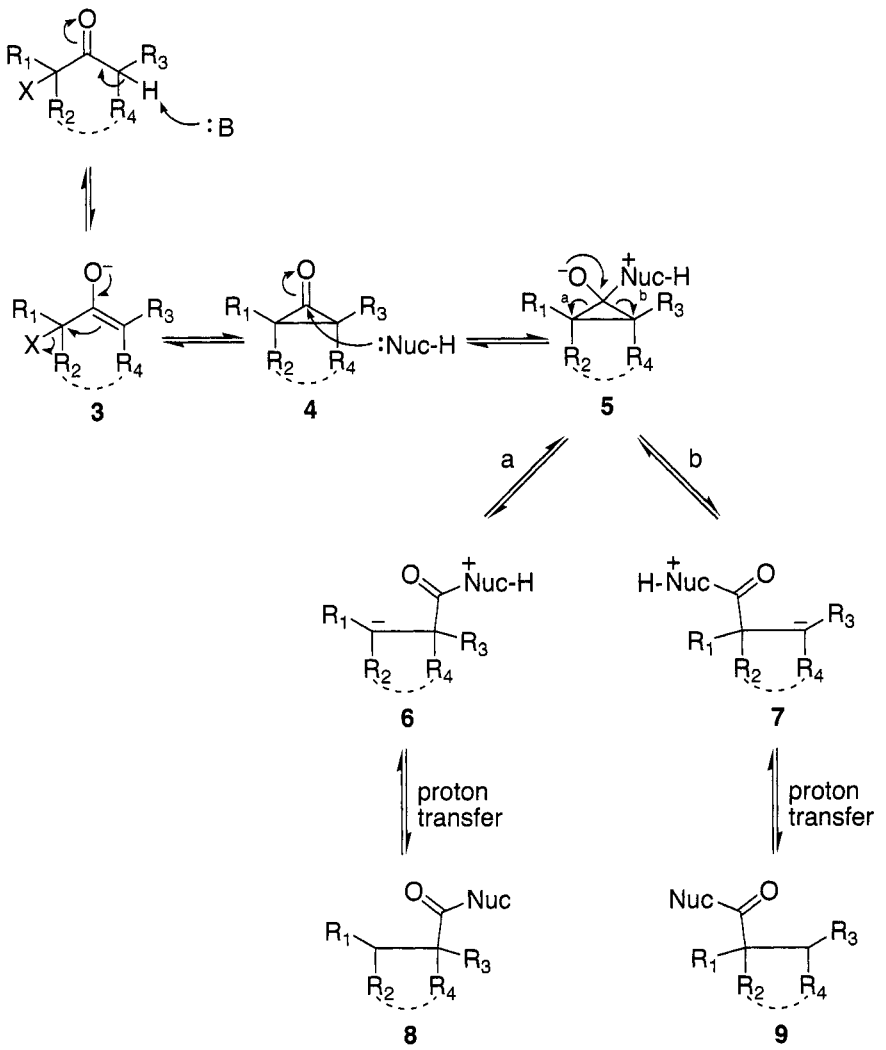
1.3.3.2 Historical Perspective

In 1894, Alexie Favorskii published an early account of the rearrangement of simple acyclic α-halo ketones.[6] This was followed in subsequent years with additional reports.[7] In 1914, he published the cyclic version featuring the ring contraction of 2-chlorocyclohexanone.[8,9] This modification makes this transformation a reliable way to synthesize 1-substituted cycloalkane carboxylic acid derivatives. Later in the century, the rearrangement found application in the modification of steroids.[4] Only in the last half of the 20th century has a clearer picture of the mechanism appeared.[5]

The first report of what would later be called the homo-Favorskii rearrangement appeared by Auwers and Hessenland in 1908, although with misassigned products.[10] Significant work around the mechanism of this version was done in several labs in the 1960's and 1970's including Wenkert and coworkers, who revised the early misassignment.[11] The quasi-Favorskii rearrangement has been known since at least the 1939 publication by Tchoubar and Sackur on the synthesis of 1-phenylcyclohexanecarboxylic acid,[12] who also first suggested its currently accepted semi-benzylic mechanism.[2] Further mechanistic work was done in the 1960s and 1970s. The photo-Favorskii rearrangement involves a similar carbon skeletal rearrangement but occurs via a partial radical mechanism and has only in recent decades been explored.

1.3.3.3 Mechanism

Various mechanisms have been proposed for this rearrangement.[2,4,5] The currently accepted mechanism begins with a base-mediated deprotonation adjacent to the carbonyl to form an enolate **3**. Intramolecular enolate attack on the α′-carbon bearing the leaving group, X, results in the formation of cyclopropanone **4**. The formation of this intermediate was evidenced through carbon labelling work done by Loftfield in 1950.[13] The nucleophile then attacks the carbonyl to form the quaternary alkoxide **5**. Subsequently, this intermediate regioselectively opens to generate the thermodynamically more stable carbanion (**6** or **7**). Lastly, proton transfer to form product **8** or **9** completes the sequence. In certain cases, such as cyclobutanones (i.e., R_2–R_4 is CH_2),[2] steric factors prevent this cyclopropanone mechanism and instead a semi-benzylic mechanism proceeds.[3,5]

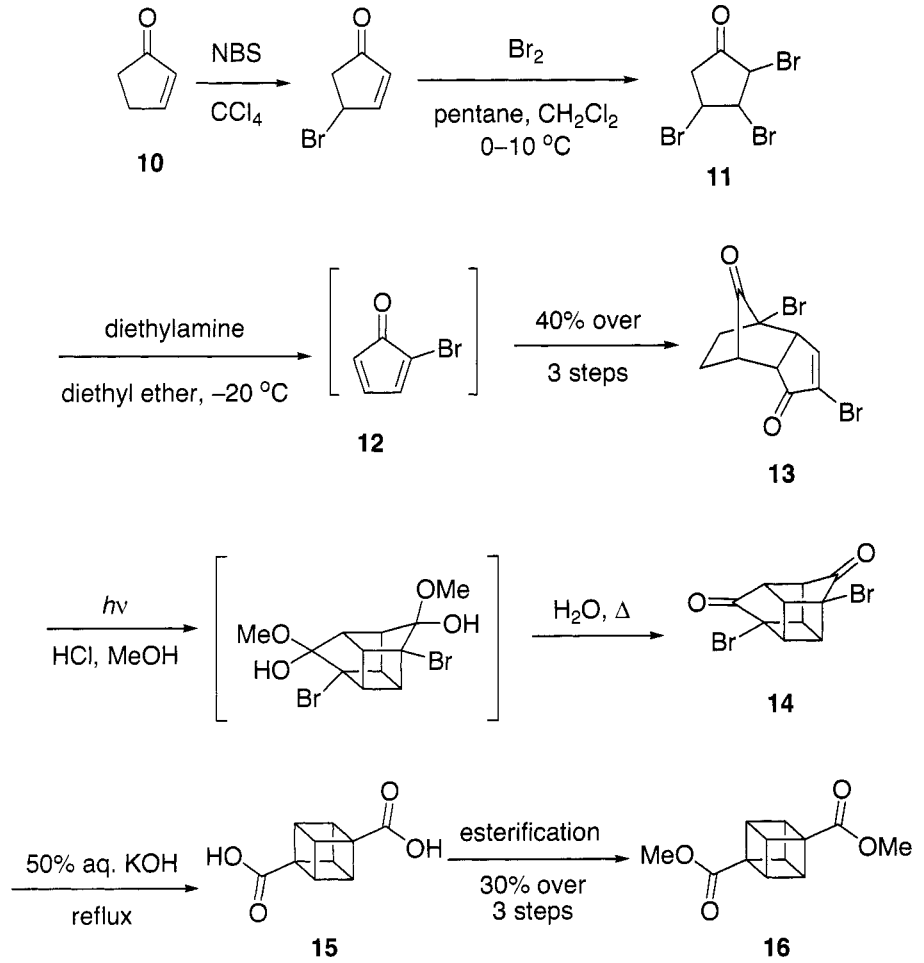


1.3.3.4 Synthetic Utility

Highly Branched Carboxylic Acids

An elegant example of the use of the Favorskii rearrangement was in the first deliberate synthesis of the cubane carbon skeleton in 1964 by Eaton and Cole.[14] Their sequence begins with 2-cyclopentenone **10**, which is first mono-brominated with NBS and then di-brominated using Br_2 to give **11**. Double dehydrobromination is achieved using diethylamine to form transient species **12**, which immediately self-dimerizes via a Diels–Alder reaction to form **13**. Subsequent ultraviolet light irradiation in the presence of HCl

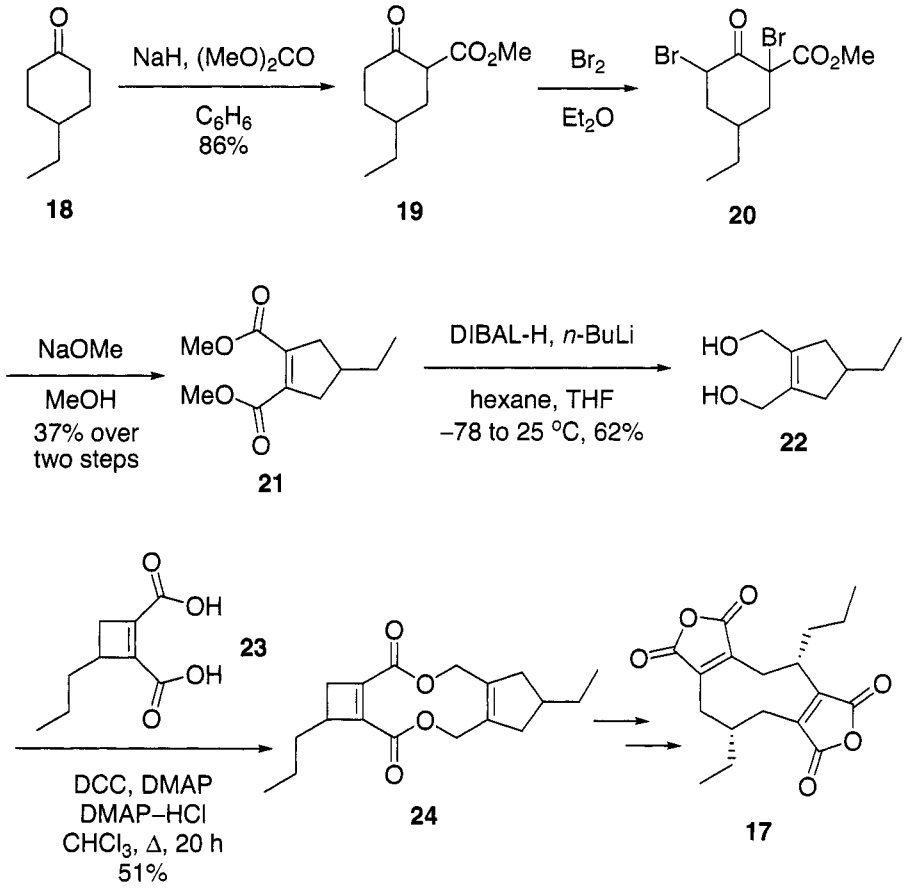
forms the bishemiketal of **13**, which upon heating in water deketalizes to form the Favorskii precursor **14**. The Favorskii rearrangement itself is carried out with aqueous KOH over several hours to form the cubane **15**, which was then converted to the bis-methyl ester **16** for characterization purposes.



Natural Product Synthesis

White and coworkers used a Favorskii rearrangement in their synthesis of the natural product (±)-byssochlamic acid **17**.[15] 4-Ethylcyclohexanone **18** synthesized by Jones oxidation of the corresponding alcohol, was carboxylated to **19** and then dibrominated to **20**. The Favorskii rearrangement was carried out with NaOMe to form the unsaturated diester

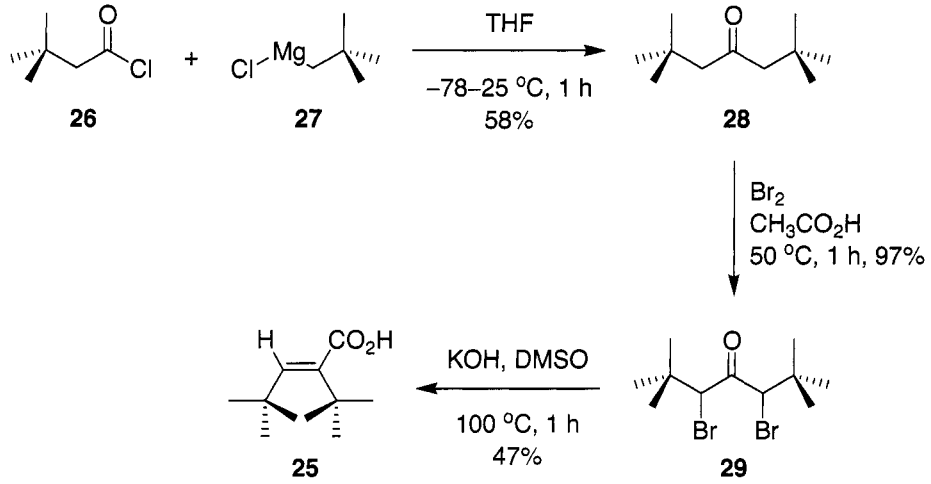
21 followed by reduction to the diol **22**. Diacid **23** was separately synthesized in four steps in 45% overall yield (not shown). A mixture of **22** and **23** was treated under Steglich–Keck conditions to produce diolide **24**. Four additional steps with 23% total yield were necessary to carry intermediate **24** onto (±)-byssochlamic acid **17**.



Formation of Unsaturated Carboxylic Acids

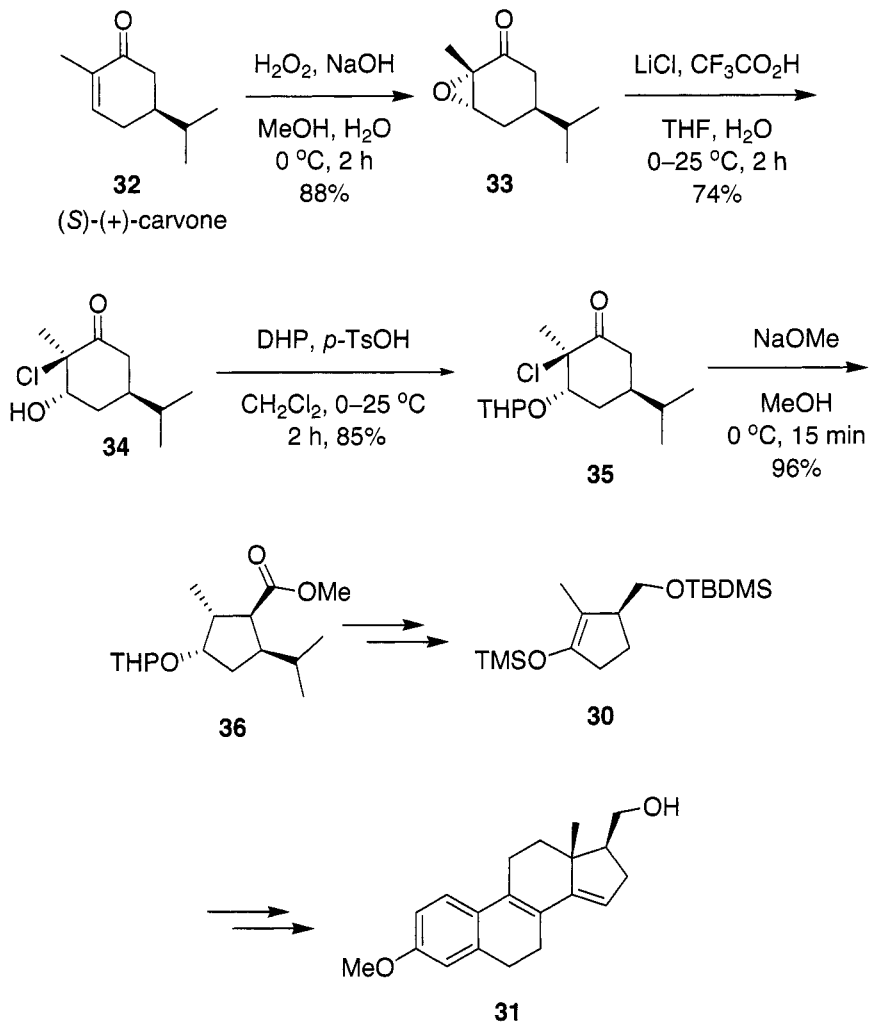
In 2008, Ionkin and coworkers[16] published the synthesis of a highly sterically hindered olefin **25** using the Favorskii rearrangement of an α,α′-dihaloketone, a reaction class initially disclosed by Favorskii in 1913.[17] A Grignard reaction between *tert*-butylacetic acid chloride **26** and neopentylmagnesium chloride **27** produced dineopentyl ketone **28**. This was then dibrominated using bromine in acetic acid to yield the α,α′-dibromoketone **29**. The Favorskii rearrangement was then carried out using

the superbase KOH with DMSO to give exclusively the E-isomer of the α,β-unsaturated carboxylic acid **25**. The Favorskii rearrangement selectively produces this geometric isomer owing to attack of the hydroxyl anion from the face opposite as the *t*-butyl groups of the cyclopropanone intermediate.



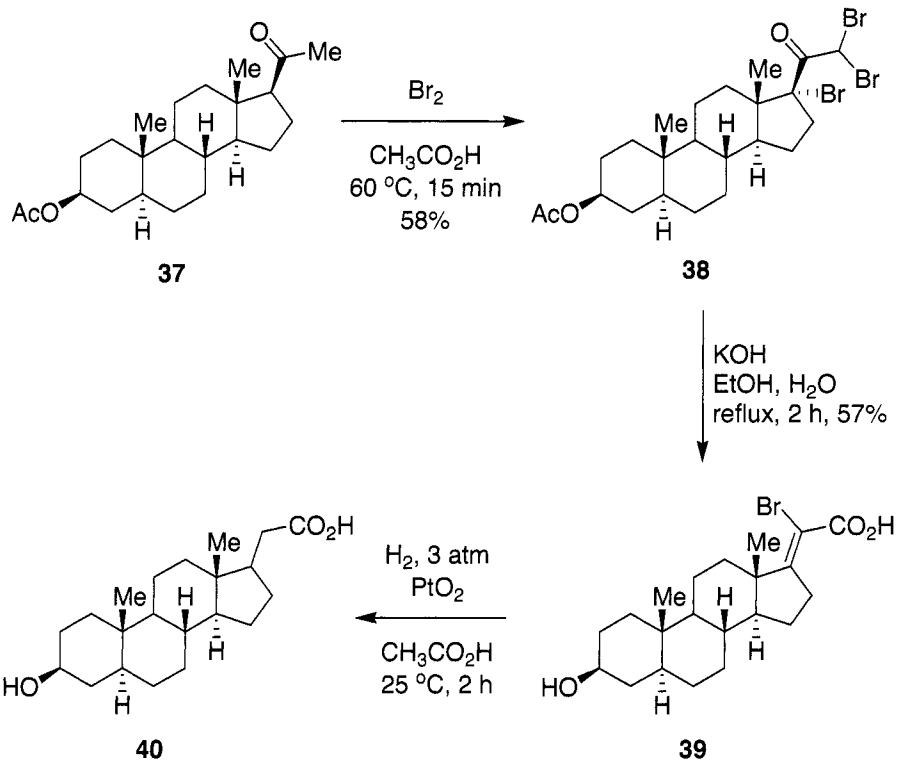
Steroids

The Favorskii rearrangement has also found significant utility in the field of steroid chemistry. As part of a synthesis of steroid **31**, Progrebnoi and coworkers required access to silyl enol ether **30**.[18] They chose to start their sequence with (*S*)-(+)-carvone **32**. This was first epoxidated to **33** and the resulting epoxide was then opened using LiCl and trifluoroacetic acid to give **34** in good yield. The hydroxyl was protected as the tetrahydropyran ether to give **35**. A Favorskii rearrangement on this cyclohexanone to yield cyclopentyl ester **36** proceeded in 96% yield. This tetrasubstituted cyclopentane was converted to **30** in three steps and ultimately **31** after two additional transformations. Interestingly, the Favorskii rearrangement was also attempted on **33**, utilizing the epoxide as the leaving group; however, nucleophilic attack at the epoxide itself was a significant side product rendering this approach not synthetically viable. Protection of the alcohol as diastereomeric THP ethers was necessary for complete stereo- and regioselectivity during the rearrangement.



Rearrangement of Trihaloketones

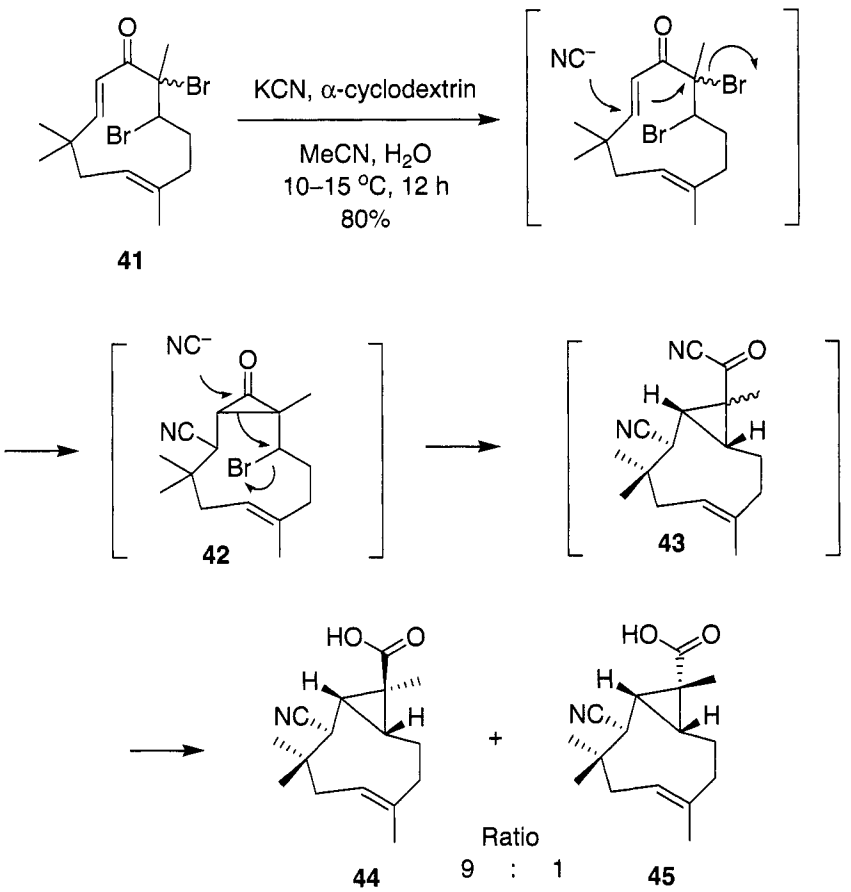
Wagner and Moore successfully performed a Favorskii rearrangement on a tribromoketone to yield an α-bromo-α,β-unsaturated acid in their exploration of steroid chemistry.[17] They began the sequence with acetyl-protected methyl ketone **37** and tri-brominated using bromine in acetic acid to yield **38**. The Favorskii rearrangement was carried out in 57% yield using refluxing aqueous KOH in ethanol to give the α-bromo-α,β-unsaturated carboxylic acid **39**. This product was ultimately converted to **40** by using a platinum-catalyzed hydrogenation and dehalogenation.



37 38 39 40

Sequential Cyclopropane Formation

Kitayama has reported on an interesting sequential Favorskii rearrangement involving the successive formation of two cyclopropane rings.[19] The bromination of zerumbone to **41** (not shown) provides the substrate for the rearrangement. Conjugate addition of cyanide followed by intramolecular nucleophilic attack provides intermediate **42** with the classic Favorskii cyclopropanone configuration. A second equivalent of cyanide then attacks the carbonyl causing the anion to displace the β′-bromide. In the process one cyclopropane ring is exchanged for a different cyclopropane ring. The resulting acyl cyanide **43** is then rapidly hydrolyzed to the corresponding carboxylic acid. This forms products **44** and **45** in a 9:1 ratio of diastereomers.



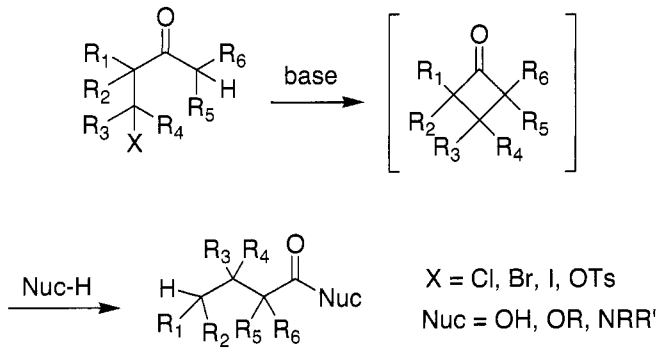
1.3.3.5 Variations

There are three significant variations on the Favorskii rearrangement, the homo-, quasi-, and photo-Favorskii rearrangements. The homo-Favorskii and quasi-Favorskii rearrangements occur if the precursor does not possess the classic α-hydrogen and α'-halide. The photo-Favorskii is a variation involving a light-induced radical mechanism.

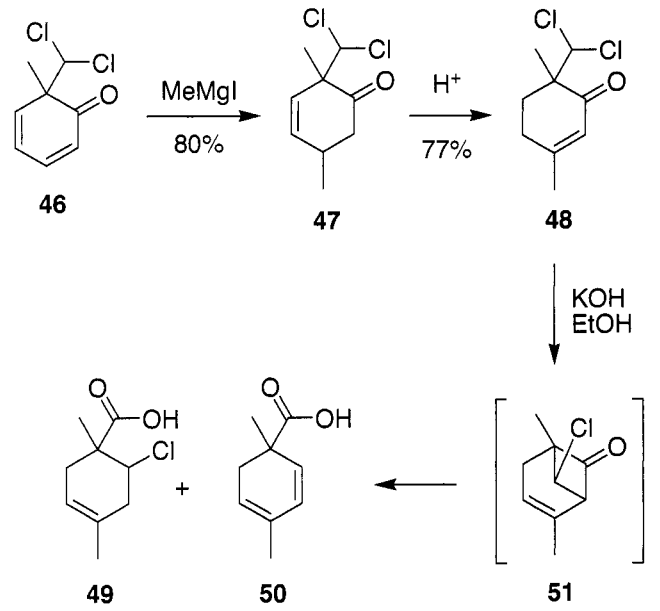
Homo-Favorskii Rearrangement

If the halide is on the β'-carbon instead of the α'-carbon, then a rearrangement occurs through a cyclobutanone intermediate. This transformation is referred to as the homo-Favorskii rearrangement.[1] Treatment of most β'-haloketones with base would produce α',β'-unsaturated ketones, so in order for the homo-Favorskii rearrangement to take place the

substrate must be devoid of α′-hydrogens or sterics must make this more common transformation unfavorable.[11]

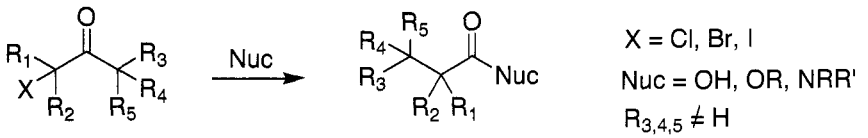


Wenkert and coworkers published the homo-Favorskii rearrangement shown below.[11] Dienone **46** was subjected to Grignard conditions to give the methylated product **47**. Acid-catalyzed isomerisation to α,β-unsaturated ketone **48**, followed by homo-Favorskii rearrangement under ethanolic KOH conditions yielded a mixture of chloroolefinic acid **49** and dienoic acid **50** via the cyclobutanone intermediate **51**.

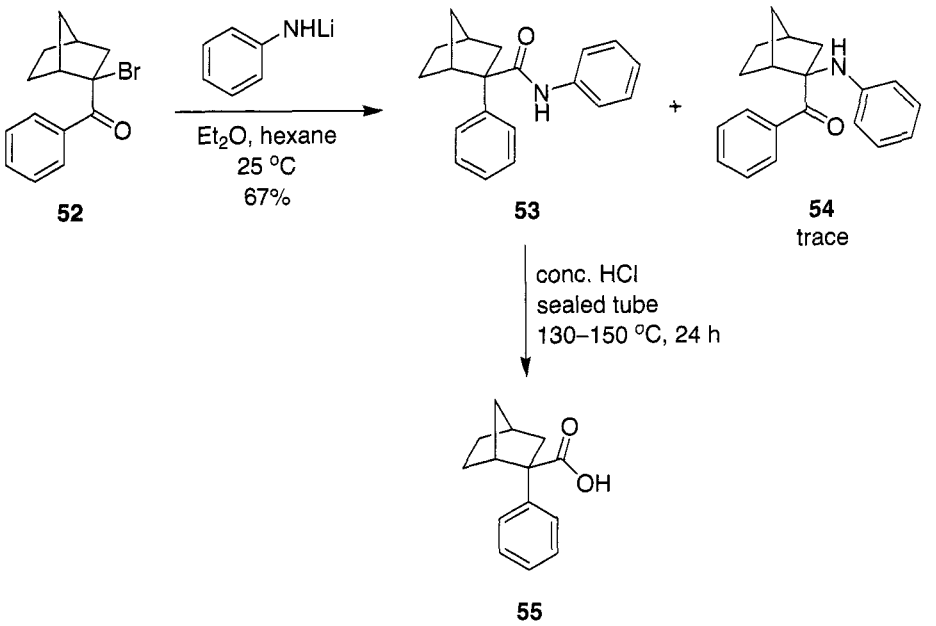


Quasi-Favorskii Rearrangement

If there are no enolizable hydrogens present, the classical Favorskii rearrangement is not possible. Instead, a semi-benzylic mechanism can lead to a rearrangement referred to as quasi-Favorskii.[1–3,20]



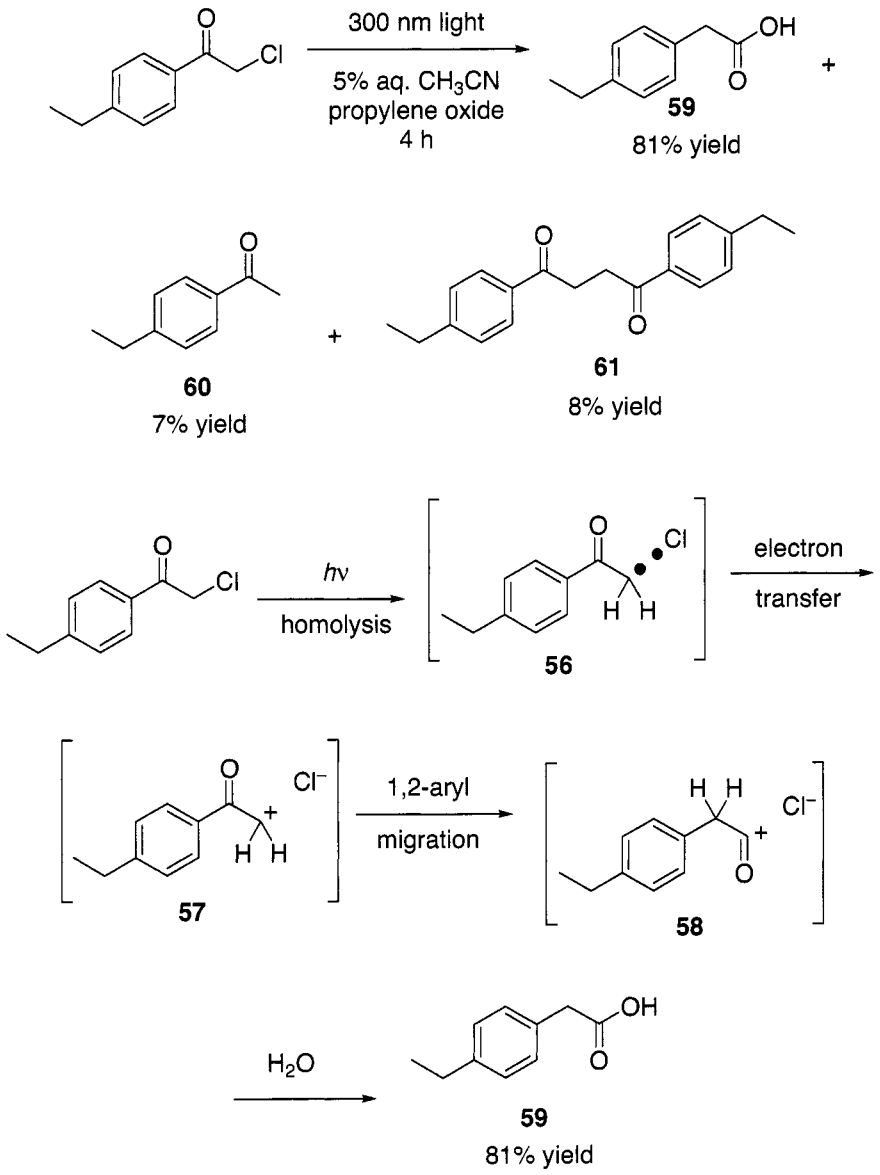
In this mechanism, a nucleophile adds to the carbonyl in the first step. The α-carbon than migrates to the α′-carbon, which expels the leaving group. This transformation is regioselective if only one of the α-carbons contains a leaving group.



Stevens and coworkers reported on the quasi-Favorskii rearrangement of a norborane derivative.[20] The *exo*-2-bromo-*endo*-2-benzoyl norborane **52** undergoes a rearrangement with lithium anilide as the nucleophile to form **53**. The concerted semi-benzylic mechanism of this reaction produces only one of the possible isomeric products. A trace amount of the bromo-displaced product **54** was also observed. The rearranged product was

hydrolyzed to known carboxylic acid **55** to confirm the structure of the rearrangement.

Photo-Favorskii Rearrangement

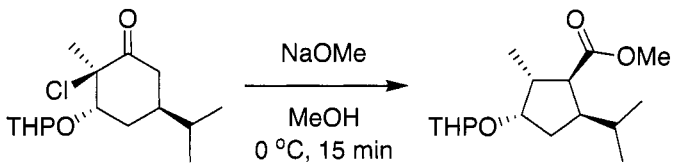


The photo-Favorskii rearrangement involves a similar carbon skeletal rearrangement but occurs via a partial radical mechanism. Dhavale and coworkers explored the synthesis of phenylacetic acids via photo-Favorskii rearrangement.[21] The initial step is carbon–halogen bond homolysis initiated by UV light to form radical **56**. Subsequent electron transfer between the radical pair leads to an ionic intermediate **57**, which undergoes a 1,2-aryl shift to generate carbocation **58**. Quenching with water yields phenylacetic acid **59** in 81% yield. Also formed in this reaction are minor amounts are **60**, produced by hydrogen abstraction, and **61**, resulting from radical-radical coupling.

1.3.3.6 Experimental

Classic Favorskii Rearrangement to an Ester

(1*S*,2*R*,3*S*,5*R*)-methyl 5-isopropyl-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)cyclopentanecarboxylate (36)[18]



35 **36**

To 20 mL of an ice-cooled solution of NaOMe (1.2M) in methanol, 4.7 g of **35** in 10 mL of dry methanol was added drop wise over a period of 10 min. During the addition, a precipitate started to form and it appeared necessary to keep the temperature of the reaction below 15 °C. The reaction mixture was stirred for a further 15 min before water (300 mL) was added. The mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 4.43 g of crude product **36** as a slightly yellow oil as a mixture of two diastereomers (96% yield). The crude product was used without any further purification in the next step.

1.3.3.7 References

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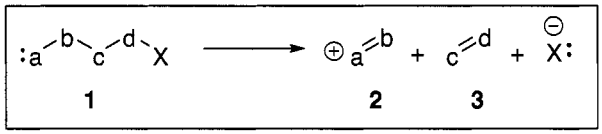
1.3.4 The Grob Fragmentation

Kevin M. Shea

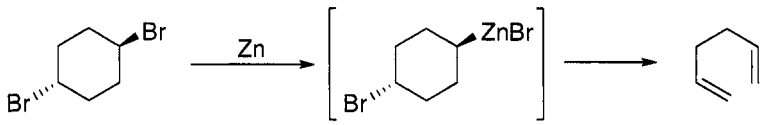
1.3.4.1 Description

The Grob fragmentation involves the heterolytic cleavage of a 1,3-difunctionalized system (**1**) to yield two unsaturated fragments (**2** and **3**) and a leaving group. The starting material must contain an electrofuge (a) and a nucleofuge (X), and a variety of functional groups can play these roles. Oxygen- and nitrogen-containing groups are the most common electrofuges, while the nucleofuge can be any stable leaving group including halide-, sulfonate-, and carboxylate anions, amines, water, and dinitrogen. Anionic electrofuges (a) yield neutral fragments **2**, and cationic nucleofuges (X) provide neutral leaving groups. The connecting atoms (b–c–d) are typically single-bonded carbons, but can also include alkenes, oxygen, and nitrogen. Fragmentations are most useful for rigid cyclic systems; acyclic compounds often yield unwanted byproducts as a result of competing substitution, elimination, and ring closure reactions. Concerted heterolytic cleavage in cyclic compounds is highly stereoselective and, thus, finds many uses in synthesis.[1]

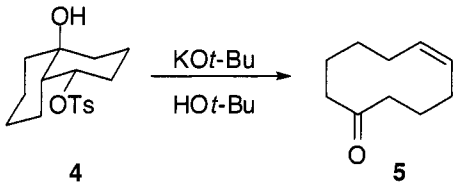


1.3.4.2 Historical Perspective

Cyril A. Grob (1917–2003) was a professor at the University of Basel, Switzerland from 1951–1987, and his studies into heterolytic cleavage reactions began early in his academic career.[2] He first reported the reaction that would ultimately bear his name in 1955.[3] This report details fragmentation of a variety of substrates including the cleavage of *trans*-1,4-dibromocyclohexane in the presence of zinc to yield 1,5-hexadiene.



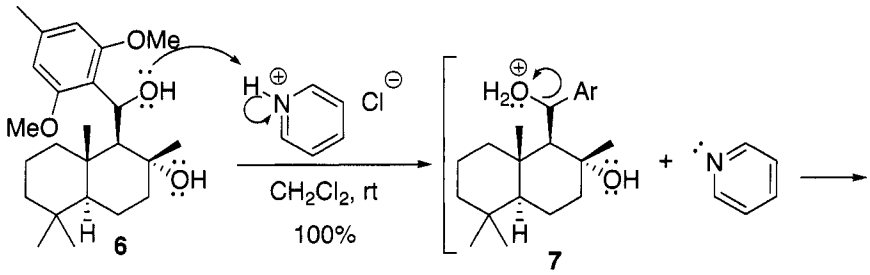
Interestingly, Eschenmoser was the first to report this type of heterolytic cleavage reaction;[4] however, Grob's exhaustive studies into the scope, limitations, and mechanism of this fragmentation process led to his association with these reactions.[5] Another key player in this field was Wharton who focused his research on one specific type of Grob fragmentation. Wharton studied reactions of cyclic 1,3-diol derivatives; hence transformations of these substrates are often referred to as Wharton fragmentations.[1c,6] For example, combining decalin derivative **4** with potassium *t*-butoxide yields 10-membered ring enone **5** via a fragmentation reaction.[7]



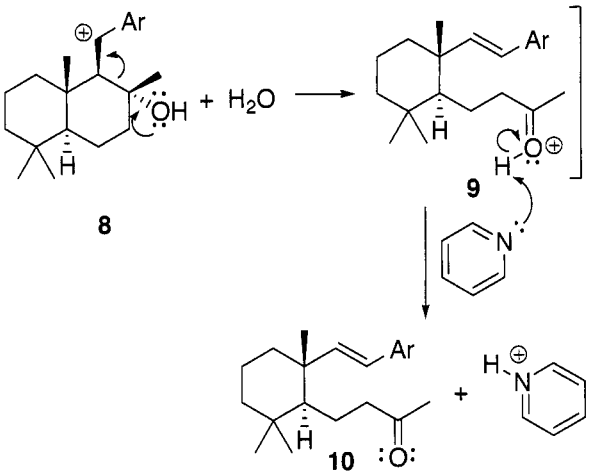
4 **5**

1.3.4.3 Mechanism

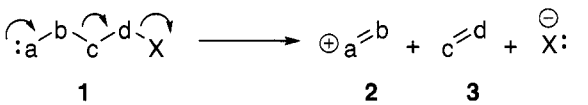
There are three potential options for the mechanism of Grob fragmentation reactions, one concerted and two stepwise. The stepwise reactions, which result from initial loss of either the nucleofuge or electrofuge, are less useful in synthesis since they often promote side reactions.[1] However, one highly efficient stepwise transformation was reported by Kato. Treatment of diol **6** with pyridinium chloride results in formation of benzyl carbocation **8**. Cleavage of this alcohol yields monocycle **9** and, ultimately, the ketone product **10**.[8]



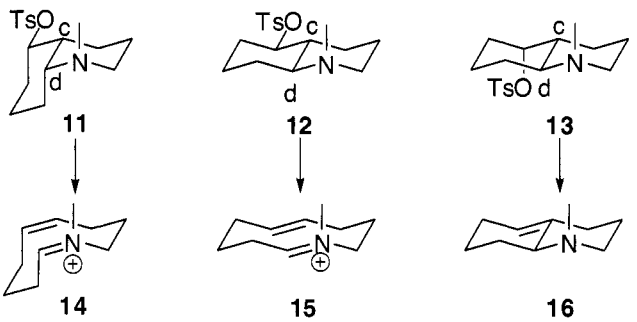
6 **7**



The key stereochemical requirement for a concerted fragmentation is an *anti* orientation between the leaving group and the b-c bond in **1**. This enables constructive orbital overlap in the transition state between the forming and breaking bonds. The orientation of the a-b bond has no effect on the outcome of the reaction.[1]



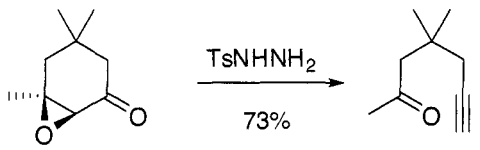
Grob clearly demonstrated these mechanistic details in a variety of systems including reactions of the *N*-methyldecalin derivatives shown below.[5b] In tosylates **11** and **12**, the C-OTs and Cc-Cd bonds are oriented *anti*, thus these molecules efficiently fragment to monocycles **14** and **15**, respectively.[9]



Further demonstration of the stereoselectivity of the reaction is that *cis* decalin **11** leads to a *cis* alkene in **14**, while *trans*-decalin **12** generates a *trans* alkene in **15**. Compound **13** is unable to undergo fragmentation since the C-OTs and Cc-Cd bonds are oriented *gauche*. Instead, this molecule reacts either by substitution or elimination (to yield **16**).[9]

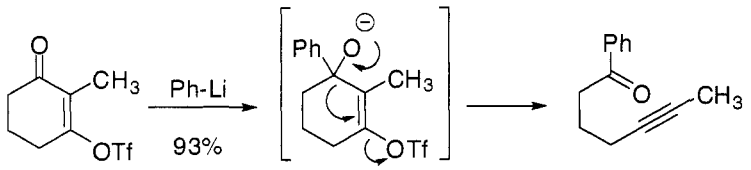
1.3.4.4 Variations and Improvements

Most contemporary Grob fragmentations are strikingly similar to the reactions that Grob investigated fifty years ago. The most common variation is known as the Eschenmoser–Tanabe fragmentation which begins with an epoxy ketone and ultimately yields a fragmented alkynone.[1a,b] Eschenmoser and Tanabe independently reported this reaction in 1967.[10,11] One example from Eschenmoser's lab involves treatment of epoxy ketone **17** with tosylhydrazine to furnish ynone **18**.[12]



17 **18**

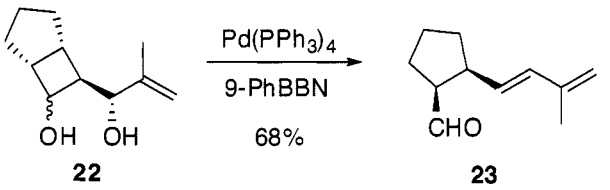
A recent variant of the Grob fragmentation that is related to the Eschenmoser–Tanabe fragmentation was reported by Dudley. In Dudley's fragmentation, reaction of a vinylogous acyl triflate with a variety of nucleophiles yields alkynyl ketones, amides, or alcohols. For example, vinyl triflate **19** combines with phenyllithium to provide tetrahedral intermediate **20** which quickly collapses to furnish ynone **21**.[13] In an interesting extension of this methodology, Dudley reported earlier this year that fragmentation of dihydropyrones yields homopropargyl alcohols.[14]



19 **20** **21**

Another variation involves metal-catalyzed Grob fragmentations. Tamaru reported nickel and palladium catalysts for the fragmentation of 1,3-diols and 1,3-diol derivatives.[15] Early research by the Tamaru group

demonstrated that $Pd(PPh_3)_4$[16] and $Ni(cod)_2$[17] promote fragmentation of six-membered ring cyclic carbonates. Recently, they have expended this methodology to the cleavage of 1,3-diols using a $Pd(PPh_3)_4$ and 9-PhBBN catalyst system (e.g., **22**→**23**).[18]

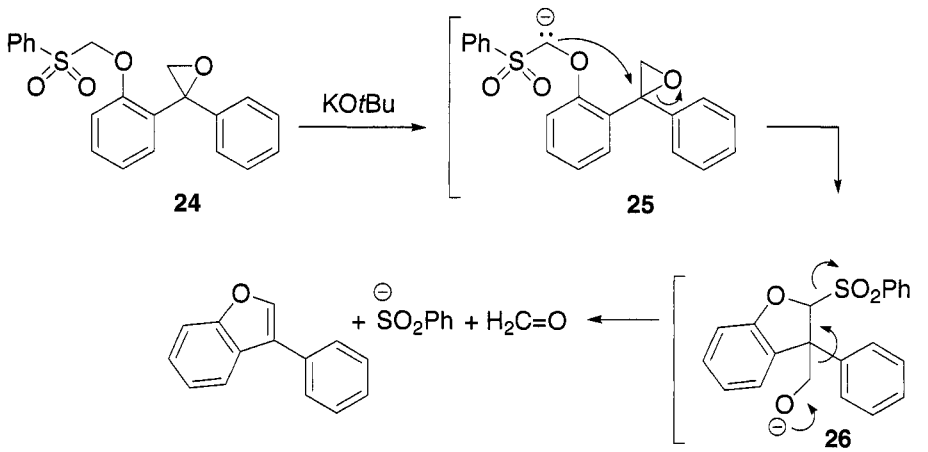


22 **23**

1.3.4.5 Synthetic Utility

The Grob fragmentation has seen extensive use in synthesis since its discovery more than fifty years ago.[1] The most popular applications involve fragmentation of a polycyclic system to furnish a functionalized product containing one fewer ring. Commonly, reactions in which bicyclic rings are fragmented reveal newly functionalized rings with six to ten members; this is an excellent strategy for the construction of challenging medium sized rings. The Grob fragmentation has also found use in systems that cleave acyclic or monocyclic portions of molecules.

Fragmentations that Yield Three Products

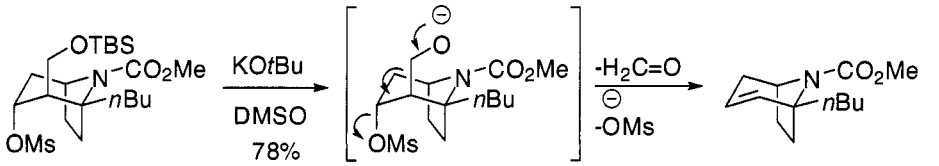


24 **25** **26**

Unlike most Grob fragmentations, reactions in which the nucleofuge and electrofuge are not tethered yield three product molecules. Several groups have exploited this strategy in synthesis. Nicolaou designed a novel

cyclofragmentation-release pathway as part of a solid-phase synthesis of 3-arylbenzofurans. In an example of the analogous solution phase reaction, deprotonation of sulfone **24** generates carbanion **25** which attacks the epoxide to yield alkoxide **26**. Grob fragmentation of this compound furnishes 3-phenylbenzofuran along with formaldehyde and phenylsulfinate anion.[19]

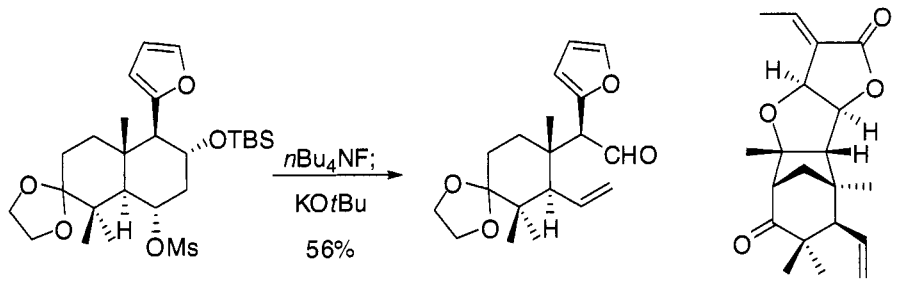
Thomas investigated the chemistry of 8-azabicyclo[1.2.1]octanes, the core structure of the tropane alkaloids, and unexpectedly observed a Grob fragmentation instead of the predicted elimination reaction. Upon treatment of mesylate **27** with potassium *t*-butoxide in dimethyl sulfoxide, silyl cleavage affords alkoxide **28** which fragments to yield formaldehyde, a mesylate anion, and bicycle **29**. Exposure of **27** to DBU in acetonitrile leads to the desired E2 reaction with complete suppression of the Grob fragmentation.[20]



27 **28** **29**

Fragmentations of Monocyclic Fragments

Monocyclic portions of molecules can be fragmented to generate acyclic enone moieties. In Wong's total synthesis of pallavicinin (**32**) and neopallavicinin, Grob fragmentation of a tetracycle yields a tricyclic enal. Silyl ether **30** provides target aldehyde **31** upon exposure to tetrabutylammonium fluoride followed by potassium *t*-butoxide.[21]

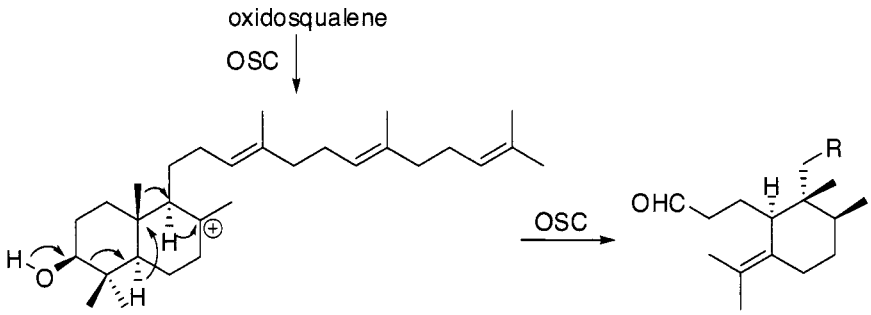


30 **31** **32**

Rychnovsky reported that the Grob fragmentation is one step in the mechanism for the solvolysis of a tetrahydropyranyl mesylate. In this

interesting mechanistic study, Rychnovsky also demonstrates that a Prins cyclization and a 2-oxonia-Cope rearrangement are involved in the process.[22]

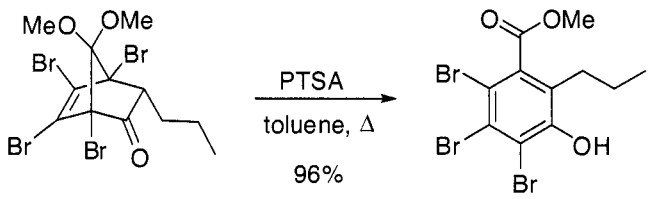
Several groups have demonstrated that oxidosqualene cyclase (OSC) catalyzes Grob fragmentations in biosynthetic pathways. Ebizuka reported the synthesis of a multitude of *seco*-triterpene skeletons, several of which result from stepwise Grob fragmentations. For example, oxidosqualene cyclase converts oxidosqualene into carbocation **33** which undergoes a series of hydride and alkyl shifts before fragmenting to yield marneral (**34**).[23] Matsuda reported a similar process for the biosynthesis of a triterpene iridal skeleton.[24]



33 **34**

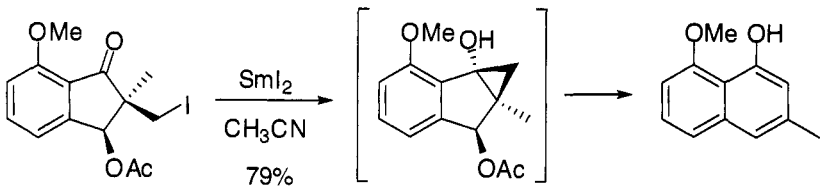
Fragmentations of Bicyclic Fragments to Yield 6- to 8-Membered Rings

The Grob fragmentation is a useful synthetic tool for the construction of rings with six to eight members beginning with a bicyclic structural moiety. One example enables the production of substituted benzenes from readily available bicycles. Khan demonstrated that polyhalogenated (chloro and bromo) phenols (e.g., **36**) result from treatment of bicyclic ketones (e.g., **35**) with PTSA in toluene.[25]



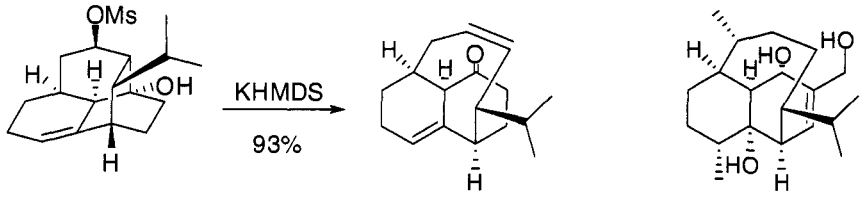
35 **36**

Suzuki reported the use of a Grob fragmentation as a step in the conversion of benzocyclobutenols into substituted naphthols. Beginning with indanone **37**, samarium iodide-induced Barbier reaction yields tricycle **38** which fragments under the reaction conditions to yield naphthol **39**.[26]



37 38 39

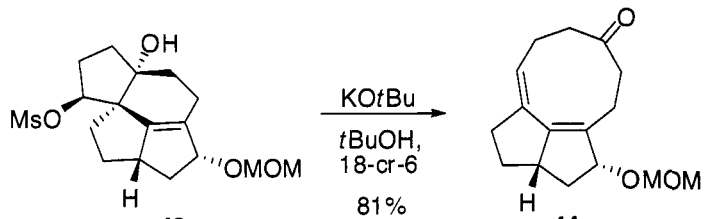
Baran recently disclosed a concise approach to the synthesis of vinigrol (**42**) that utilizes a Grob fragmentation as the key step to generate an eight-membered ring. Vinigrol was discovered in 1987 and has yet to be synthesized in the lab. Baran's approach relies on two Diels–Alder reactions to generate a tetracycle that is then fragmented to yield the desired 6–6–8 tricyclic framework of vinigrol. Mesylate **40** is available in eight steps and is efficiently converted to the vinigrol core structure **41** upon exposure to base.[27]



40 41 42

Fragmentations of Bicyclic Fragments to Yield 9-Membered or Larger Rings

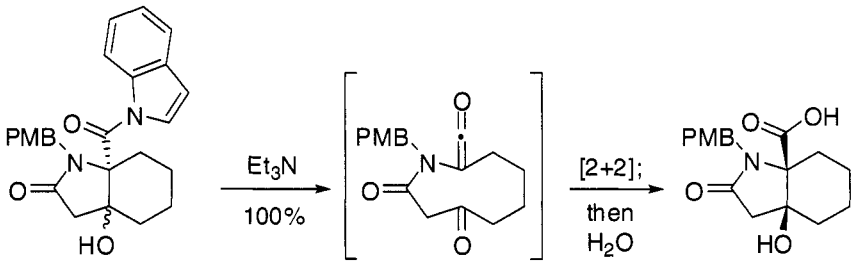
Synthetically challenging medium- to large-sized rings are frequently prepared using the Grob fragmentation. For example, Burnell generated the 9-membered ring in the tricyclic 5-5-9 aquariane skeleton via fragmentation of a tetracycle. Reaction of mesylate **43** with potassium *t*-butoxide furnished target **44** in 81% yield. Protection of the secondary alcohol in **43** as a MOM ether proved essential for efficient conversion to **44**.[28]



43 44

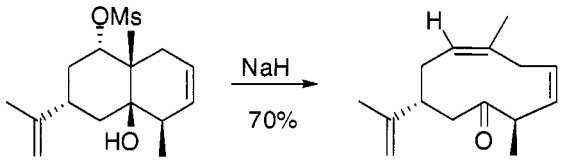
While investigating the synthesis of bicyclic pyroglutamic acid, Kobayashi discovered that treatment of a diastereomeric mixture of amides

45 with triethylamine followed by an aqueous workup furnished a single diastereomer of carboxylic acid **47**. Kobayashi explained this unexpected result by proposing that a Grob fragmentation of **45** generates 9-membered ring ketene **46** which undergoes a transannular ketene [2 + 2] cycloaddition followed by hydrolysis to yield **47**. This is the first invocation of a ketene intermediate arising as the product of a Grob fragmentation.[29]



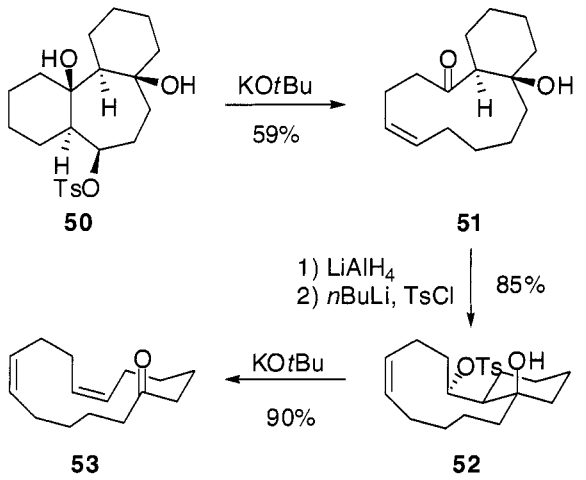
45 **46** **47**

Mehta demonstrated the utility of the Grob fragmentation for the generation of 10-membered rings in his syntheses of several sesquiterpenoid germacrenes. The title reaction is used as the final step in the synthesis of six different germacrenes. For example, reaction of mesylate **48** with sodium hydride furnishes *Z,Z*-germacratrienone **49** in 70% yield.[30] Chen also successfully prepared a 10-membered ring using the Grob fragmentation as part of his investigation into the synthesis of the taxane ABC ring system.[31]



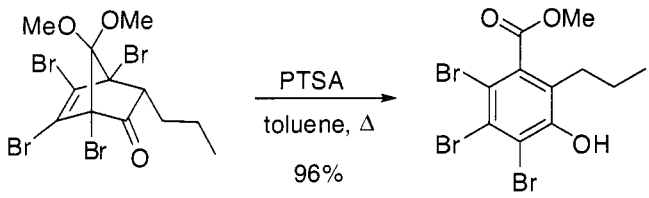
48 **49**

An intriguing use of the Grob fragmentation for the synthesis of a macrocycle was reported by Fehr. He employed a cascade of two fragmentations for the synthesis of a 15-membered ring. Although it cannot be performed in one flask, the four-step sequence outlined below demonstrates how tricyclic tosylate **50** fragments to form 11-membered ring ketone **51**. Reduction and conversion of the resulting secondary alcohol to the corresponding tosylate yields bicycle **52** which fragments to yield 15-membered ring dienone **53**.[32]



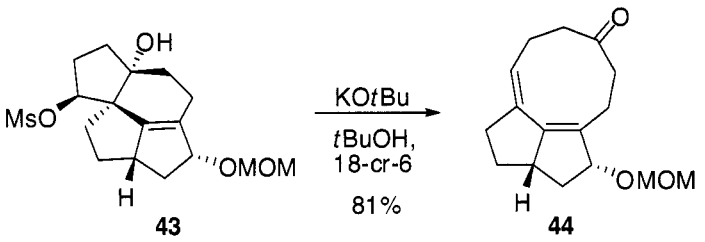
50 **51** **53** **52**

1.3.4.6 Experimental



35 **36**

Methyl 2,3,4-tribromo-5-hydroxy-6-propylbenzoate:[25]
p-Toluenesulfonic acid monohydrate (PTSA) (284 mg, 1.49 mmol) was added to a solution of the bicyclic ketone **35** (1.565 g, 2.97 mmol) in toluene (10 mL) and the reaction mixture was refluxed at 110–120 °C for 30 min. After the reaction was complete (TLC monitoring), the reaction mixture was diluted with water (10 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was concentrated *in vacuo* to furnish a residue which was purified by silica gel column chromatography to afford the phenol derivative **36** (1.234 g, 96%).



43 44

(2a*R,4*S**)-2,2a,3,4,5,6,8,9-Octahydro-4-(methoxymethoxy)cyclonona-[*cd*]pentalen-7(1*H*)-one** (44):[28]

To a solution of **43** (10 mg, 0.027 mmol) in *t*-BuOH (0.3 mL) at rt was added KO*t*Bu (4 mg, 0.04 mmol) followed by 18-crown-6 (8 mg, 0.03 mmol). The mixture was stirred for 4 h after which time TLC analysis showed that no starting material remained. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine and then dried over Na_2SO_4. Evaporation of the solvent *in vacuo* followed by flash chromatography (5% EtOAc/hexanes) gave **44** (5 mg, 81%) as a colorless oil.

1.3.4.7 References

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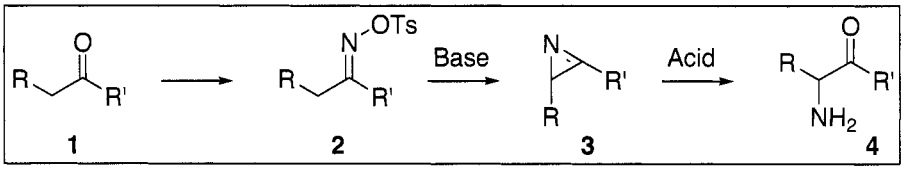
1.3.5 Neber Rearrangement

Jeremy M. Richter

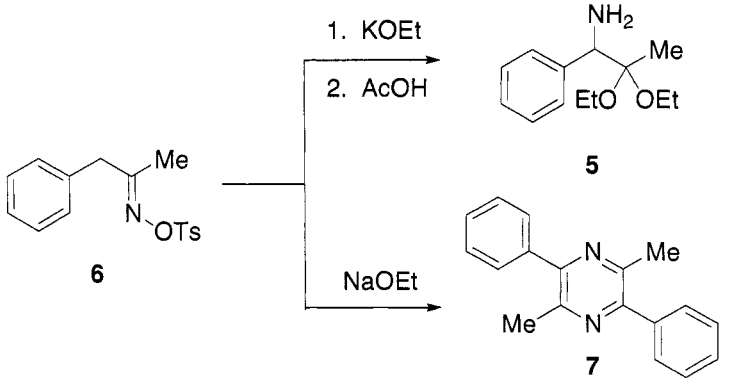
1.3.5.1 Description

The net conversion of a ketone into an α-aminoketone *via* the oxime is known as the Neber rearrangement.[1–5]



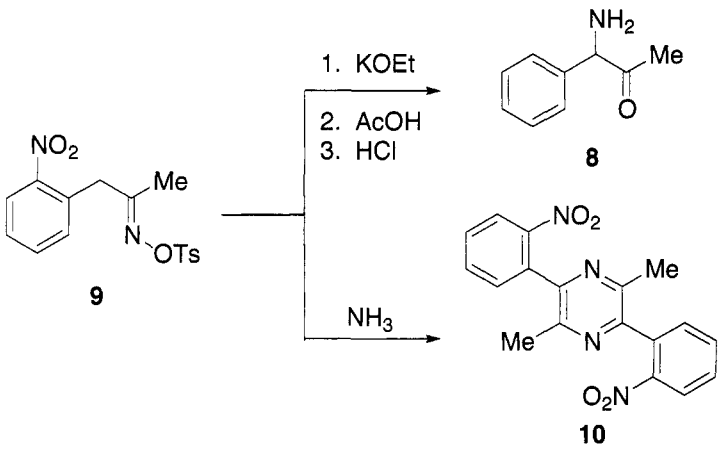
The reaction begins with conversion of the carbonyl compound (**1**) to the oxime (**2**), which is then treated with base to form the 2*H*-azirine (**3**). Subsequent hydrolysis under acidic conditions generates the α-aminoketone (**4**).

1.3.5.2 Historical Perspective



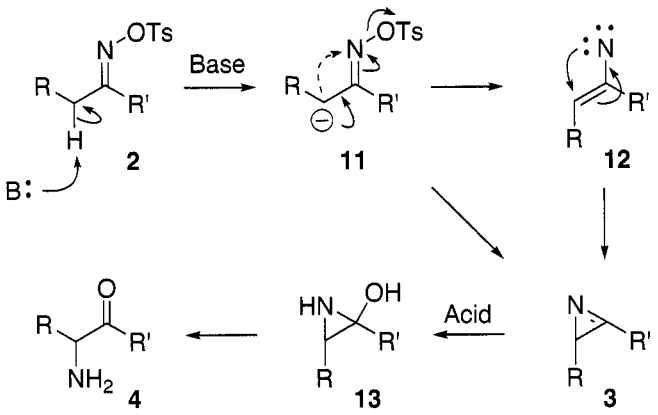
During the course of investigating the Beckmann rearrangement, Neber observed unexpected reactivity of some tosyloximes.[1] When he treated oxime **6** with sodium ethoxide he obtained pyrazine **7**, clearly not the result of a Beckmann rearrangement. Furthermore, he learned that by treating **6** with potassium ethoxide followed by acetic acid, the product obtained was aminoacetal **5**. Similarly, treatment of **9** with ethanolic ammonia provided pyrazine **10**, whereas treatment with potassium ethoxide followed by acid gave the α-aminoketone **8**, which could be converted to **10** *via* treatment with

ethanolic ammonia. He continued to study this reaction, providing more examples of such rearrangements. He was also able to characterize azirine-containing byproducts, which shaped the mechanistic interpretation of this reaction.[3,4] Neber's seminal investigations provided the impetus for further study of this reaction in the ensuing decades.[6]



1.3.5.3 Mechanism

After formation of oxime **2** from the corresponding ketone **1**, which is accomplished using standard methods, treatment with base (typically alkoxides) deprotonates alpha to this moiety, thus forming carbanion **11**. The precise nature of the ensuing step is still a matter of some debate in the literature, as two potential pathways exist by which formation of the 2*H*-azirine might be explained. One could envision an ionic pathway by which the anion directly displaces the tosylate on the nitrogen, forming **3** in one step (dashed arrow). This mechanistic interpretation is supported by the fact that acceptable enantiomeric excesses can be observed upon performing the reaction under chiral phase transfer catalysis.[7] Alternatively, departure of the tosylate, without concomitant ring-closure would generate the vinyl nitrene **12** (solid arrow), which could then cyclize to form **3**. This mechanistic interpretation is supported by the fact that an S_N2 displacement on an oxime nitrogen is unlikely and that no preference is observed for *trans*-oximes over *cis*-oximes, which would be expected in the anionic mechanism.[8,9] Although neither mechanistic interpretation for this step has yet to be conclusively proven, evidence certainly points towards the vinyl nitrene pathway. With **3** in hand, acidic hydrolysis proceeds through intermediate **13** to provide the α-amino ketone (**4**).

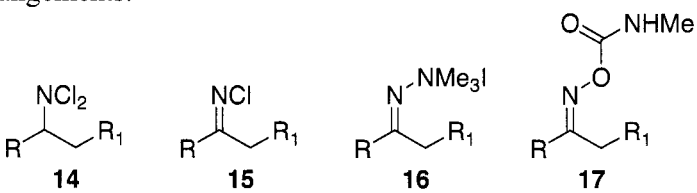


It is also important to note that several intermediates in this sequence have been isolated and characterized, further bolstering the mechanistic interpretation. Neber isolated an azirine of type **3**,[3,4] which has been conclusively corroborated.[10] In fact, there are many reports which do not hydrolyse the azirine to the aminoketone, but rather isolate these moieties in good yields (vide supra). Intermediates of type **13** have been isolated, after alkoxide addition to the azirine.[8] Furthermore, the azirine was shown to be non-isomerizing under the reaction conditions,[11] allowing predictable application of this reaction. Finally, it was shown that when two ionizable α-centers are present, deprotonation occurs at the most acidic site.[8,9]

1.3.5.4 Variations

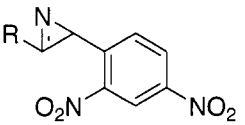
Oxime Replacements

Oximes are not the only functional groups capable of undergoing Neber-type rearrangments. Dichloroamines (*e.g.*, **14**) can rearrange under basic conditions,[12] presumably proceeding through iminochlorides of type **15**,[13] which can be independently prepared and rearranged.[14,15] Trimethylhydrazonium iodides (**16**) can be prepared and rearranged.[16–18] Finally, even oximocarbamates (**17**) have been reported to undergo Neber-type rearrangements.[19]

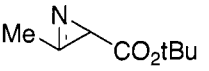


2H-Azirine Formation

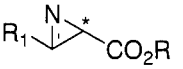
Perhaps the most widespread variation of the Neber rearrangement is its utility in preparing 2*H*-azirines. The first reported isolation of such a product (**18**), albeit in a special case, was reported by Neber in his seminal studies of this reaction.[3,4] Since then, numerous reports have appeared which prepare these moieties in good yields under predictably selective conditions, usually utilizing milder bases and by omitting of the final acidic hydrolysis. [20,21] For example, **19** was formed in good yield from the corresponding oxime when treated with triethylamine.[22] Since then, special attention has focused on the asymmetric preparation of 2*H*-azirines *via* this modification of the Neber rearrangement. As such, compounds of type **20**, from the corresponding β-oximoester,[23,24] and **21**, from the corresponding β-oximophosphine oxide,[25-27] are readily produced in generally good yields, with low to moderate enantiomeric excesses.



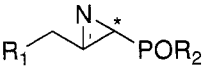
18 (59%)



19 (70%)



20 (29–85%)
ee = 44–82%

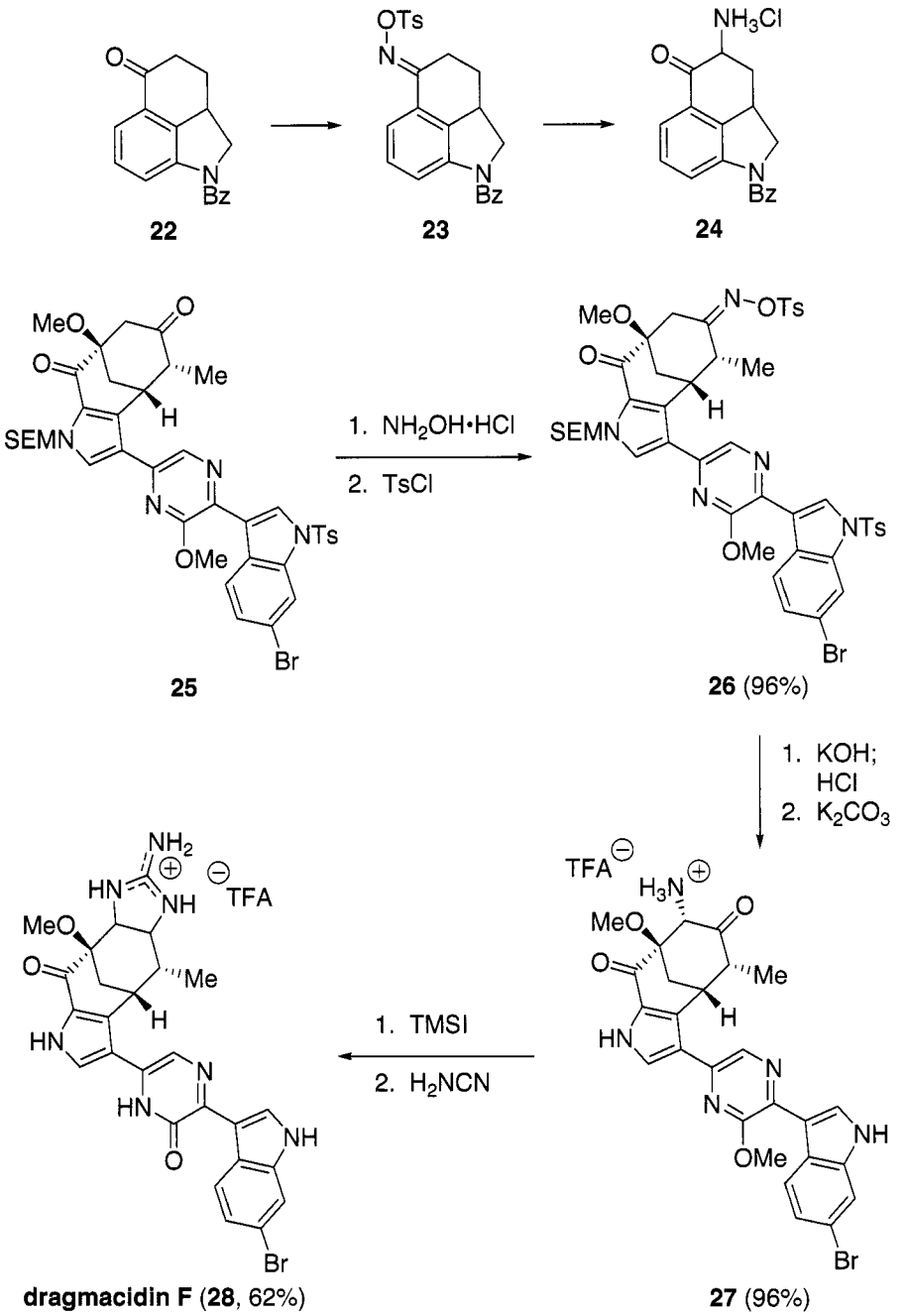


21 (35–96%)
ee = 2–82%

1.3.5.5 Synthetic Utility

Natural Product Total Synthesis

Despite the powerful potential of the Neber rearrangement, it has been scarcely utilized in the total synthesis of complex natural products. The earliest such application was in Woodward's total synthesis of lysergic acid.[28] Although not utilized in the successful route to this alkaloid, an early approach to the α-aminoketone (**24**) exploited the Neber rearrangement on compound **22**. Preparation of the oxime (**23**) followed by rearrangement provided the amine hydrochloride **24** in "good yield"; however, this compound was unstable as a free base and could not be processed further *en route* to lysergic acid.

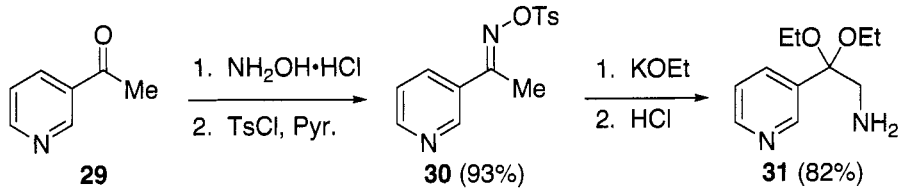


Perhaps the most complex natural product total synthesis that features a Neber rearrangement is Stoltz's total synthesis of dragmacidin F.[29,30] Oxime formation and tosylation on **25** efficiently provided **26**. Neber

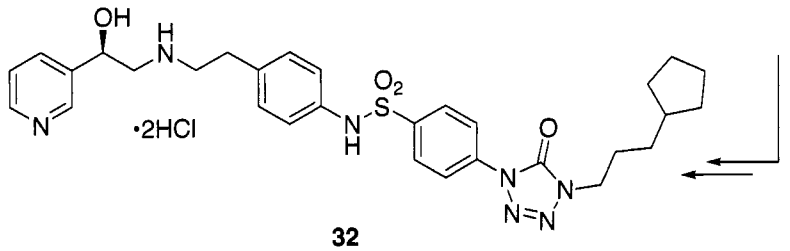
rearrangement, followed by hydrolysis, provided the desired α-aminoketone **27** in excellent overall yield, which could be converted to the natural product (**28**) *via* deprotection and guanidine formation. This particular example demonstrates the utility of the Neber rearrangement, even in the context of a complex natural product total synthesis with various other sensitive functional groups.

Medicinal Chemistry

As was the case with the total synthesis of natural products, the Neber rearrangement has received limited attention in the context of the preparation of medicinally relevant compounds. However, the Merck process group has utilized this reaction in the large-scale preparation of a β_3 adrenergic receptor agonist (**32**).[31] As such, 3-acetylpyridine (**29**) was efficiently converted to oxime **30**, which was then submitted to Neber rearrangement conditions to provide aminoketal **31** in excellent yield. Agonist **32** was eventually prepared from this intermediate on kilogram scale. This was not the first report in which the amino acetal was obtained directly from the Neber rearrangement. Previously, researchers from Pfizer had developed generalized conditions by which this moiety can be selectively obtained after Neber rearrangement by utilizing ethanolic HCl to promote azirine hydrolysis.[32]



29 **30** (93%) **31** (82%)

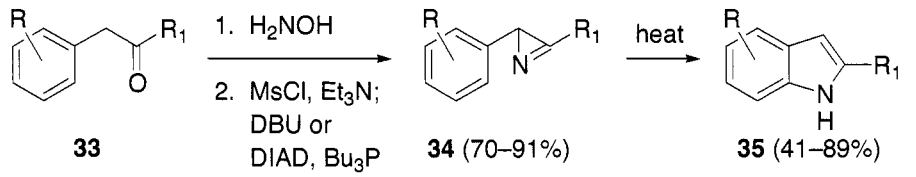


32

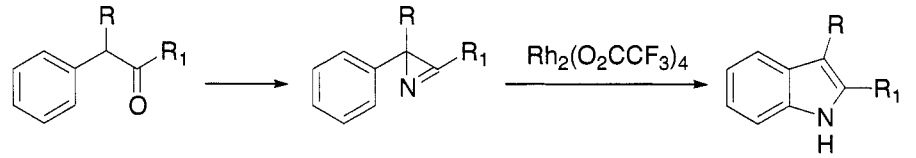
Heterocyclic Chemistry

In addition to the pyrazines (**7**, **10**)[1] formed in the early Neber rearrangements (which are theoretically accessible from any α-aminoketone), several other heterocycles have been prepared using this reaction as a key

transformation. The Taber group discovered that arylazirines (**34**) could be accessed from the corresponding ketones (**33**) in excellent yields and efficiently converted into the indoles (**35**) upon thermolysis in *o*-xylene.[33] Alternatively the Narasaka group discovered that similar azirines (**37**) could be formed *via* the Neber reaction of ketone **36**, followed by metal-catalyzed rearrangement to the indole (**38**) in generally high yields.[34]

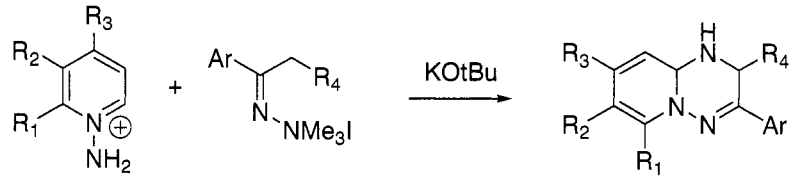


33 **34** (70–91%) **35** (41–89%)



36 **37** **38** (34–91%)

Finally, a synthesis of 2*H*-pyrido[1,2-*b*]-*as*-triazines was reported, exploiting an intercepted Neber rearrangement.[35,36] For this reaction, the trimethylhydrazonium iodides (**40**) were treated with KO*t*-Bu to presumably form the intermediate azirines. Rather than hydrolyzing these intermediates, the azirines were instead intercepted with 1-aminopyridinium salts (**39**) to directly furnish the heterocyclic products (**41**) in moderate yields.

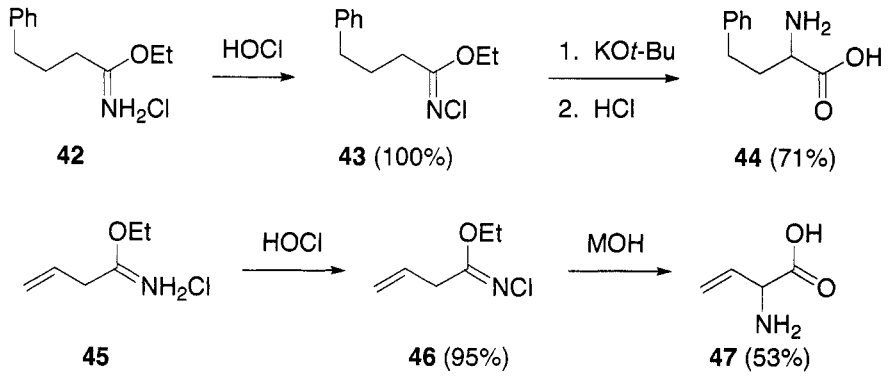


39 **40** **41** (10-57%)

α-Amino Acids

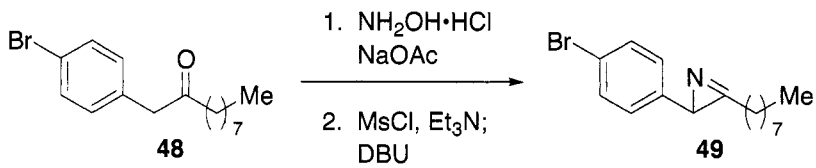
The Neber rearrangement has the potential to be a powerfully simplifying transformation in the synthesis of unnatural or isotopically labelled α-amino acids and, indeed, several such syntheses have been reported. Homophenylalanine (**44**) has been prepared from ethylimidate **42** *via* chlorination to form the chloroimidate **43**. Neber rearrangement of **43** provided **44** in excellent yield, allowing access to labelled versions of this α-amino acid.[37] A synthesis of vinylglycine (**47**) has also been reported

utilizing this reaction. Treatment of ethylimidate **45** with bleach provided chloroimidate **46** in excellent yield, which could be rearranged directly to the α-amino acid **47**.[38] Of crucial importance to the direct preparation of such compounds is the ability to perform a Neber rearrangement on heteroatom-substituted oxime equivalents. As such, thiooximates[39] and amidooximates,[40,41] some bearing chiral auxiliaries,[42] can be utilized in the Neber rearrangement.



1.3.5.6 Experimental

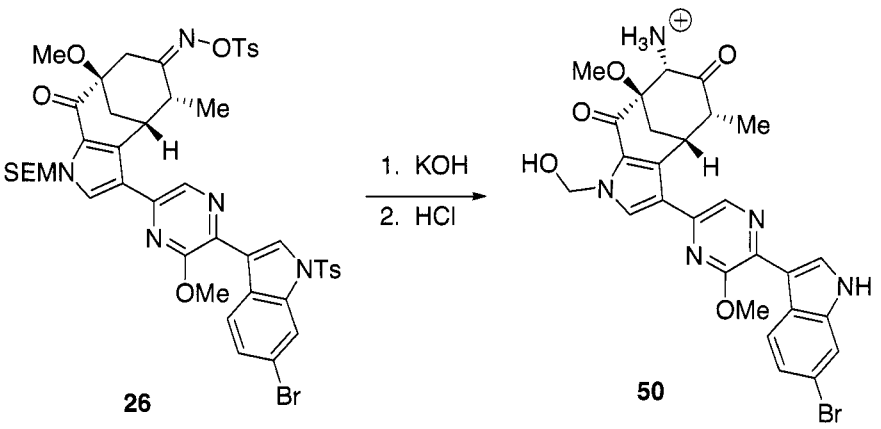
Preparation of 2H-Azirines[33]



Methanol (20 mL) and water (1 mL) were added to a mixture of [**48**] (0.631 g, 2.03 mmol), NH_2OH•HCl (0.212 g, 3.05 mmol) and sodium acetate (0.250 g, 3.05 mmol) in a round bottom flask. After stirring at rt for 4 h, the solvent was removed *in vacuo*. The reaction mixture was partitioned between MTBE and, sequentially, water, saturated aqueous $NaHCO_3$ and brine. The combined organic extract was dried (Na_2SO_4). Concentration led to the crude oxime (0.635 g), which was used directly in the next reaction. To a solution of the crude oxime (0.635 g) in 35 mL of THF was added triethylamine (296 mg, 2.93 mmol) and methanesulfonyl chloride (332 mg, 2.93 mmol) sequentially at rt. The solution got cloudy after the addition of methanesulfonyl chloride. After 30 min, DBU (890 mg, 5.86 mmol) was added over 1 min. After 30 min, the reaction mixture was passed through a pad of silica gel, washing with MTBE. The mixture was concentrated *in*

vacuo and the residue was chromatographed to give the azirine (**49**, 437 mg, 1.42 mmol, 70% yield from the ketone) as a colorless oil.

Preparation of α-Aminoketone[29]



To a stirred solution of tosyl oxime [**26**] (23.3 mg, 0.0236 mmol) in EtOH (3.5 mL) at 0 °C was added 50% aq. KOH (450 μL) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 3 h, then 6 N aq. HCl (5 mL) was added. The reaction mixture was heated to 60 °C for 10 h, cooled to 23 °C, and purified.

1.3.5.7 References

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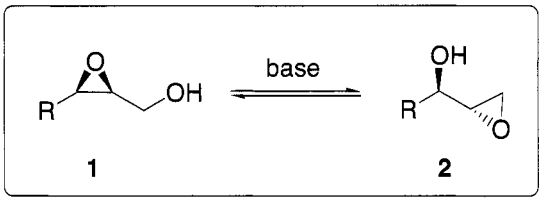
1.3.6 Payne Rearrangement

Raju Ranjith Kumar and Subbu Perumal

1.3.6.1 Description

The isomerization of 2,3-epoxy alcohol **1** under the influence of a base to 1,2-epoxy-3-ol **2** is referred to as Payne rearrangement.[1–10] It involves an equilibrium of the epoxy alcohol **1** with the isomeric **2** and the reaction is stereospecific, proceeding with inversion of configuration at C-2 carbon of the epoxide ring via S_N2 type mechanism.

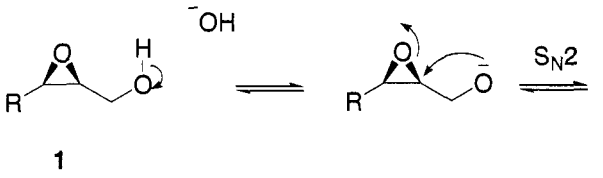


1.3.6.2 Historical Perspective

The isomerization of one epoxy alcohol to another under basic conditions was first reported by Lake *et al.*[11] Later Angyal *et al.*[12] revealed the possibility of an intramolecular nucleophilic displacement of the hydroxy group on C-1 of **1** furnishing a more stable epoxy alcohol of the type **2** and referred as 'epoxide migration', which became a well known reaction in carbohydrate chemistry. In 1962 Payne[1] described the epoxide migration of simple racemic 2,3-epoxy alcohols under the influence of a base. He showed that, in general, the epoxy alcohols with less substituted carbinol carbon was favored over its more highly substituted one. The term 'Payne rearrangement' has been adopted in honor of Payne's pioneering work and the considerable synthetic potential of the rearrangement.

1.3.6.3 Mechanism

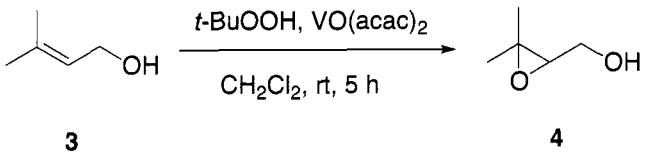
The mechanism of Payne rearrangement involves intramolecular nucleophilic attack by an alkoxide on an adjacent epoxide to form an isomeric alkoxide. This isomerisation results an equilibrium mixture of the two epoxides, the position of which is controlled by the relative thermodynamic stabilities of the two compounds.

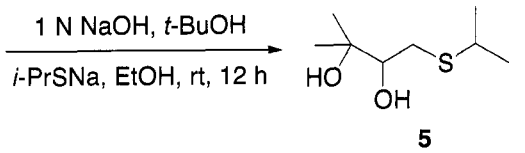


1.3.6.4 Variations and Improvements

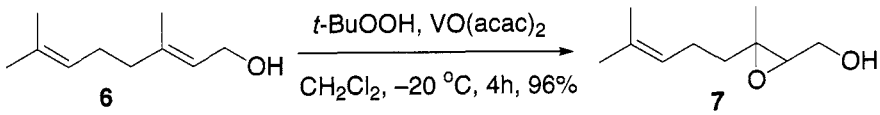
Payne rearrangement

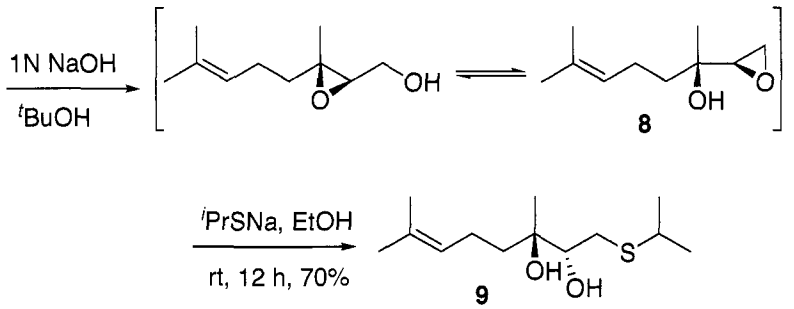
The diol **5** was obtained from 2,3-epoxy-3-methyl-1-butanol (**4**) under Payne rearrangement conditions in the presence of sodium isopropyl mercaptide. The epoxide **4,** in turn, was obtained from the Sharpless epoxidation of the alkene **3**. The diol **5** served as a precursor for the synthesis of 2,2,5-trimethylchroman-3-ol.[13]



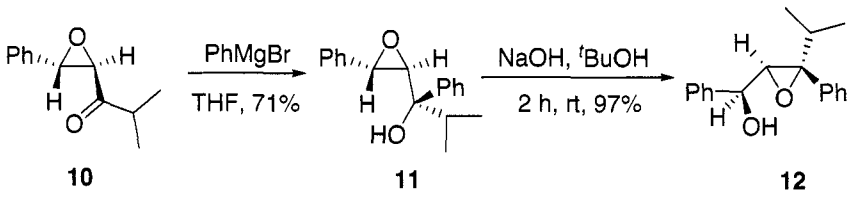


The same group[13] reported the synthesis of 2,6-dimethyl-2-homoprenylchroman-3-ol via a Payne rearrangement of the epoxide **7** followed by epoxide ring opening reaction.

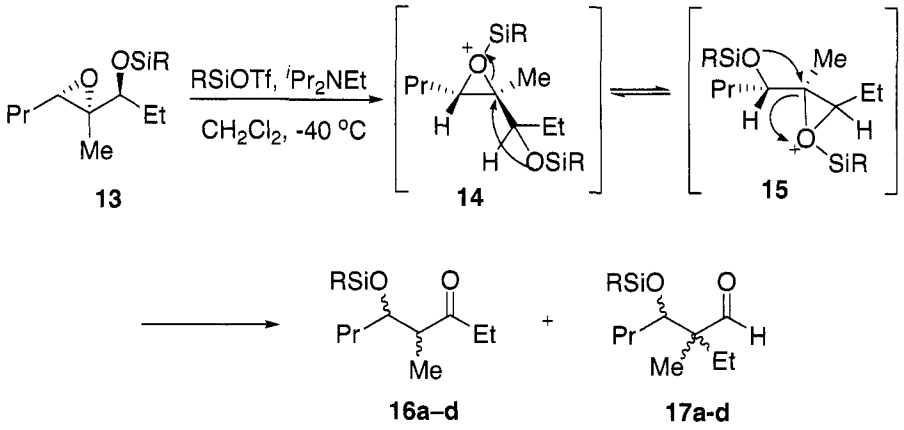




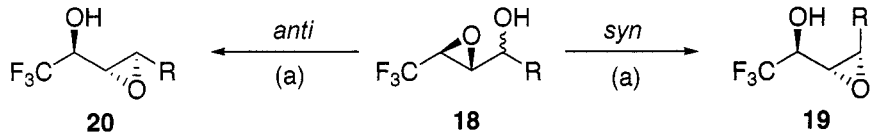
Bickley *et al.*[14] reported that the treatment of non-racemic epoxyketone **10** with phenylmagnesium bromide gave the epoxy alcohol **11** diastereoselectively, which then underwent Payne rearrangement to afford the secondary alcohol **12,** the ratio of **11** and **12** being 3:97.



A novel silyl triflate-promoted Payne rearrangement of silyloxy epoxides was reported by Jung *et al.*[15] When the ethyl substituted epoxy silyl ether **13** was treated with silyl triflate in the presence of a base, a mixture of four ketones, **16a–d** and four aldehydes **17a–d** were obtained. It has been assumed that two ketones and two aldehydes could be formed via a non-aldol process and an epoxide rearrangement, whereas the other four products through **14** and **15**, a silyl triflate promoted Payne rearrangement.



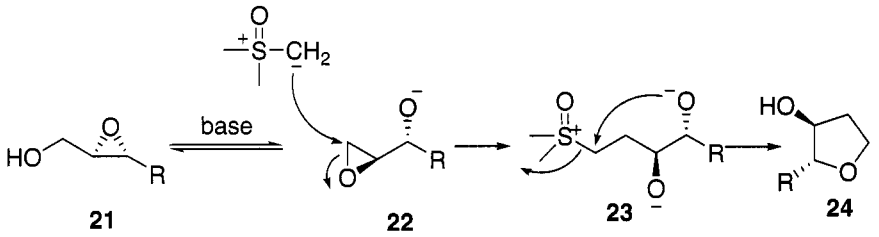
Selective Payne rearrangement was achieved for the epoxyalcohol **18** with CF_3 group in the presence of 5 eq. of HMPA and sodium hydride.[16] The electron withdrawing nature of the CF_3 group played a significant role and was proved to overcome the increased steric instability of epoxides from syn-*E* to anti-*Z* isomers (**19** and **20**).



20 **18** **19**

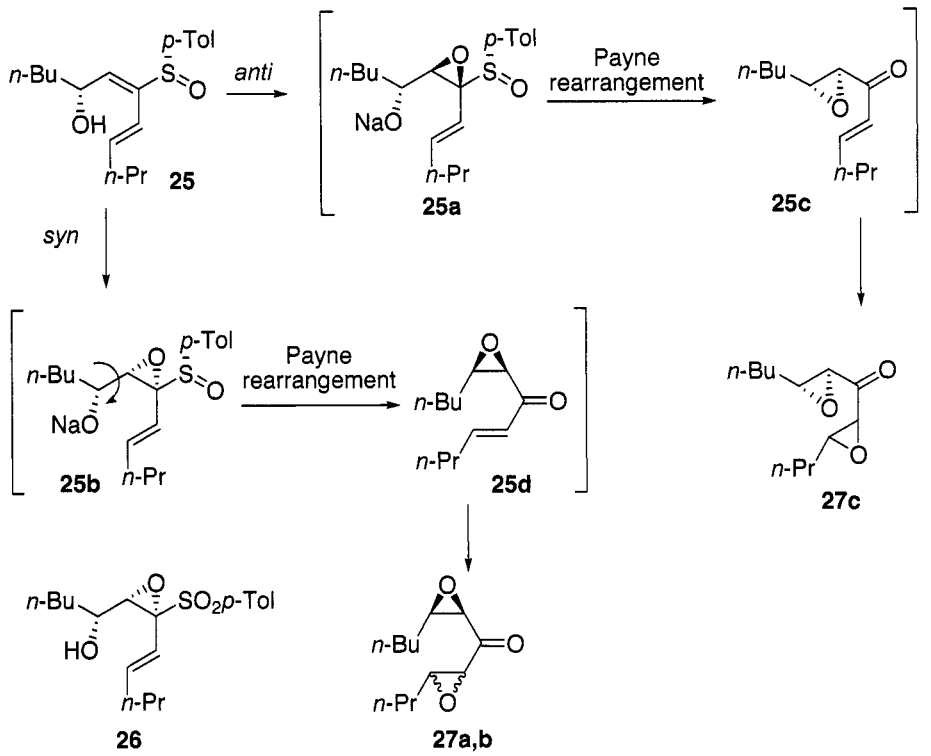
(a) NaH, HMPA (5 equiv)/THF, rt, 3 h

Schomaker *et al.*[17] found that the Payne rearrangement is useful for controlling the regioselectivity of the reaction of dimethylsulfoxonium ylide with the epoxy alcohol **22**. Thus the rearrangement of chiral non racemic epoxy alcohol **21** led to the more sterically accessible terminal epoxide **22,** which then underwent nucleophilic epoxide opening with the ylide at C-1 to afford bis alkoxide **23**. The *5-exo-tet* ring closure of **23** resulted in the formation of 2,3-disubstituted tetrahydrofuran ring **24**.

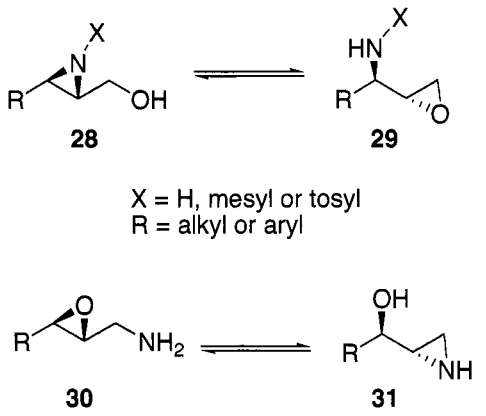


21 **22** **23** **24**

It has been reported that the treatment of **25** with sodium *t*-butyl-hydroperoxide furnished the sulfonyl oxirane **26** as minor product (27%) along with bis-epoxides **27a,b** as a 44:55 mixture of diastereoisomers (52%) and **27c** as a single isomer (21%).[18] The formation of **27a–c** has been rationalized in terms of a Payne rearrangement of the sulfinyl oxiranes **25a** (*anti*) and **25b** (*syn*) to afford the α,β-unsaturated epoxy ketones **25c** and **25d**. These epoxy ketones undergo second nucleophilic epoxidation to furnish **27a–c**. In this process, **25a** experiences a fast Payne rearrangement, whilst **25b** would require rotation around Cβ–Cγ for a suitable orientation and hence slows down the rearrangement.



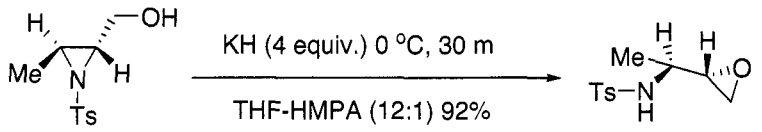
Aza-Payne rearrangement



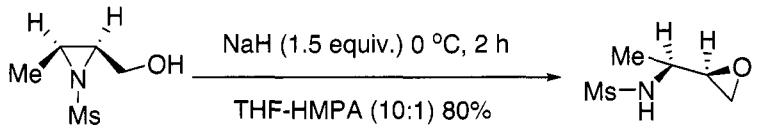
Aziridine rings constitute a vital sub-structure of biologically active molecules. This renders the synthesis of such compounds through aza-Payne rearrangement[9] of aziridinemethanols **28** and 2,3-epoxy amines **29** of much interest in connection with the synthesis of bioactive compounds.[19–22]

Ibuka *et al.*[23] investigated the aza-Payne rearrangement of various (i) 2-aziridinemethanols, (ii) organocopper-mediated reaction of *N*-tosyl-3-methyl-2-aziridinemethanols, and (iii) 2,3-epoxy amines. It has been found that the rearrangement of activated 2-aziridinemethanols with *t*-BuOK, NaH or KH near 0 °C in THF, toluene, 1,2-dimethoxyethane, 1,4-dioxane or a mixture of THF-HMPA, followed by quenching at −78 °C gave the epoxysulfonamides. The 2,3-epoxy amines upon treatment with an equimolar mixture of *t*-BuOK–*n*-BuLi in a mixture of THF and *n*-hexane at −78 °C led to an equilibrium lying exclusively towards the hydroxyaziridine forming direction.

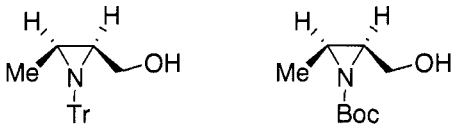
The aza-Payne rearrangement is reversible and the epoxide can be favored over the aziridine, if the nitrogen anion is well stabilized. The rearrangement of the *N*-tosylated aziridine **32** in the presence of KH affords excellent yields of the epoxide **33**. The mesyl functions as an effective activating group and hence the reaction of **34** under Payne conditions results in the formation of epoxide **35** in good yields.[23] However, the protecting groups such as Boc and trityl on the nitrogen atom (**36** and **37**) are reported to be not effective in promoting rearrangement.[20]



32 **33**

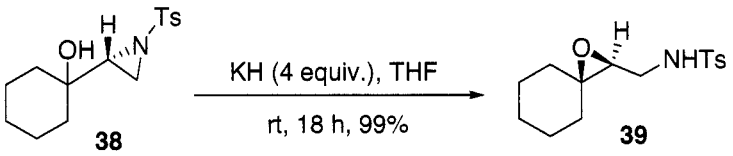


34 **35**



36 **37**

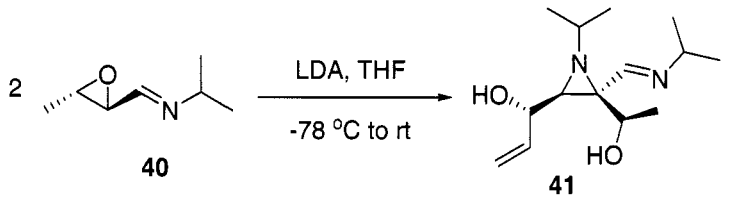
The aziridine **38** possessing a tertiary hydroxyl group undergoes aza-Payne rearrangement in the presence of KH slowly in THF to give the epoxy sulfonamide **39** exclusively.[23]



38 39

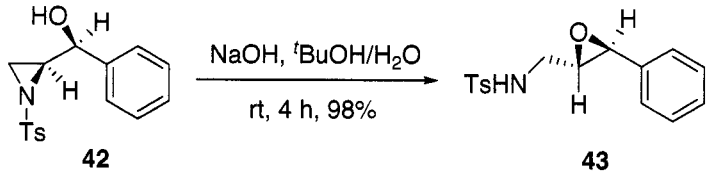
Ibuka *et al.*[24] also developed a one-pot regio- and stereoselective synthetic route to 1,2-amino alcohols from the readily available 2-aziridine-methanols, wherein the intermediates resulting from the aza-Payne rearrangement were not isolated.

A new type of aza-Payne rearrangement was reported by Bilke *et al.*[25] in which oxiranyl carbaldimines **40** upon treatment with lithiumorganic nucleophiles, are transformed to aziridinyl alcohols **41** regio-and diastereoselectively. This is the first case wherein an amine anion is generated as an intermediate by the attack of a nucleophile on an imine functionality. They suggested that this aza-Payne rearrangement reaction is fully supported by quantum chemical calculations of structural and electronical properties of the lithiated intermediates and transition states on the SCS-MP2/6-31+G*//RHF/6-31+G* level.



40 41

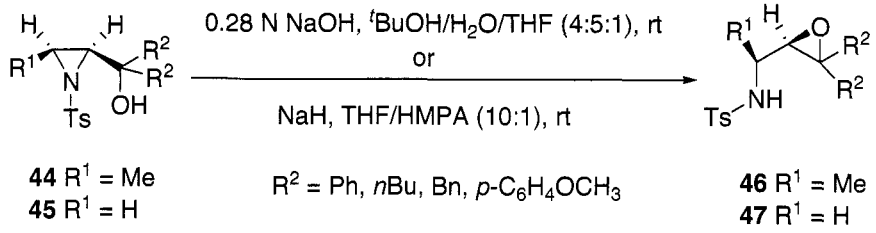
It has been shown that aziridine **42** bearing a phenyl adjacent to the hydroxyl group, undergoes aza-Payne rearrangement to **43** in the presence of NaOH in excellent yield.[26]



42 43

The aza-Payne rearrangement of the tosylates **44** and **45** in the presence of either NaOH or NaH proceeded at room temperature to afford the epoxy sulfonamides **46** and **47**. The aziridines **44** and **45** were obtained starting from the reaction of *N*-tritylaziridine-2-carboxylates with Grignard reagent in THF at room temperature, followed by removal of the trityl group

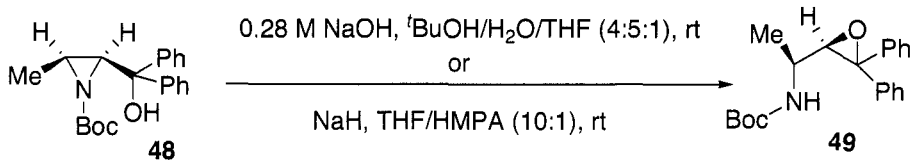
in situ with H_2SO_4 in $MeOH/H_2O$ solvent, which resulted in the formation of aziridinemethanols. Further tosylation of these aziridinemethanols afforded **44** and **45**.[27]



44 R^1 = Me
45 R^1 = H

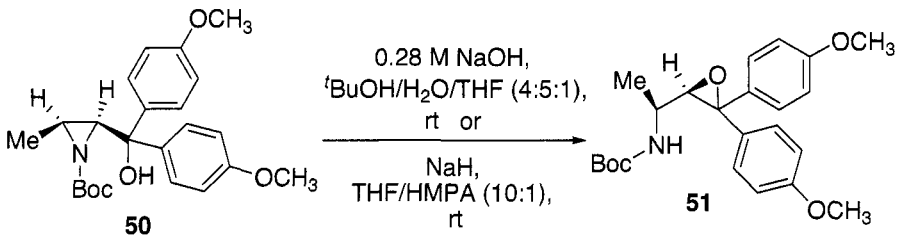
46 R^1 = Me
47 R^1 = H

The aza-Payne rearrangement of *N*-Boc protected aziridinemethanols was also studied. Hence, the reaction of *N*-Boc aziridinemethanol **48** rearranged to epoxy sulfonamide **49** in 70% yield in presence of NaOH in mixed solvent, $^tBuOH/H_2O/THF$ (4:5:1). The yield increased to 96% on reaction with NaH in THF/HMPA (10:1).[27]



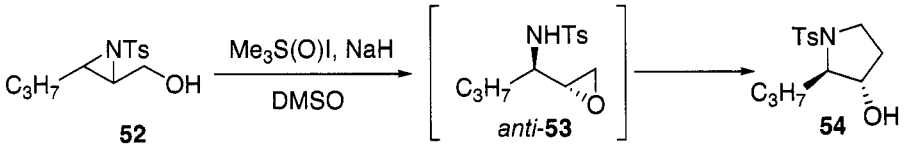
48 **49**

In a similar manner, the reaction of *N*-Boc aziridine **50** in presence of NaOH afforded a low yield (30%) of aza-Payne rearrangement product **51,** while the reaction of **50** with NaH gave a higher yield (80%).[27]

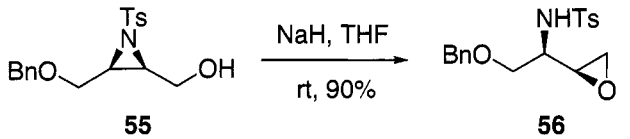


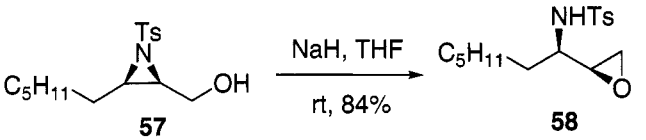
50 **51**

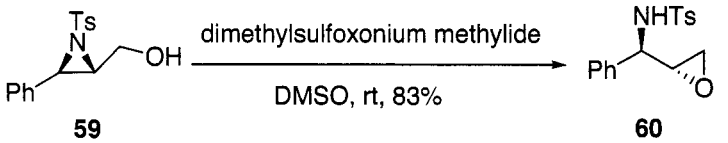
The *in situ* aza-Payne rearrangement of 2-aziridinemethanol **52** under Borhan's conditions *viz.* $Me_3S(O)I$ (10 equiv.), NaH (10 equiv.) in DMSO led to the formation of 3-hydroxypyrrolidine **54** via epoxysulfonamide **53**.[28]

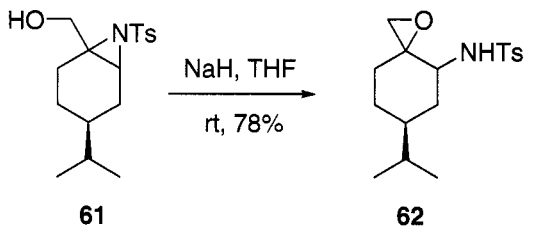


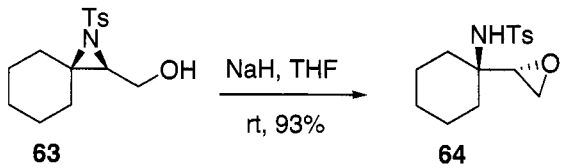
Schomaker *et al.*[29] reported a general methodology for conversion of hydroxy aziridines into pyrrolidines via a one-carbon homologative relay ring expansion initiated by an aza-Payne rearrangement. The rearrangement of tosylated aziridinols **55–63** was accomplished in excellent yields using 4 equiv of NaH in THF or in some cases with dimethylsulfoxonium methylide in DMSO to furnish epoxy amines **56–64**.



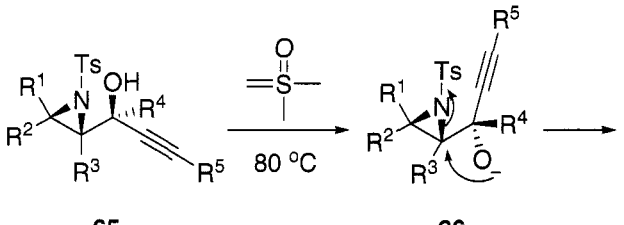




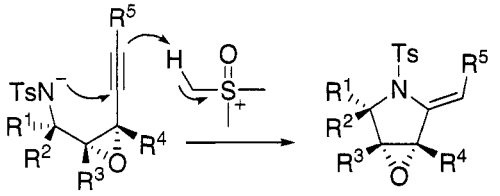




The epoxy amine products **56–64** were treated with dimethylsulfoxonium methylide in DMSO at 85 °C to afford the 2,3-disubstituted pyrrolidines in good yields with complete control of diastereoselectivity.



65 **66**



67 **68**

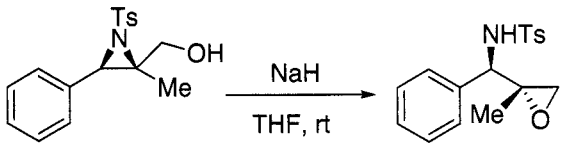
R^1	R^2	R^3	R^4	R^5
CH_3	CH_2OBn	H	H	H
H	C_7H_{15}	H	H	H
H	Ph	CH_3	H	H
H	*p*MeOPh	CH_3	H	H
H	CH_2OBn	CH_3	H	CH_3
H	CH_2OBn	CH_3	CH_3	H

A tandem aza-Payne/hydroamination reaction of aziridinols **65**, mediated by dimethyl-sulfoxonium methylide afforded highly functionalized pyrrolidine ring systems in one pot at room temperature.[30]

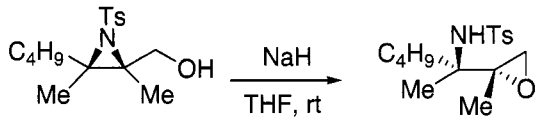
1.3.6.5 Synthetic Utility

Synthesis of epoxy amines

Several epoxy amines have been synthesized via aza-Payne rearrangement of the respective 2,3-aziridin-1-ols.[29] These epoxy amines (**70, 72**) can serve as synthons for the construction of enantiomerically pure nitrogen heterocycles.



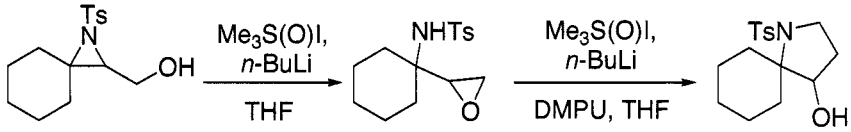
69 **70**



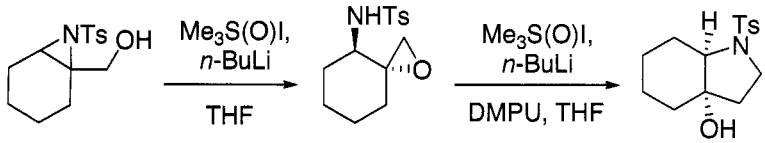
71 **72**

Synthesis of spiro- and fused-hydroxypyrrolidines

Spiro- and *cis*-fused hydroxypyrrolidines **75** and **78** were prepared from the aza-Payne rearrangement of the aziridines **73** and **76** via the epoxy sulfonamides **74** and **77** respectively.[28] It is pertinent to note that 3-hydroxypyrrolidines are found in naturally occurring bioactive alkaloids, pharmaceuticals and drug intermediates.



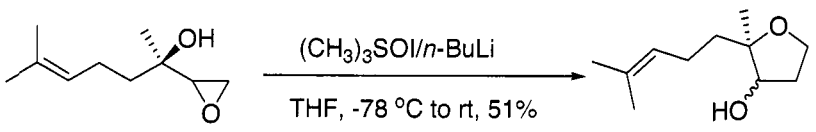
73 **74** **75**



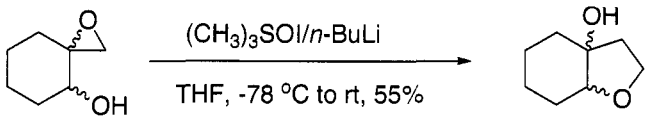
76 **77** **78**

Synthesis of 2,3-disubstituted tetrahydrofuran rings

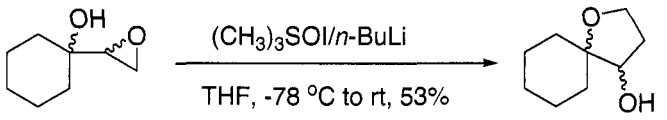
The Payne rearrangement of the respective epoxy alcohols **79–85** led to the formation of highly substituted 2,3-disubstituted tetrahydrofurans **80–86** stereoselectively.[17]



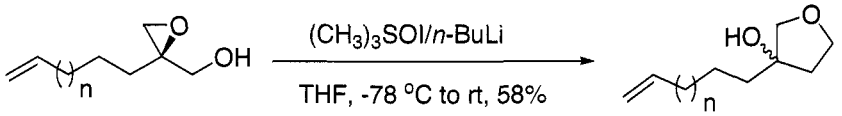
79 80



81 82

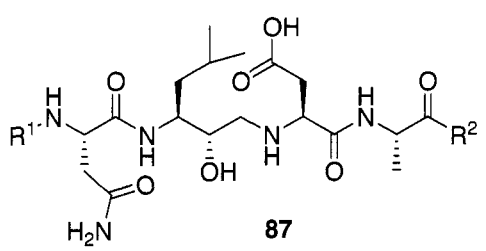


83 84



85 86

Synthesis of peptidomimetics



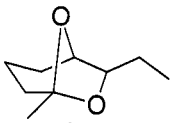
87

R^1	R^2
H-	$-NH_2$
H-Val	$-NH_2$
H-	-Glu-NH_2
H-Val	-Glu-NH_2
H-	-Glu-Phe-NH_2
H-Val	-Glu-Phe-NH_2

A novel methodology employing aza-Payne rearrangement and *O,N*-intramolecular acyl transfer reactions was reported by Tamamura *et al.*[31] for the synthesis of peptidomimetics containing hydroxyethylamine dipeptide isosteres (**87**). This method is also applicable for the synthesis of hydroxyethylamine dipeptide isosteres containing pseudopeptides and also for combinatorial chemistry using solid-phase techniques.

Total synthesis (+)-exo-Brevicomin

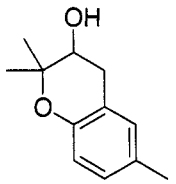
The organo-copper and -cuprate reagent has been used in the Lewis acid-catalysed Payne rearrangement, which found application as a key step in the enantioselective total synthesis of (+)-*exo*-brevicomin (**88**), an aggregation pheromone of the Western Pine beetle *Dendroctonius brevicomis*.[10]



88

Synthesis chroman-3-ol

2,2-Dialkylchroman-3-ol (**89**) was synthesized employing Payne rearrangement in the initial steps followed by acetylation, ortho-alkylation, deprotection and cyclization process.[13]



89

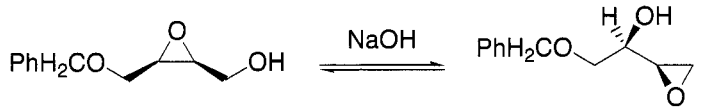
1.3.6.6 Experimental

The epoxyalcohol **90** (0.28 mole) was treated with a solution of sodium hydroxide (150 ml, 0.5 N) previously cooled to 5 °C. The solution was allowed to warm to room temperature and remain there for 1 hr. After saturation with ammonium sulfate (100 g), the solution was extracted with chloroform (3 × 50 ml). The combined chloroform extract was washed with half-saturated ammonium sulfate (25 ml), dried over magnesium sulfate, and concentrated on the steam bath to an internal temperature of 80–85 °C. The crude mixture was distilled through the glass spiral packed column at 20 mm pressure to give the desired product **91**.[1]

90 **91**

To a stirred solution of NaOH (10 ml, 0.28 M) in a mixture of ^{t}BuOH-H_2O-THF (4:5:1) was added **44** (2.5 mmol) at room temperature and then stirring was continued for several hours. The reaction was quenched with water (20 ml) at 0 °C with stirring. The mixture was extracted with diethyl ether and the extract washed successively with saturated citric acid, brine, 5% $NaHCO_3$, and brine and dried over magnesium sulfate. The usual workup followed by flash chromatography over silica gel with petroleum ether-ethyl acetate (5:1) afforded **46**.[27]

The aziridinol **55** (2.9 mmol) dissolved in a small amount of THF was added to a suspension of NaH (60% dispersed in mineral oil, 11.5 mmol) in dry THF. The reaction was stirred at room temperature for 4 h and then cooled to 0 °C and quenched carefully with saturated ammonium chloride. The aqueous layer was extracted three times with portions of ethyl acetate and the combined organic layer was washed with brine, dried over sodium sulfate and the volatiles removed. The residue was purified by column chromatography to give the epoxy amine **56**.[29]



92 **93**

To a solution of **92** (1.04 mmol) in THF (5 ml) at 0 °C under argon atmosphere was added, dropwise, butyllithium (1.43 M solution in hexane 1.04 mmol) and the reaction mixture was stirred for 5 min. The temperature of the alkoxide solution was then adjusted as required and the complexing agent added using syringe. Finally, the product was purified through gas chromatography.[10]

1.3.6.7 References

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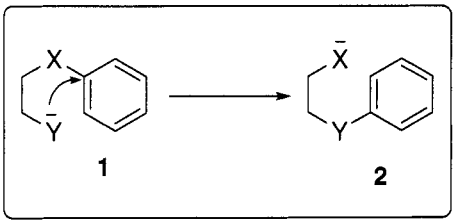
1.3.7 Smiles Rearrangement

Raju Ranjith Kumar and Subbu Perumal

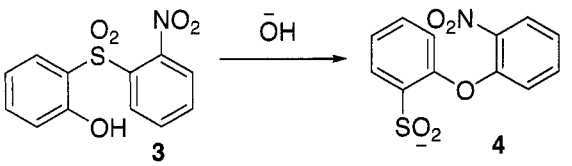
1.3.7.1 Description

Smiles rearrangement[1-21] represents a class of intramolecular nucleophilic aromatic substitution reactions in which a nucleophile, Y, displaces an aromatic electrophile, X. This rearrangement is enabled when X is generally S, O, SO, SO_2, COO, NR, CONR, SO_2NR or any other substituent capable of acting as a nucleofuge, while Y is a strong nucleophile, for exampe OH, NH_2, NHR, SH.[1] The rearrangement is facilitated usually when the ring is activated by nitro groups at *ortho* or *para* positions.



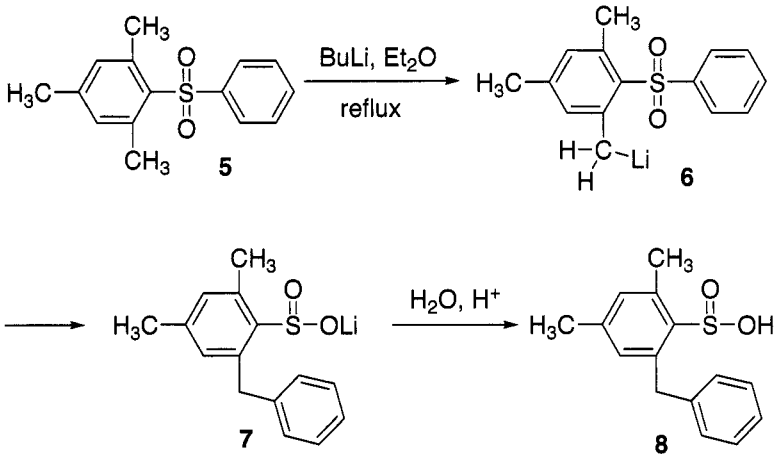
1 2

For example, **3** undergoes Smiles rearrangement to afford **4**, in which SO_2Ar is the leaving group, ArO^- is the nucleophile and the nitro group serves to activate its *ortho* position.



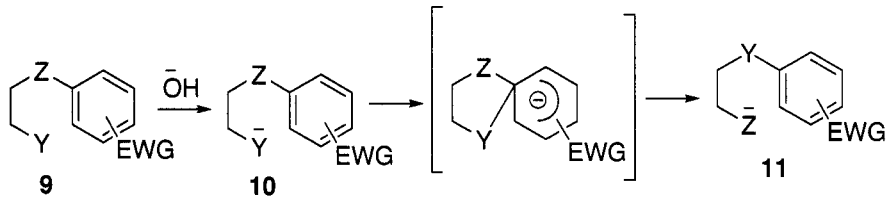
3 4

In a modified Smiles rearrangement called the Truce-Smiles rearrangement,[9] the nucleophile when strong enough, for example, when it is a carbanion generated by organolithium, activation of the ring by *ortho* substituent is not required. Thus **5** upon Truce-Smiles rearrangement in the presence of butyllithium furnishes the sulfinic acid **8.**



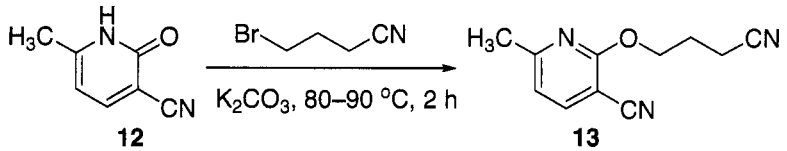
1.3.7.2 *Mechanism*

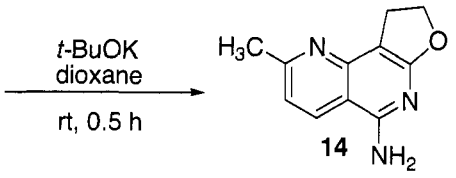
The Smiles rearrangement occurs via an intramolecular nucleophilic aromatic substitution as shown below.[1a]



1.3.7.3 *Variations and Improvements*

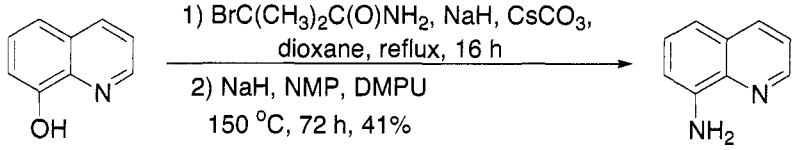
The Smiles rearrangement followed by intramolecular cyclization of 2-(3-cyanopropoxy)-6-methylpyridine-3-carbonitrile (**13**) in the presence of potassium *tert*-butoxide in dioxane afforded 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine (**14**) in 83% yield.[22] The structure of **14** was assigned with the help of spectroscopic data and elemental analysis. The precursor **13,** in turn, was obtained from the reaction of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**12**) with 4-bromobutyronitrile in DMF.





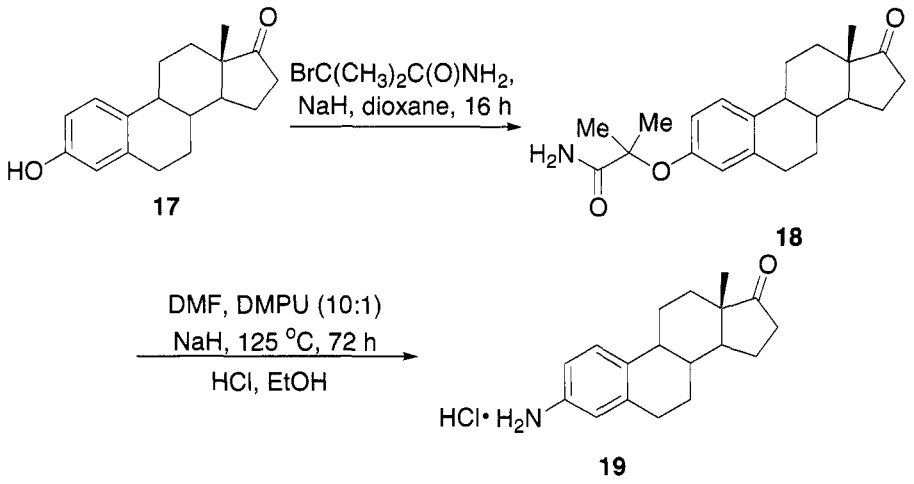
14

Weidner *et al.*[23] described a one-pot Smiles rearrangement method for the synthesis of various aminoquinolines from the corresponding hydroxyquinolines and showed that the tendency for the conversion depends on the electron-deficient nature of the quinolines. In a specific example, the reaction of **15** with (i) 2-bromo-2-methylpropionamide, 3 equiv. each of NaH and cesium carbonate in dioxane at reflux for 16 h and (ii) *N*-methylpyrrolidinone (NMP), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (10:1 ratio) and 1 equiv. of NaH at 150 °C for 72 h afforded the amine **16**.



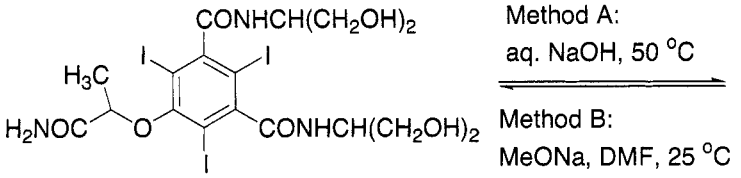
15 **16**

Similarly, the two-step, one-pot alkylation and Smiles rearrangement procedure has been applied for the successful conversion of estrone **17** into 3-aminoestratriene derivatives **19**.[24]



17 **18** **19**

The Smiles rearrangement of various amides has been investigated under two different conditions in order to avoid the formation of side products. The amides were converted into an equilibrium mixture of the amide and the rearranged product within a few hours in method A and few minutes in method B. The formation of side products in either of the methods depends highly on the nature of the substituent on the phenoxyacetamide nitrogen atom. Hence, in one case, the Smiles rearrangement of **20** with aqueous NaOH at 50 °C for 19 h afforded **21** in 18% yield, whereas the reaction with MeONa and DMF at 25 °C resulted in the formation of **21** within 45 min in 99% yield.[25]



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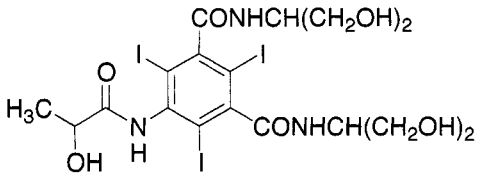

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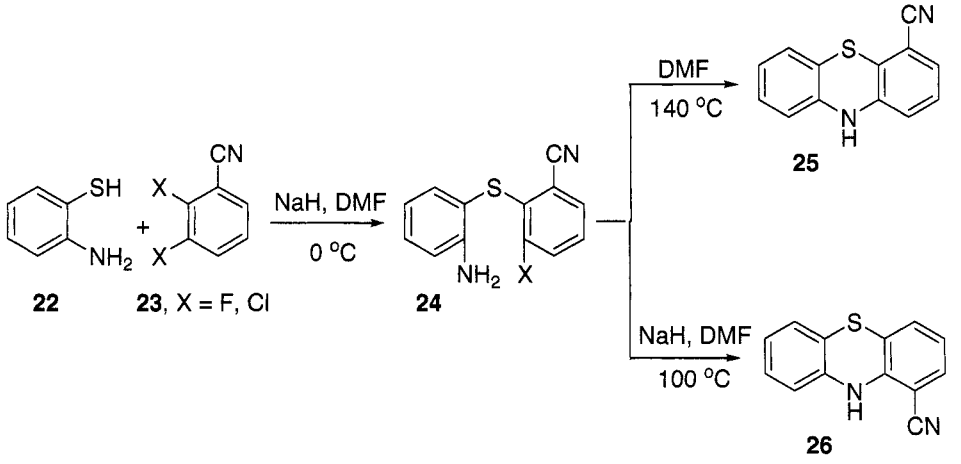
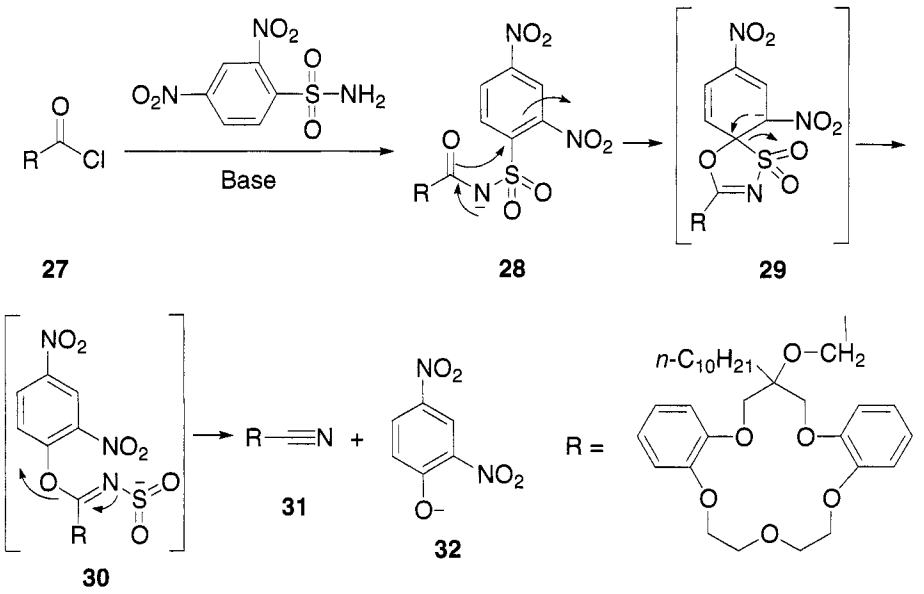


22 **23**, X = F, Cl **24** **25** **26**

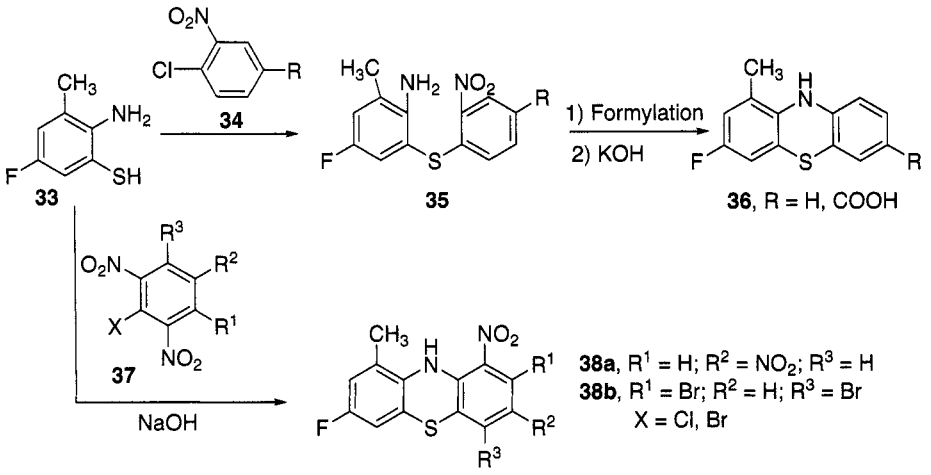
The reaction of 2,3-difluoro- or dichlorobenzonitriles **23** with 2-aminothiophenol **22** in the presence of NaH at 0 °C afforded the diphenyl sulfides **24**. The 4-cyanophenothiazine (**25**) was obtained by heating **24** in DMF at 140 °C, whereas the Smiles rearrangement of **24** in the presence of

NaH in DMF at 100 °C gave 1-cyanophenothiazine (**26**), therefore providing selective procedures for the synthesis of different regioisomers.[26]

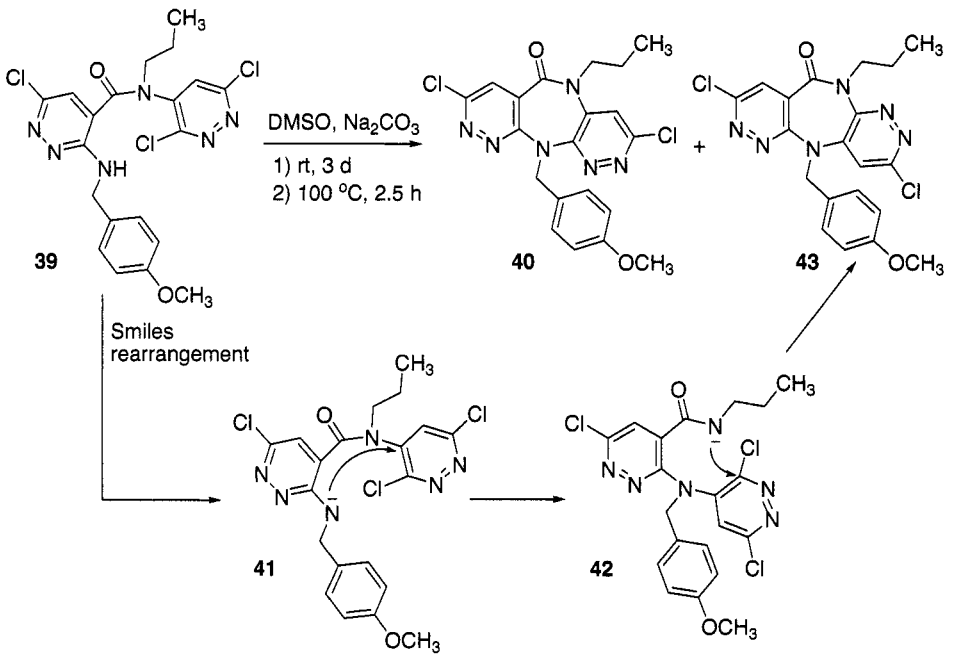


The key step in the reaction of 2,4-dinitrobenzenesulfonamide with acyl chlorides **27** in the presence of an excess of triethylamine in THF affording the nitrile compounds **31** occurs through the Smiles rearrangement of the initially formed *N*-(2,4-dinitrobenzenesulfonyl)amide **28** to form the nitrile **31**, 2,4-dinitrophenol **32** and sulfur dioxide.[27]

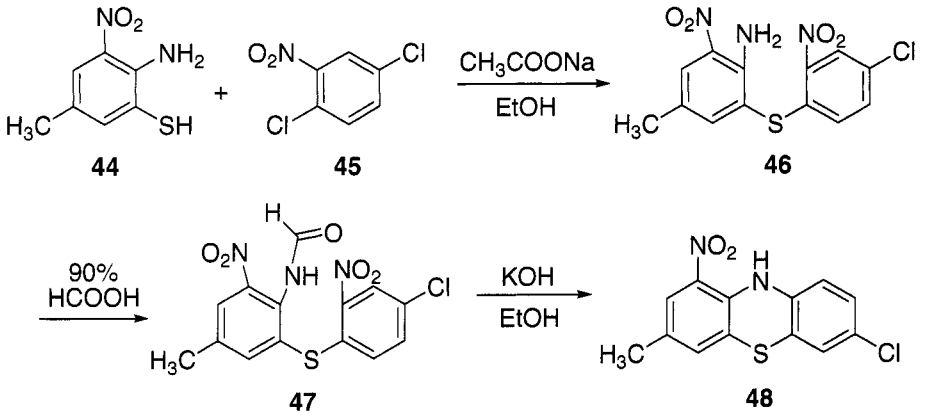
The reaction of 2-amino-5-fluoro-3-methylbenzenethiol **33** with 2-halonitrobenzenes **34** afforded the diphenyl sulfides **35,** which upon formylation followed by Smiles rearrangement with potassium hydroxide gave the phenothiazines **36,** whereas the reaction of **33** with **37** containing nitro group at *ortho* and *para* or both *ortho* positions to the halogen atom activates the Smiles rearrangement followed by cyclization in a single step affording nitrophenothiazines **38**. The presence of nitro groups in **37** increases the resonance effect as well as the inductive effect activating the *in situ* Smiles rearrangement without the formation of diphenyl sulfides.[28] Similarly, the Smiles rearrangement resulting from other aminothiophenols and nitrobenzenes have also been reported.[31,32, 41-44, 49]



The cyclization reaction of **39** under basic conditions furnished a 1:1 mixture of diazepines **40** and **43**. The unexpected formation of **43** has been rationalized by a Smiles rearrangement involving a nucleophilic attack of the deprotonated 3′-nitrogen at position 4 of the second pyridazine ring resulting in the displacement of a carboxamide anion followed by cyclization to afford **43**.[29]

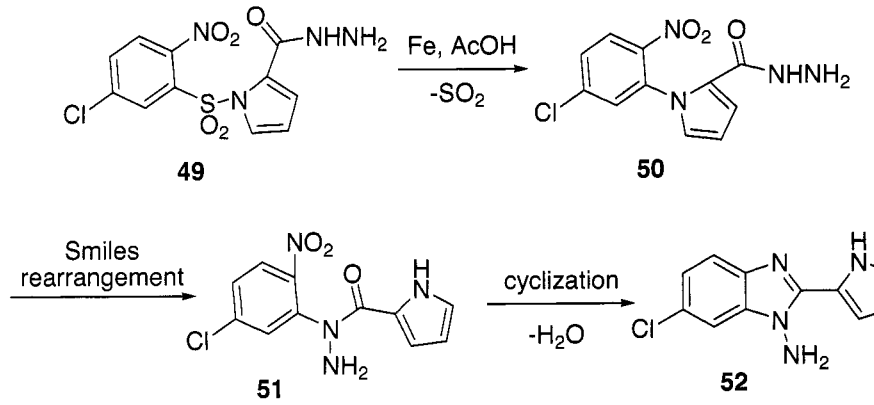


The Smiles rearrangement of the sulfide **47** in the presence of potassium hydroxide in ethanol under reflux for 2.5 h furnished the phenothiazines **48**. The sulfide **47,** in turn, was obtained from the reaction of aminothiophenol **44** and 2,5-dichloronitrobenzene **45** followed by formylation.[30]



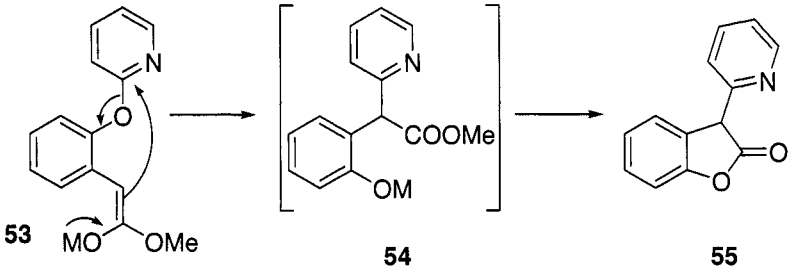
44 **45** **46** **47** **48**

Silvestri *et al.*[33] showed that the reduction of the nitro sulfone **49** with iron-acetic acid led to the formation of carbohydrazide **50** with extrusion of sulfone group. Further, **50** undergoes Smiles rearrangement affording an intermediate **51**, which then cyclizes to give benzimidazole **52**.[33]



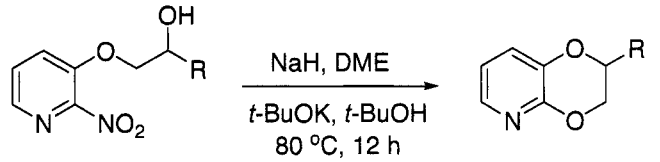
49 **50** **51** **52**

An unexpected Truce-Smiles type rearrangement of the acid ester **53** in the presence of KH or NaH in THF afforded the benzofuranones **55** via the intermediate **54**.[35]



53 54 55

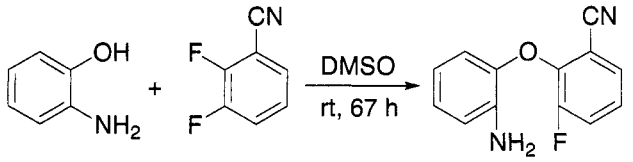
The Smiles rearrangement of the alcohols **56–58** involving the attack of an alkoxide on the position 3 of the pyridine ring with displacement of alkoxide and the subsequent cyclization of the delivered alkoxide into the position 2 of the pyridine ring gave the dioxinopyridines **59–61**. The presence of electron-withdrawing groups in the aromatic ring such as the nitro group facilitates the reaction.[36]



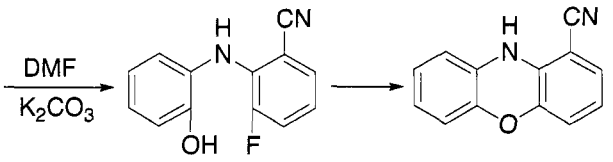
56, R = CH_2OCH_2Ph
57, R = CH_2NHBoc
58, R = $CH_2NCH_3CH_2Ph$

59, R = CH_2OCH_2Ph
60, R = CH_2NHBoc
61, R = $CH_2NCH_3CH_2Ph$

The reaction of 2-aminophenol **62** with benzonitrile **63** at room temperature in DMSO for 67 h afforded the diphenyl ether **64** in 88% yield. The ether **64** upon treatment with potassium carbonate in DMF was then rapidly converted into the phenol **65,** followed by cyclization to furnish **66**.[37] In contrast the reaction of **62** with **63** at 130 °C in DMF resulted in the formation of cyanophenoxazine **66** as a yellow, fluorescent compound within 1 h.[37]

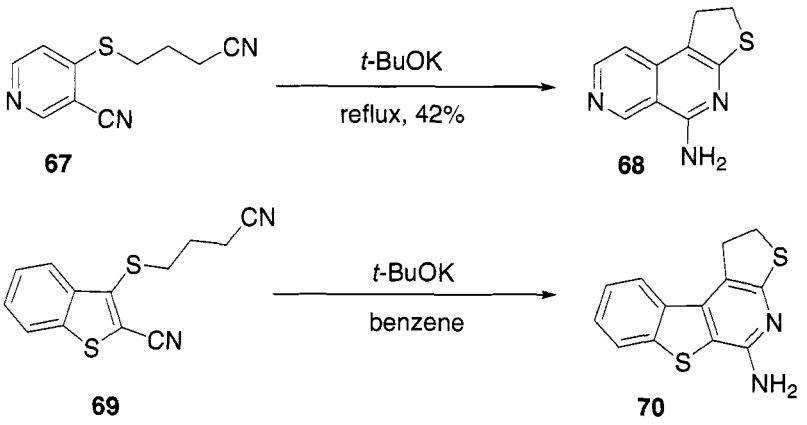


62 **63** **64**



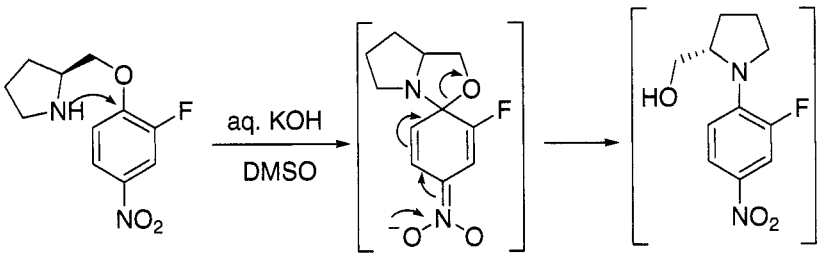
65 **66**

A solution of **67** in dioxane when refluxed in the presence of *t*-BuOK afforded 5-amino-1,2-dihydrothieno[2,3-*c*][2,7]naphthyridine **68** in 52% yield via Smiles rearrangement followed by cyclization. Similarly, the reaction of hot benzene solution of compound **69** in the presence of *t*-BuOK gave the rearranged and cyclized product **70** in 8% yield.[38]

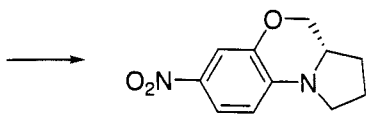


67 **68** **69** **70**

Selvakumar *et al.*[39] reported the Smiles rearrangement of compounds with two or three alkyl carbons in between X and Y groups in **1**. Hence amine nitrogen in **71** undergoes an intramolecular aromatic nucleophilic addition affording the intermediate **72**, which then rearranges to the alcohol **73** and finally cyclizes to afford **74**. The evidence for the occurrence of Smiles rearrangement has been obtained by the isolation of **73** in high yields from the reaction of **71** in the presence of aqueous KOH in THF-DMSO (3:1) before completion of the reaction at ambient temperature. Similarly, the rearrangement of cyclic and primary acyclic amines of the type **75–79** and compounds with three aliphatic carbons in between X and Y groups **80** has also been studied.[39]



71 72 73



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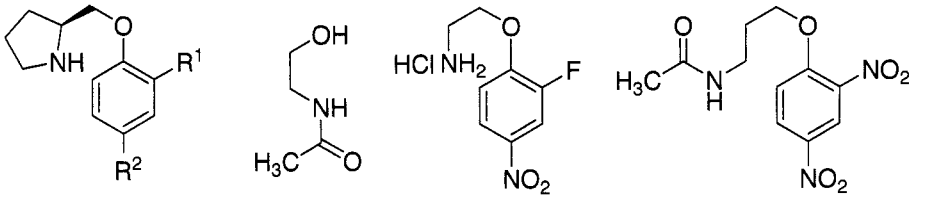
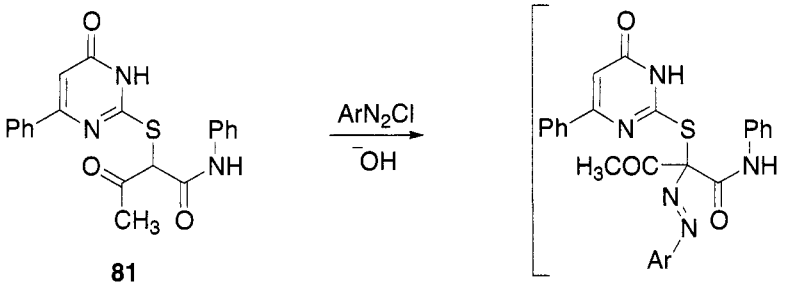


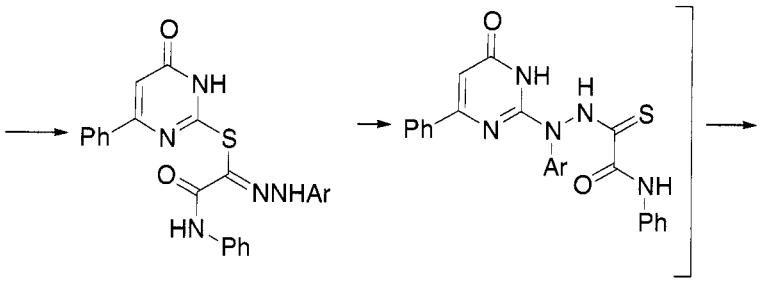
75, R^1 = H; R^2 = NO_2
76, R^1 = NO_2; R^2 = H
77, R^1, R^2 = NO_2

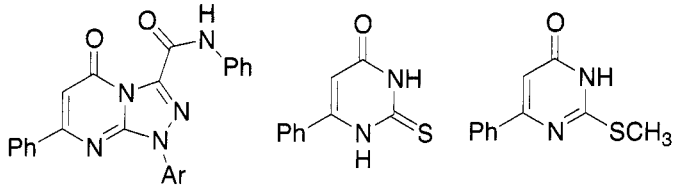
78 79 80

The reaction of S-alkylated compound **81** with diazotized anilines proceeded via a one pot tandem Japp–Klingemann, Smiles rearrangement and cyclization reactions to afford triazolo-pyrimidines **82**.[40] The reaction of **83** and **84** were also studied using this tandem protocol.

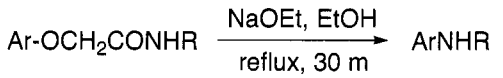


81





82 83 84



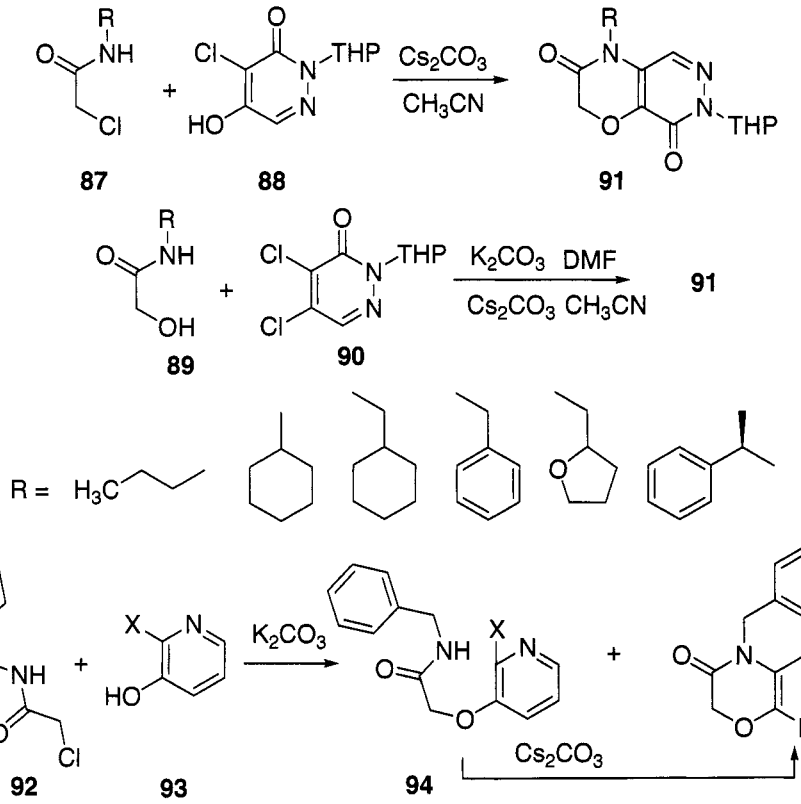
85 86

R	Ar	R	Ar
Ph	4-nitrophenyl	Ph	2-nitrophenyl
3-tolyl	4-nitrophenyl	Et	2,4,6-trichlorophenyl
3-anisyl	4-nitrophenyl	Et	2,4-dichlorophenyl
Ph	2,4,6-trichlorophenyl	Ph	Ph
Ph	2,4-dichlorophenyl	4-anisyl	Ph
Ph	3-nitrophenyl	2,4,6-trichloro phenyl	Ph

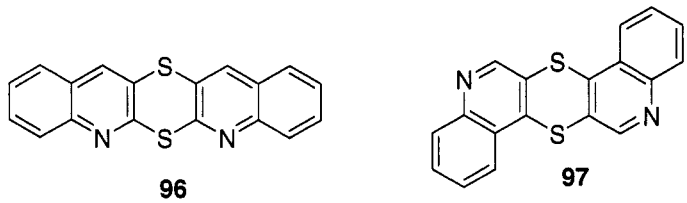
Wadia *et al.*[45] reported that the Smiles rearrangement of several substituted aryloxyacetamides **85** in which the oxygen and nitrogen are separated by $COCH_2$ group afforded *N*-alkyl and *N*-arylamines **86** even when the aryloxy ring had weak or no electron withdrawing group.

The synthesis of pyridazino[4,5-*b*][1,4]oxazin-3,8-dione **91** was reported for the first time by Cho *et al.*[46]from the reaction of either *N*-substituted 2-chloroacetamide **87** and the pyridazin-3-one **88** or the *N*-substituted alcohol **89** and the dichloropyridazin-3-one **90**. The reaction proceeds via Smiles rearrangement under two different conditions with different base.[46] Applying similar conditions, the synthesis of pyrido[2,3-*b*][1,4]oxazin-2-one **95** was also reported starting from *N*-benzyl-2-chloroacetamide **92** and 2-bromo-3-hydroxypyridine **93** in the presence of potassium carbonate. The reaction afforded a mixture of the amide **94** as the

major and bicyclic adduct **95** as the minor products. The former upon treatment with cesium carbonate afforded **95** in quantitative yields.[47]

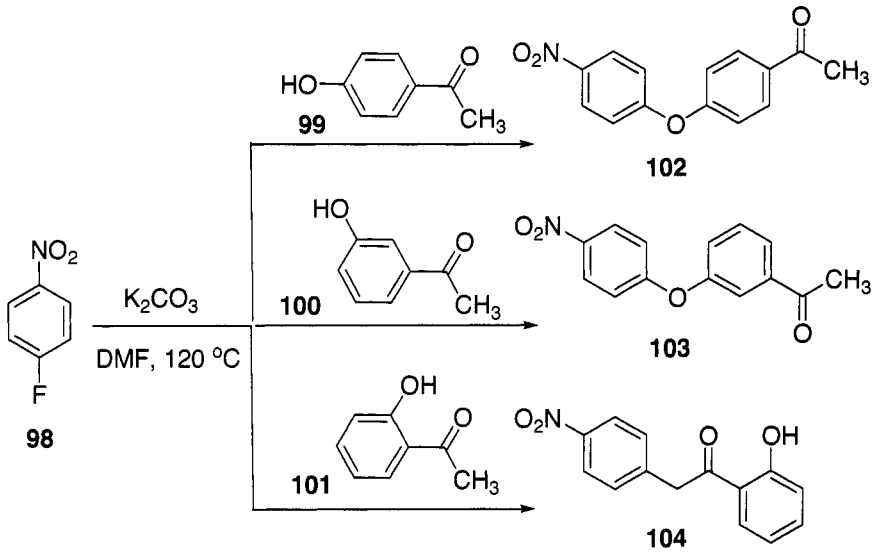


The Smiles rearrangement of the S–S type was observed in the 1,4-dithiin ring opening in diazadithiapentacene **96** leading to the synthesis of 2,3′- or 3,3′-diquinolinyl sulfide or diazadithiapentacene **97** depending on the reaction conditions.[48]

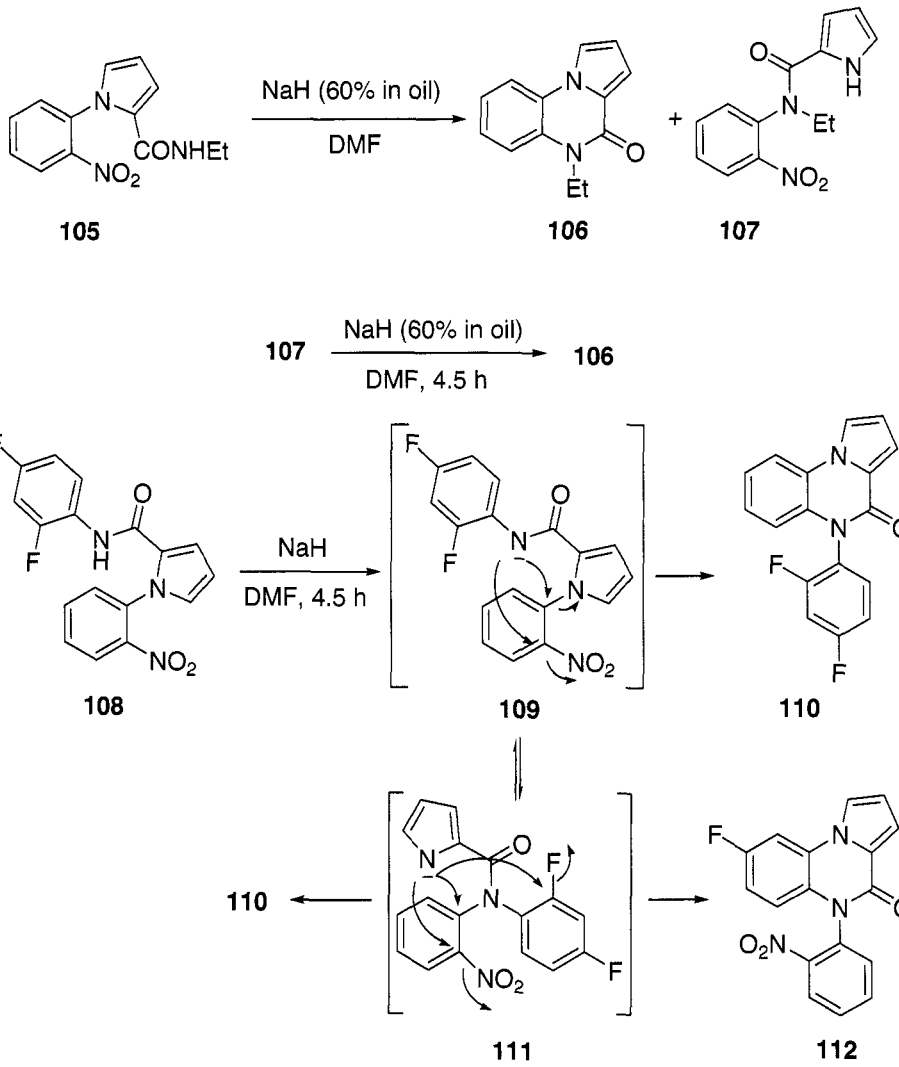


Mitchell *et al.*[50]observed that the reaction of hydroxyacetophenones (*para*- and *meta*-, **99** and **100**) with *para*-fluoronitrobenzene (**98**) in the presence of potassium carbonate in DMF at 120 °C resulted in the formation

of the desired diphenyl ethers **102** and **103**, whereas the *ortho*-hydroxyacetophenone **101** proceeded via a Truce-Smiles rerrangement furnishing a *C*-arylated product (**104**).[50] Evidence for the rearrangement emerged when the *O*-arylated product, which is an intermediate in the rearrangement was isolated when the reaction was carried out at 60 °C. Further, when this *O*-arylated intermediate was subjected to the previous reaction conditions a quantitative yield of **104** was obtained. The rate of the rearrangement is found to be substrate-dependent as seen from the formation of varying amounts of rearranged products from different substrates under similar conditions.



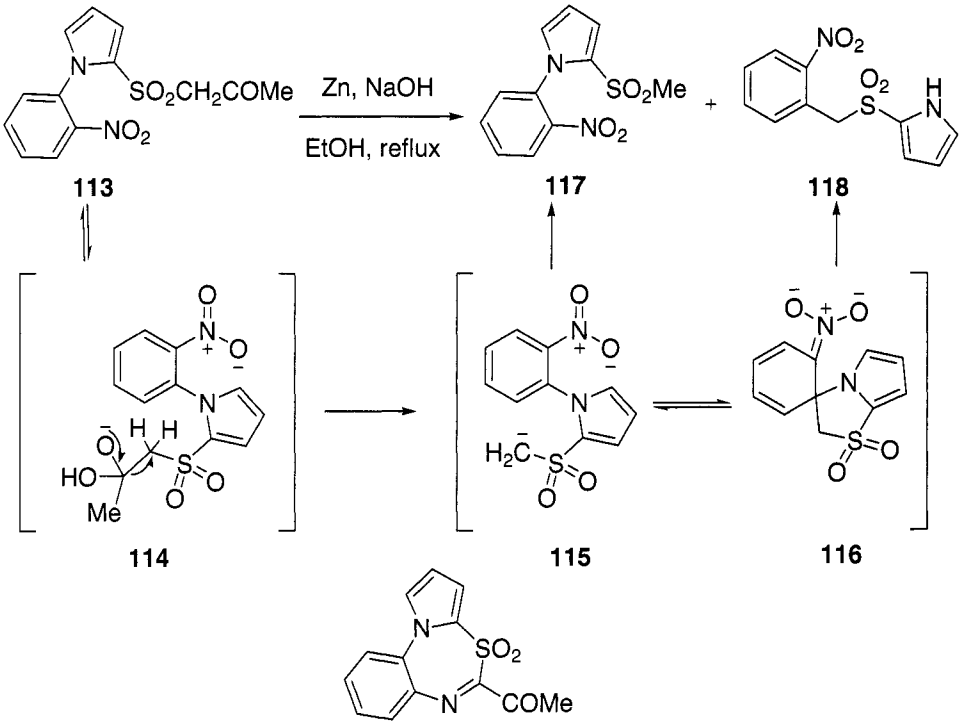
The intramolecular displacement of an aromatic nitro group by *N*-substituted carboxamides, under mild conditions, to furnish 5-substituted pyrroloquinoxalinones, has been reported.[51] The reaction of carboxamide **105** with NaH in DMF afforded pyrroloquinoxalinones **106** and a carboxamide **107**. Further, **107** when treated with NaH in DMF for 4.5 h gave **106** as the sole product. From the above reactions, it has been confirmed that the carboxamide **105** undergoes a Smiles rearrangement to give **107**.



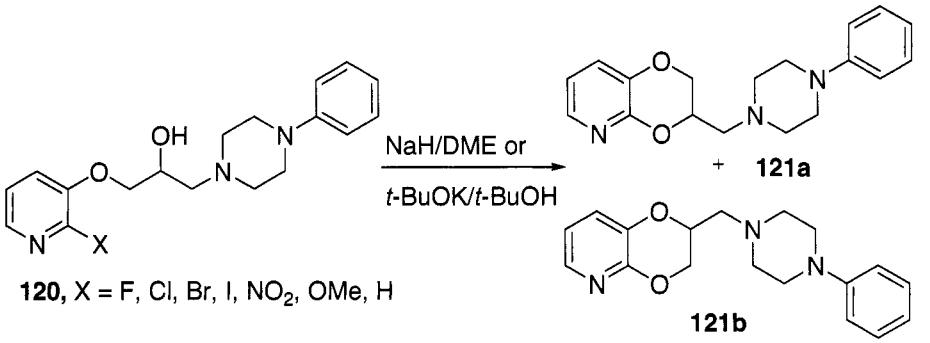
The reaction of **108** with NaH in DMF for 1.5 h afforded **110** and **112**. It has been proposed that the initially formed carboxamide anion **109** followed two paths, one leading to pyrroloquin-oxalinones **110** by direct denitrocyclization, whereas the other underwent Smiles rearrangement to give the intermediate **111** which was then converted to pyrroloquinoxalinones **112**.[51]

Kimbaris *et al.*[52] performed the reduction of sulfone **113** using zinc-sodium hydroxide anticipating the formation of the sulfone derivative of pyrrolobenzothiadiazepine **119.** However, the reaction afforded a mixture of two compounds **117** and **118.** The formation of **118** is proposed to follow a Truce-Smiles reaction[52] via the initial addition of the hydroxide ion on the

acetyl group of **113** to form the intermediate **114**, from which loss of acetate anion led to carbanion **115**. After acidification, the reaction afforded the products **117** and **118**. The formation of **118** is considered to be an unusual case of Truce-Smiles rearrangement.

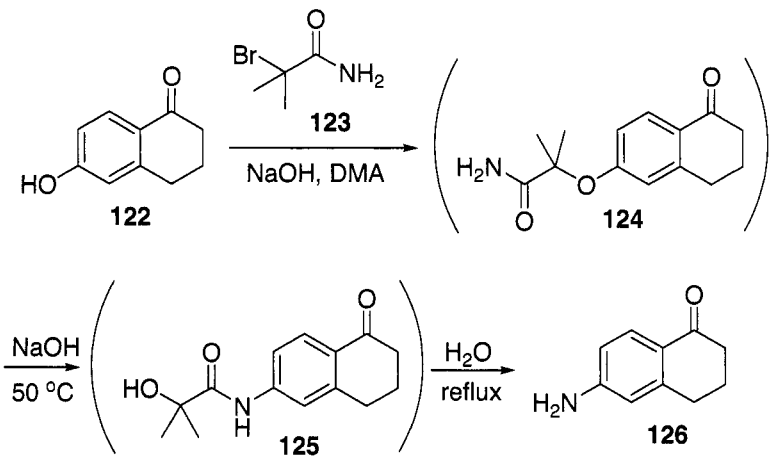


The reaction of alcohol **120** under basic conditions furnished two isomers of 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **121a** and **121b**, wherein the former is the resultant of nucleophilic aromatic substitution reaction and the latter is via Smiles rearrangement. A study of conditions affecting the rearrangement has been done by varying the nucleofuge, base and solvent. It is reported that the rearrangement is facilitated when the aromatic ring is activated by electron-withdrawing groups in the *ortho* position. Also the use of strong electron-withdrawing nitro group as leaving group increased the yield of **121**.[53]

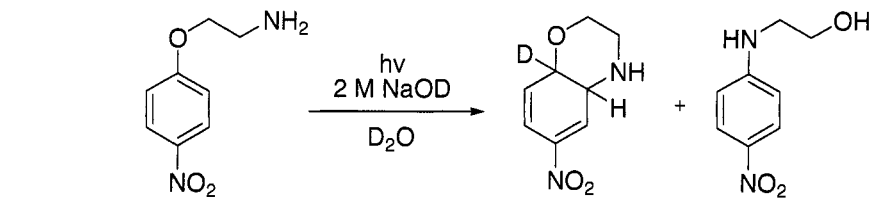


120, X = F, Cl, Br, I, NO_2, OMe, H

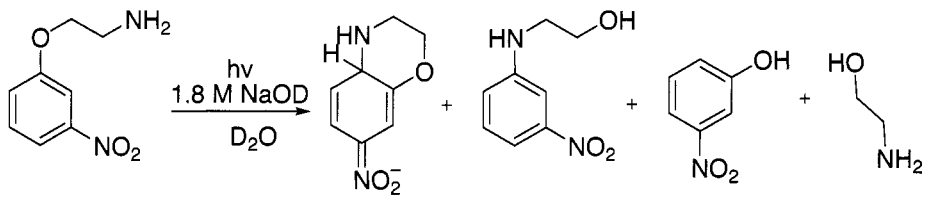
A three-step one-pot Smiles rearrangement for the synthesis of anilines from phenols with electron-withdrawing group has been developed.[54] The phenol **122**, three equiv. each of 2-bromo-2-methylpropionamide **123** and NaOH in *N*,*N*-dimethylacetamide were stirred at room temperature to afford the amide **124**. Then NaOH (9 equiv) was added to the above solution and the mixture stirred at 50 °C to get the amide **125**. Finally upon addition of water and reflux resulted in the formation of aniline **126**. All the steps have been carried out without isolating the intermediates.



The photolysis of amine **127** in D_2O containing 2.0 M NaOD in a Pyrex NMR tube at 0 °C with broadband light centered at 300 nm afforded the dihydrobenzene derivative **128** and the alcohol **129** arising from the Smiles rearrangement. Similarly, the photolysis of **130** in 1.8 M $NaOD/D_2O$ gave the Smiles photorearrangement product **132**, a nitronate anion **131**, 3-nitrophenol and ethanolamine.[55]

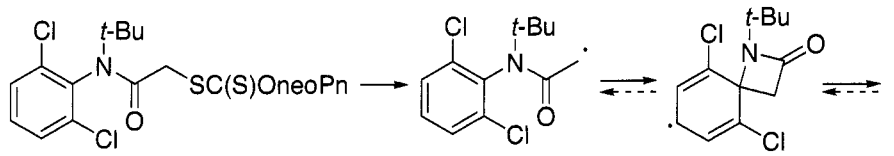


127 128 129

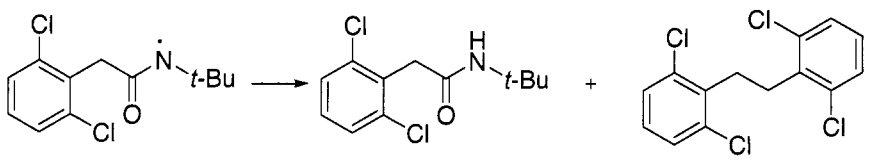


130 131 132

Bacque *et al.*[56] have reported the first ever case of a radical Smiles rearrangement going through a four-membered spiro intermediate. The xanthate **133** upon reflux with peroxide in octane afforded the Smiles product **137** via the four-membered spiro intermediate **135** along with the symmetrical diarylethane **138**.[56]

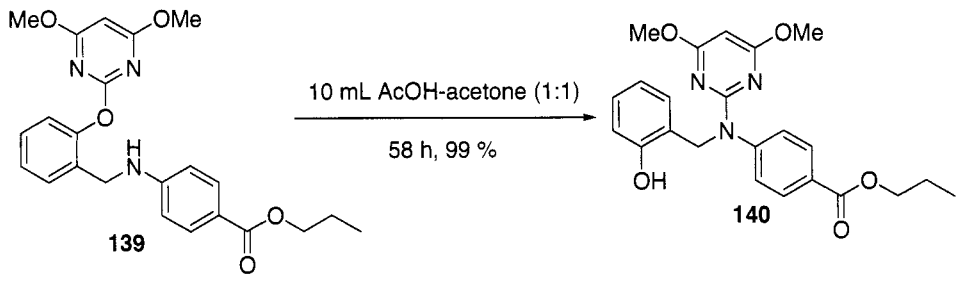


133 134 135

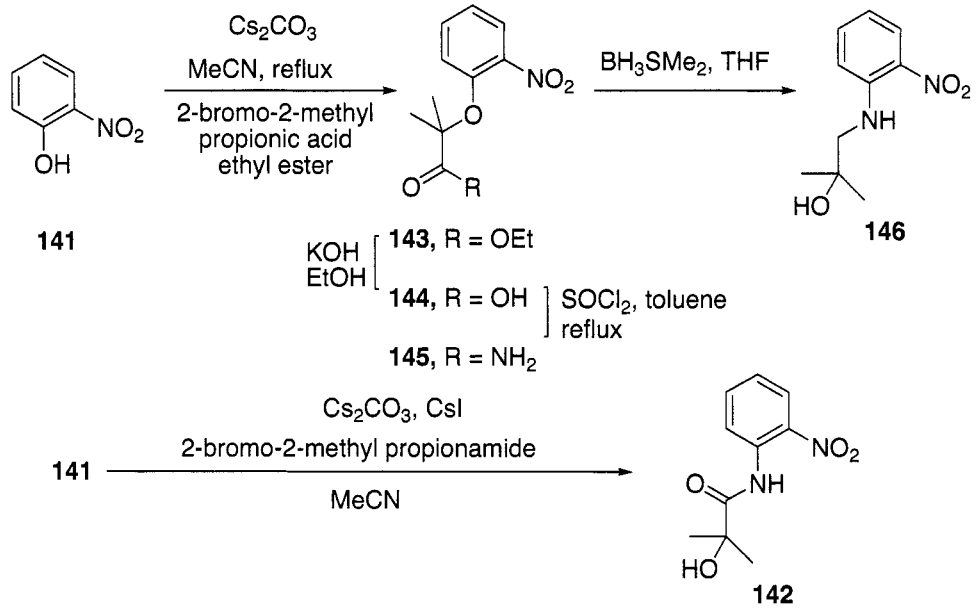


136 137 138

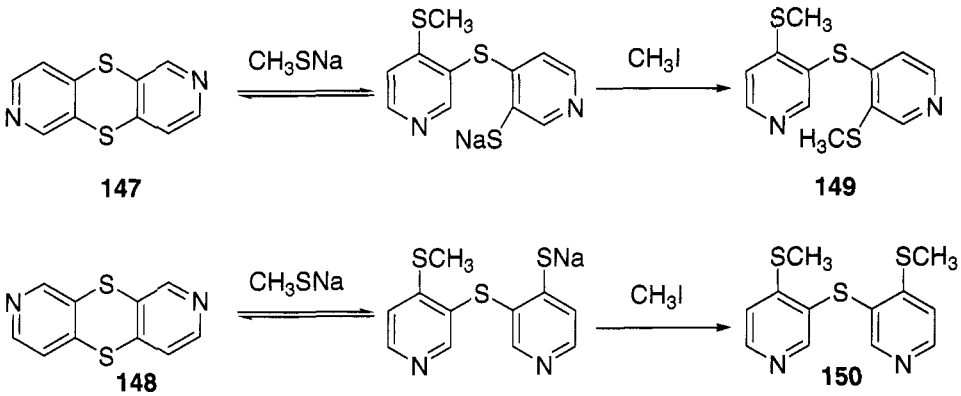
The acid-catalyzed *O-N* type Smiles rearrangement of 2-pyrimidinyloxy-N-arylbenzylamine **139** at 25 °C for 58 h. afforded quantitative yield of the rearranged alcohol **140**. It has been found that the usage of strongly acidic, neutral or basic conditions was unfavorable. It has also been envisaged from the heat of formation of the optimized structures of **139** and **140** (–115.813 and –127.822 kcal/mol respectively) that this rearrangement is a thermodynamically favorable process.[57]



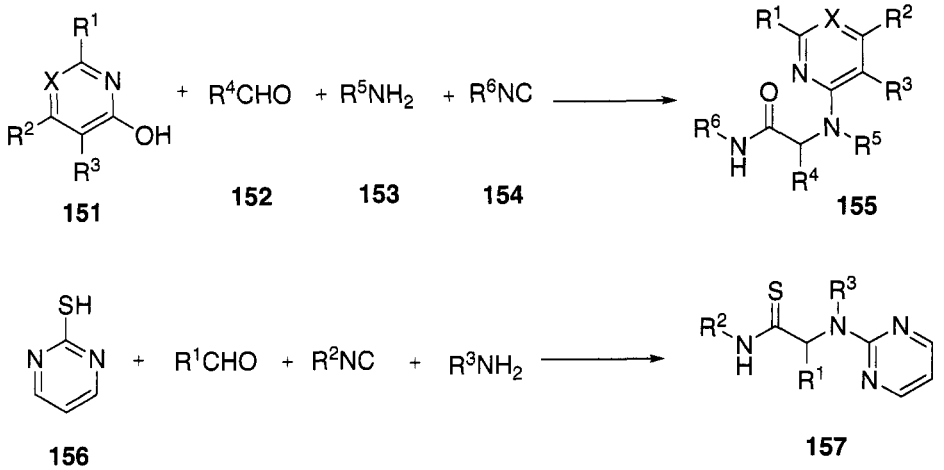
2-Nitrophenol **141** during alkylation with 2-bromo-2-methylpropionic acid ethyl ester in the presence of cesium carbonate in acetonitrile underwent Smiles rearrangement to afford the corresponding propionamide **142**. Further upon reduction of **144**, which was obtained from **141** in a three step reaction, with borane dimethyl sulfide complex in THF, a Smiles rearrangement was observed furnishing the propanol **146**.[58]



An unusual S–S type of the Smiles rearrangement has been observed during the 1,4-dithiin ring opening of **147** and **148** with sodium methanethiolate resulting in the formation of sulfides **149** and **150** after S-methylation.[59]

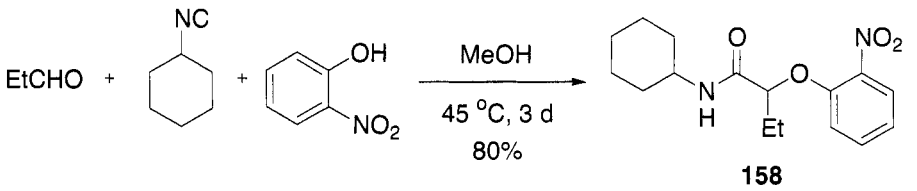


A new multi-component Ugi-Smiles coupling reaction of heteroaromatic phenols (pyridines and pyrimidines) **151** with carbonyl compounds **152**, amines **153** and isocyanides **154** involves a Smiles rearrangement to form a library of heterocyclic scaffolds **155**.[60] The first Ugi-Smiles conversion of thiols 156 was also performed. The reaction of **156** with a carbonyl compound, an amine and an isocyanide afforded the desired product **157** at 80 °C.



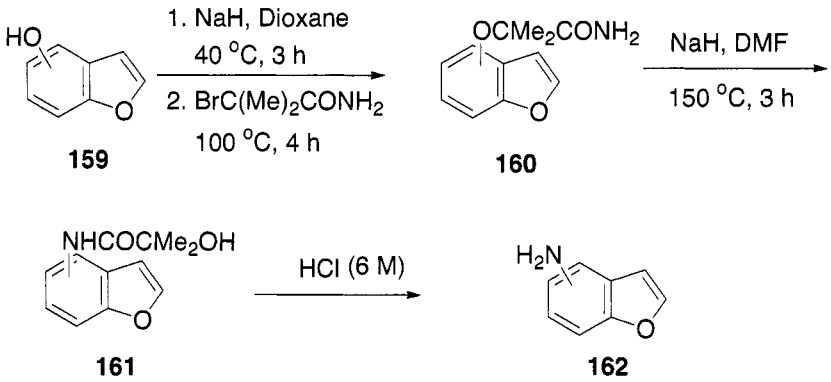
A three-component reaction comprising of Phenol-Passerini-Smiles rearrangement sequence of *o*-nitrophenol, cyclohexylisocyanide and propionaldehyde at 40 °C for 3 days provided the amide **158**. In the course of the reaction, a final Smiles rearrangement displaces all the equilibria to result in the product. Various aldehydes and isocyanides were employed to investigate the scope of this new reaction. It has been found that hindered isocyanides and aromatic aldehydes gave the desired product, whereas α,β-

unsaturated aldehydes did not result in the formation of the product.[61] Also the presence of a donor substituent on the *o*-nitrophenol had no effect on the yield of the reaction.

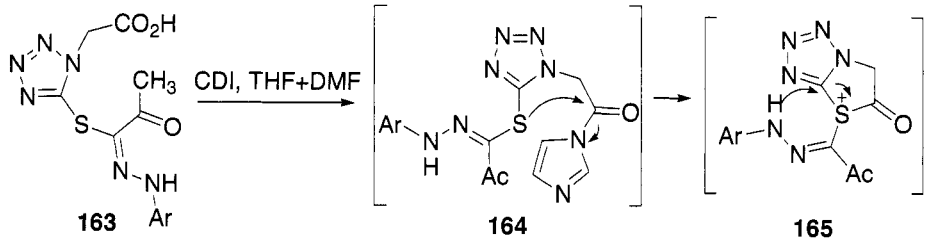


158

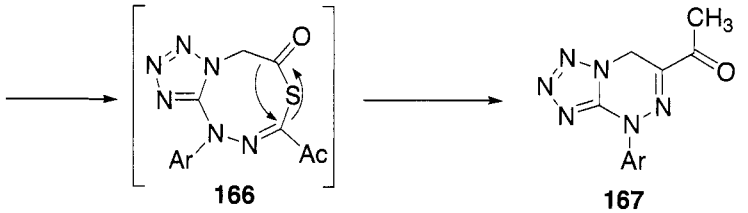
The Smiles rearrangement stategy was applied for the synthesis of amines **162**. The reaction of benzofuran **159** with 2-bromo-2-methylpropionamide afforded the amide **160**, which then underwent rearrangement in the presence of NaH in DMF at 150 °C for 3 h to yield the alcohol **161**. Finally, the hydrolysis of **161** furnished aminobenzofuran **162**.[62]



159 **160** **161** **162**



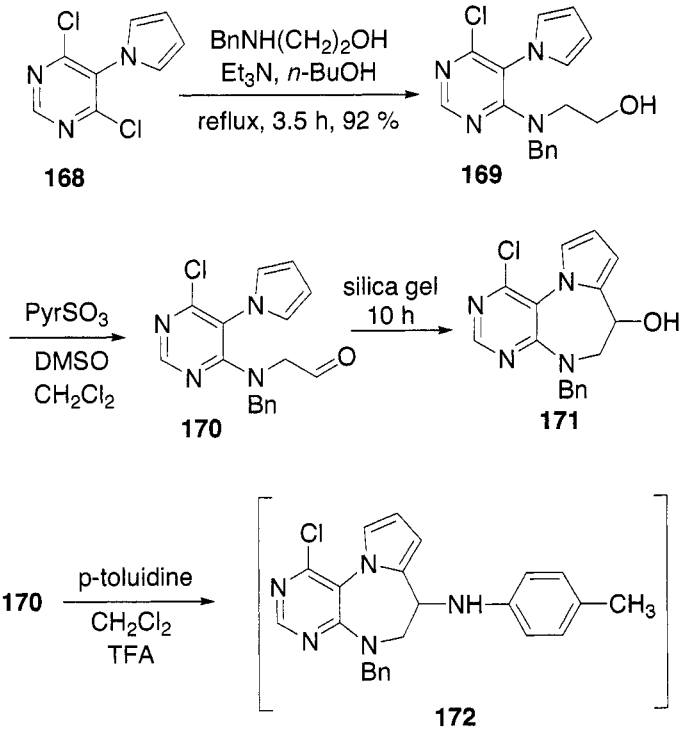
163 **164** **165**

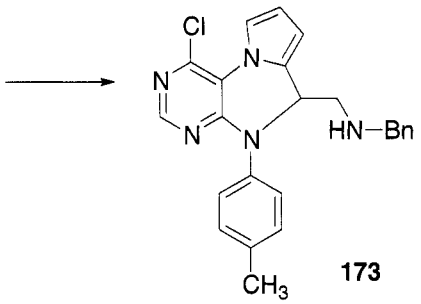


166 **167**

The carboxylic acid **163** underwent an initial loss of water and *in situ* Smiles rearrangement involving S→N migration to afford the ketone **167**. The reaction of **163** with 1,1'-carbonyldiimidazole (CDI) resulted in the formation of **164**, which then underwent intramolecular nucleophilic substitution by the sulfur atom at the activated *N*-carbonyl carbon of **164** to give the intermediate **165**. Subsequent displacement afforded **166,** which finally on ring contraction gave **167**.[63]

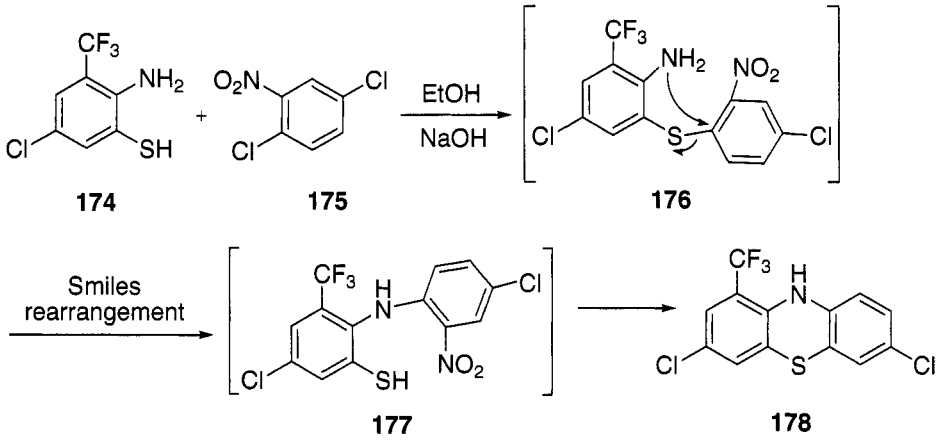
The nucleophilic substitution of the pyrimidine **168** by *N*-benzylglycinol afforded **169**, which was then oxidised under Parikh-Doering conditions to give the aldehyde **170**. Then **170** underwent cyclization to give hydroxydiazepine **171**. When the aldehyde **170** upon treatment with *para*-toluidine under Pictet-Spengler cyclization reaction conditions afforded the diazepine **172**, which was labile and quickly underwent Smiles rearrangement to afford **173**.[64]





173

Phenothiazines **178** were obtained from the Smiles rearrangement of sulfides **176** which were, in turn, prepared from the reaction of aminothiophenol **174** and nitrobenzene **175**.[65]



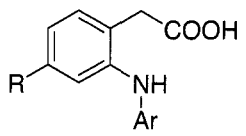
174 175 176 177 178

1.3.7.4 Synthetic Utility

The following examples illustrate the scope and utility of Smiles rearrangement towards the synthesis of some biologically important compounds.

Synthesis of analogs of antiinflammatory agent

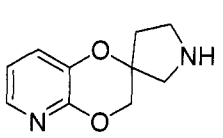
The amines **86** obtained from Smiles rarrangement of the respective amides on subsequent hydrolysis afforded compounds analogous to diclofenac (**179**).[45]



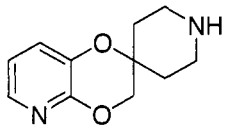
179, R = OCH_3; Ar = 2,4,6-trichlorophenyl
R = H; Ar = Ph

Synthesis of spiro-pyrrolidines

The spiro-pyrrolidine **180** and piperidine **181** containing the dioxinopyridine heterocyclic system were synthesized from 2-chloro-3-pyridinol via Smiles rearrangement.[66]



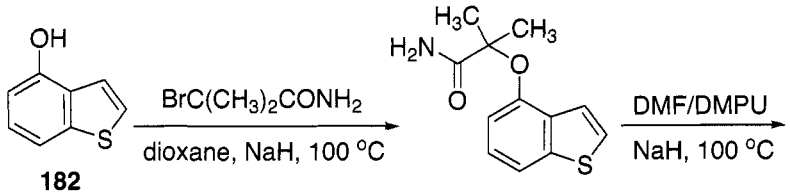
180



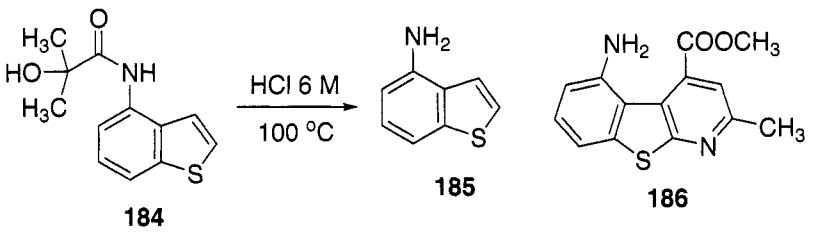
181

Synthesis of benzothienopyridine

Benzothienopyridines represent an important class of tricyclic compounds with profound biological activities. The synthesis of compounds with benzothienopyridine moiety through Smiles rearrangement has been reported. For example, the reaction of benzo[*b*]thiophen-4-ol **182** with 2-bromo-2-methylpropanamide afforded the amide **183,** which undergoes Smiles rearrangement in the presence of NaH to give the hydroxypropanamide **184**. Further treatment of **184** with HCl resulted in the formation of benzo[*b*]thiophen-4-amine **185**. Similar conditions have also been applied for the synthesis of **186**.[67]



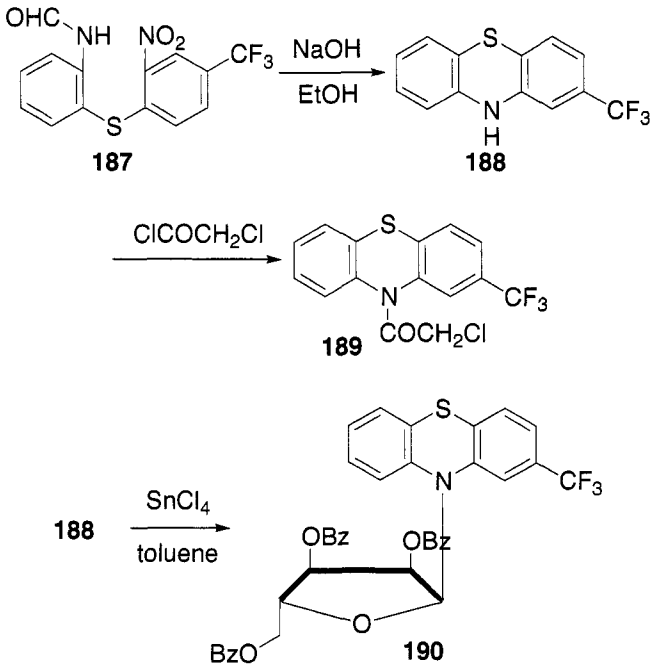
182 **183**



184 185 186

Synthesis of potential antimicrobial agents

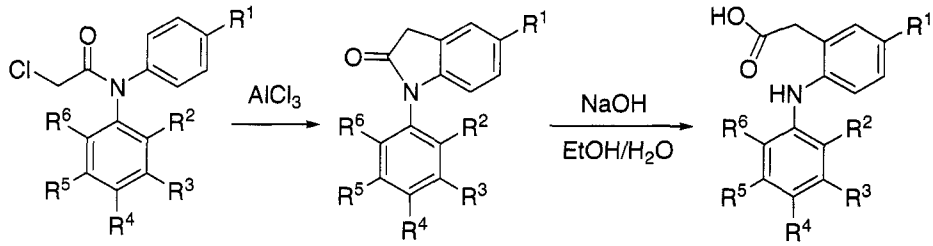
The Smiles rearrangement of the sulfide **187** with sodium hydroxide led to the formation of the tricyclic phenothiazine **188,** which upon treatment with chloroacetyl chloride afforded **189**. Further both α- and β- anomers of ribofuranosides **190** were synthesized by the condensation of these phenothiazines **188** with the sugar, β-D-ribofuranose-1-acetate-2,3,5-tribenzoate in toluene in the presence of $SnCl_4$ at 0 °C and 155–160 °C respectively.[68] These compounds were screened for their antimicrobial activities against bacteria and fungi at concentration of 100 μg/disc, using streptomycin and mycostatin as reference. These compounds showed moderate to fairly good activities against organisms such as *Escherichia Coli*, *Staphylococcus aureus* and *Aspergillus niger*.



187 188 189 190

Synthesis of intermediates for pharmacologically active compounds

N-Aryloxindoles **192,** which are intermediates for the preparation of pharmacologically active 2-(*N*-arylamino)-phenylacetic acids **193** were obtained by the Smiles rearrangement of substituted *N*-chloroacetyl-diarylamines **191**.[69] The rearrangement of 2-chloro-6-fluoro- and 2,6-difluoro-phenoxy- derivatives proceeded affording the expected product along with a major side reaction, which has been minimized by utilization of proper choice of reaction conditions.



191 **192** **193**

1.3.7.5 Experimental

*Synthesis of **21**.*

Method A: 1 M aq NaOH (1 mL, 1 mmol) was added to a suspension of **20** (1 mmol) in water (155 mL) and the mixture was stirred at 50 °C obtaining solution after 5–120 m.
Method B: 1 M solution of MeONa in MeOH (1 mL, 1 mmol) was quickly added to a 0.06 M solution of **20** (16.6 mL, 1 mmol) in DMF and the resulting mixture was stirred at 25 °C.[25]

*Synthesis of 5-amino-1,2-dihydrothieno[2,3c][2,7]naphthyridine (**68**)*

To a solution of **67** (600 mg, 2.95 mmol) in dioxane (10 mL), *t*-BuOK (600 mg, 5.35 mmol) was added and the resulting mixture refluxed for 10 min. After evaporation of the solvent, ice water (50 mL) was added to the residue. The precipitated solid was collected by filtration and the filtrate was extracted with ethyl acetate. The organic layer was treated as usual and the residue was combined to the above collected solid and recrystallized from methanol to give **68** as pale yellow needles (310 mg, 52%).[38]

1.3.7.6 References

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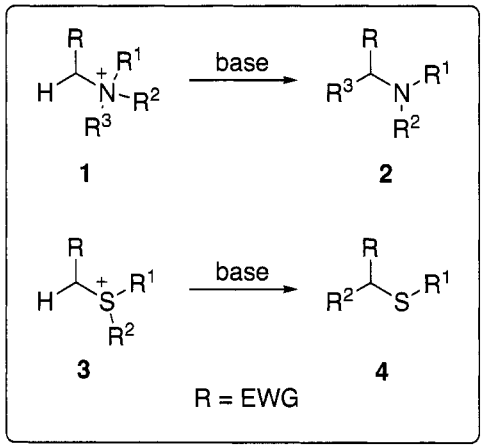
1.3.8 Stevens Rearrangement

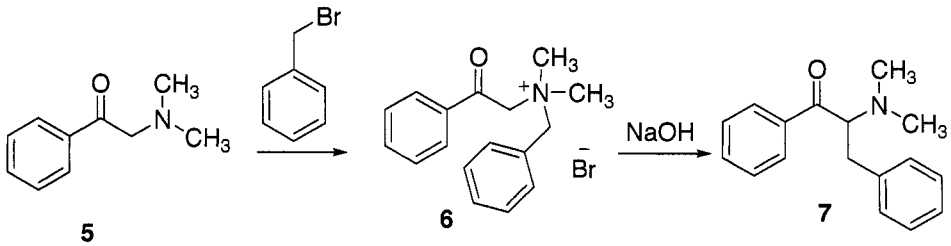
Raju Ranjith Kumar, K. Angaiyarkanni Vanitha and Subbu Perumal

1.3.8.1 Description

The transformation of quaternary ammonium salts **1** and sulfonium salts **3** to the corresponding amines **2** and sulfides **4** in the presence of a strong base is known as Stevens rearrangement.[1–29,53] The salts are usually obtained by the alkylation of the corresponding amines and sulfides. The competing reaction is the Sommelet–Hauser rearrangement.



In 1928, T. S. Stevens reported the reaction of 1-phenyl-1-(*N*,*N*-dimethyl) ethanone **5** with benzyl bromide to afford the ammonium salt **6** which upon treatment with sodium hydroxide, resulted in the formation of rearranged amine **7**.[1] The reaction of corresponding sulfur analog reaction was reported in 1932.[5]

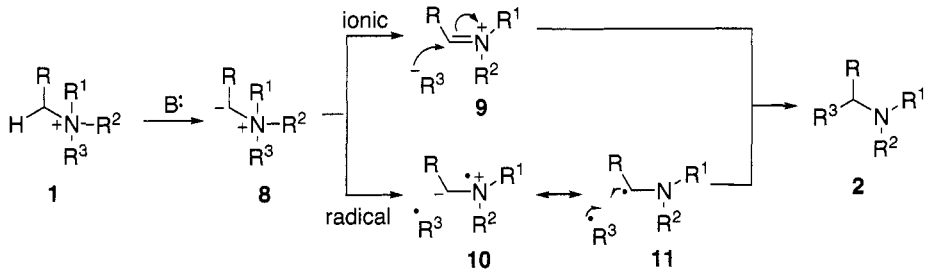


1.3.8.2 Historical Perspective

Thomes S. Stevens, a native of Renfrew, was the son of a marine engineer. His initial primary education was provided by his mother, herself a teacher before marriage. At the age of eight, he attended Paisley Grammar School and when 15 he moved to Glasgow Academy from where he obtained a bursary to study Chemistry at Glasgow University. Stevens returned to Glasgow as a Lecturer in Chemistry in 1925, having in the interim obtained a D Phil at Oxford with the support of a Ramsay Memorial Fellowship. Within three years, the Stevens rearrangement had been published in manifest display of research prowess. In this rearrangement certain carbon-based groups migrate between adjacent atoms, and for some time the reaction was thought to fall into a pattern of other formally similar rearrangements discovered mainly in Germany. However, with mischievous puckishness, Stevens had uncovered a rearrangement that went its own way; the exact pathway was not elucidated for over 40 years. Stevens was a high-calibre chess player and also a rather competitive and enthusiastic golfer.

1.3.8.3 Mechanism

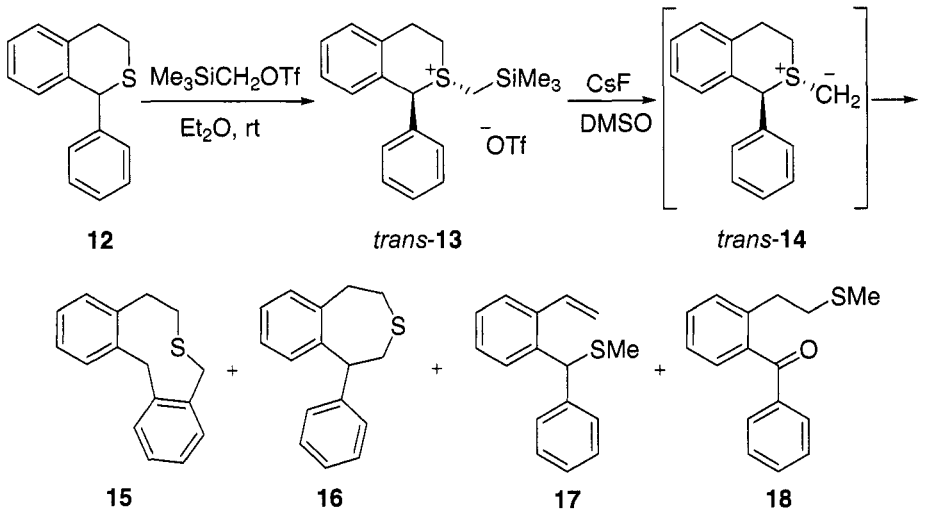
The mechanism of Stevens rearrangement for the nitrogen reaction is shown below. The key step is the formation of an ylide **8** resulting from the deprotonation of the ammonium salt **1** by a strong base, which is also supported by the electron withdrawing nature of R. The ylide **8** is converted into the rearranged product **2** either by an ionic mechanism or a radical mechanism. The former involves the formation of a cation–anion pair **9**, whilst the latter proceeds through di-radical pair **10**.



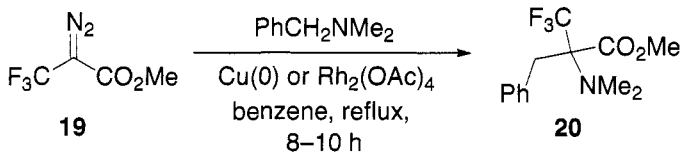
1.3.8.4 Variations and Improvements

The reaction of 1-phenyl-3,4-dihydro-1*H*-2-benzothiopyran **12** with (trimethylsilyl)methyl triflate afforded the *trans* 2-benzothiopyran triflate **13**, which upon treatment with cesium fluoride in dimethyl sulfoxide gave

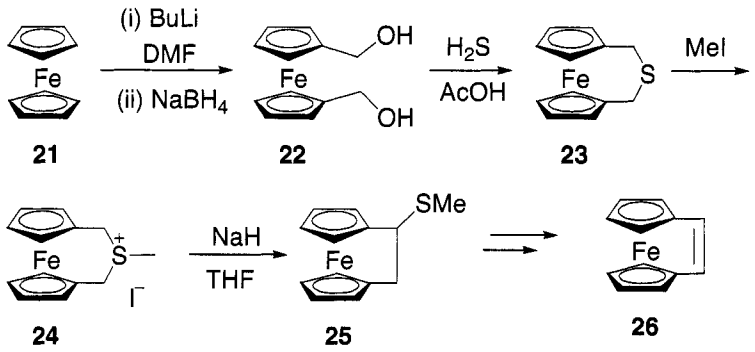
mixtures of thionine **15** due to Sommelet–Hauser rearrangement, 3-benzothiepine **16** resulting from Stevens rearrangement, the Hofmann degradation product **17** and a ketone **18**.[30]



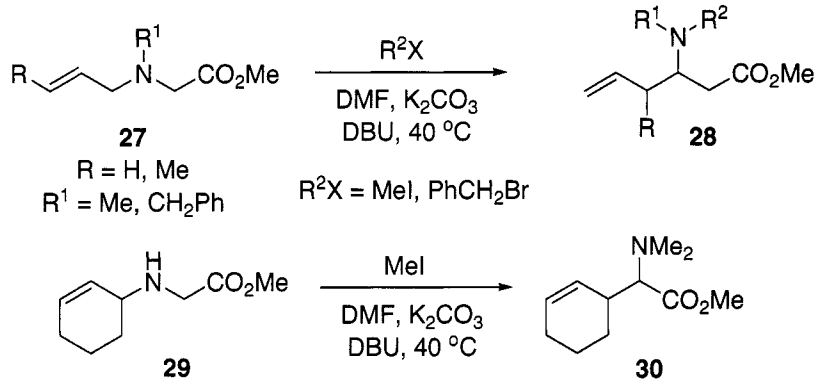
Treatment of benzyl dimethyl amine with the diazo carbonyl compound **19** in the presence of a catalytic amount of copper afforded α-trifluoromethyl phenylalanine **20** via a [1,2]-Stevens rearrangement.[31] The reaction time was reduced significantly to 1–2 h when dirhodium tetra-acetate was used as catalyst.

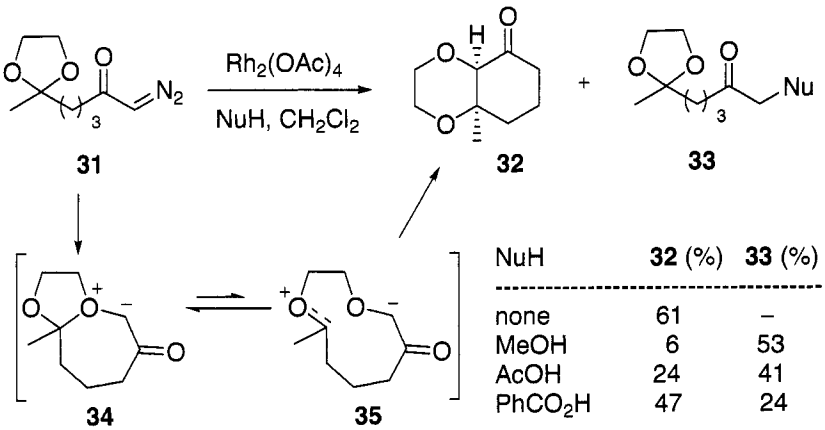


The sulfide **23** was prepared from **21** via **22** in a two step process. Alkylation of **23** with methyl iodide afforded the sulfonium salt **24**, which underwent Stevens rearrangement upon reaction with base to give the ferrocenophane **25**.[32] Oxidation of **25** followed by elimination gave the strained ethene bridged ferrocenophane **26**.



Coldham *et al.*[33] reported the one pot *N*-alkylation and [2,3]-Stevens rearrangement of *N*-allyl α-amino esters **27** and **29** in DMF in the presence of potassium carbonate and DBU to afford *N*,*N*-dialkylated allyl glycine derivatives **28** and **30**.

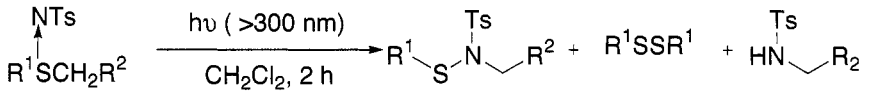




NuH	**32** (%)	**33** (%)
none	61	–
MeOH	6	53
AcOH	24	41
$PhCO_2H$	47	24

The diazo ketone **31** upon treatment with dirhodium tetraacetate underwent Stevens rearrangement resulting in a mixture of decalone **32** and a ketone **33**. It has been found that the yield of **32** is increased in the absence of a nucleophile.[34] The formation of **32** as major product indicated that the reaction proceeds through the key intermediate **34** that possesses a less-strained bicyclic structure.

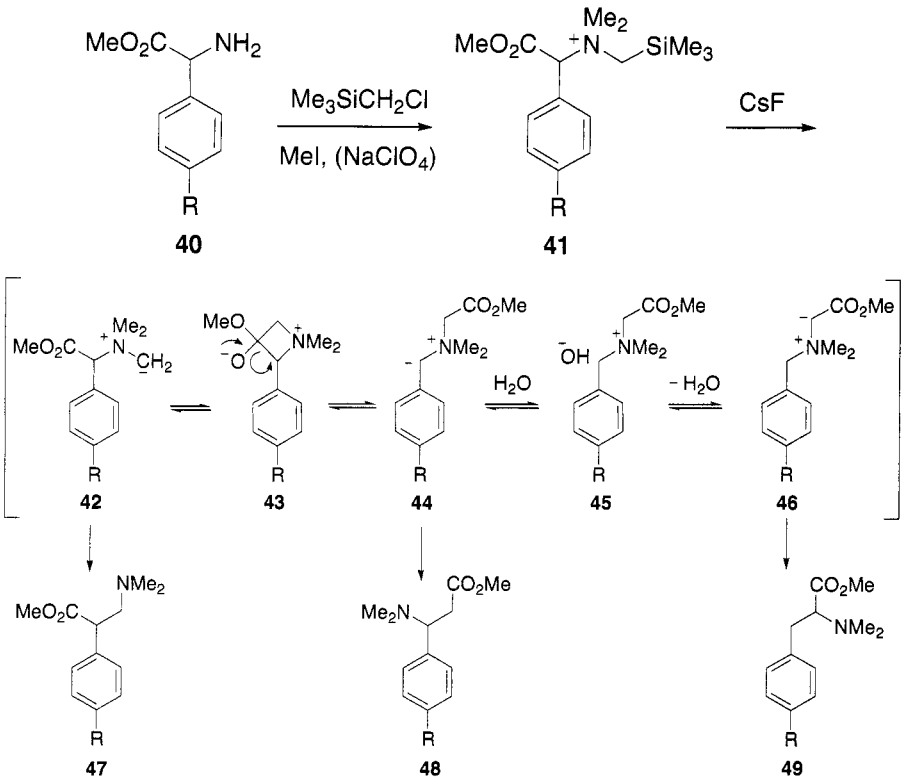
The photolysis of *S*-naphthylmethyl-*N*-*p*-tosylsulfimides **36** carried out using a high pressure mercury lamp with a Pyrex filter under nitrogen atmosphere for 2 h afforded the Stevens rearrangement product **37**, dipyridal disulfide **38** and **39**.[35] The products **38** and **39** are formed by photolysis of **37** in a secondary photochemical step. The reaction of **36e** did not proceed under similar conditions revealing that a naphthyl group is necessary in this reaction as a chromophore to accept photoirradiation and to initiate the photoreaction.



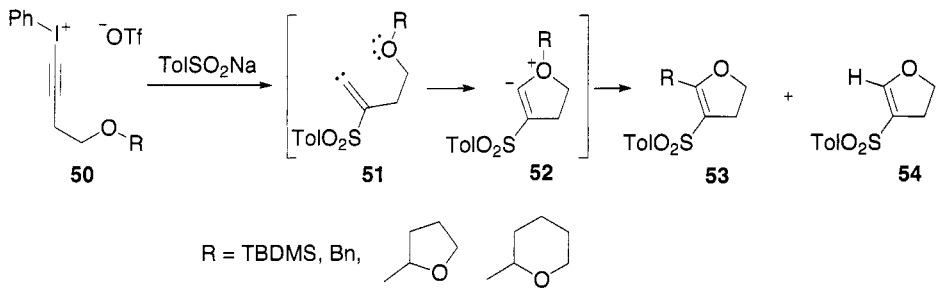
37 **38** **39**

36a: R^1 = 2-pyridyl, R^2 = 1-naphthyl
36b: R^1 = 2-pyridyl, R^2 = 2-naphthyl
36c: R^1 = Ph, R^2 = 1-naphthyl
36d: R^1 = Me, R^2 = 1-naphthyl
36e: R^1 = R^2 = Ph

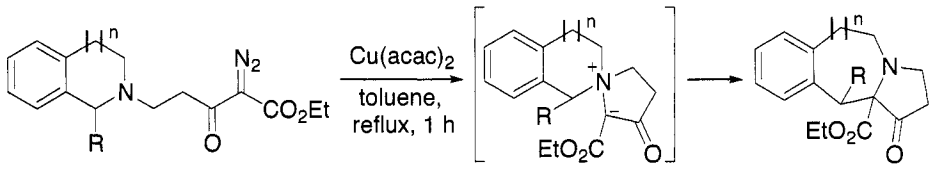
The benzylammonium salts **41** were prepared by reacting glycine methyl esters **40** with (chloromethyl)trimethylsilane followed by treatment with iodomethane. The reaction of **41** with cesium fluoride afforded a mixture of Stevens rearrangement products **47–49** formed from *N*-ylides **42**, **44** and **46** respectively.[36] Compound **49** is obtained when cesium fluoride was not predried over phosphorus pentoxide at 180 °C under reduced pressure. The ylide **42** is formed by the desilylation of **41** and the ylide **44** is due to an azetidinium ring intermediate **43**, which is the result of nucleophilic attack of the carbonyl carbon by the ylide anion **42**. The formation of **49** in the presence of a trace amount of water is due to the isomerization of **44** to **46** via ammonium hydroxide **45**.



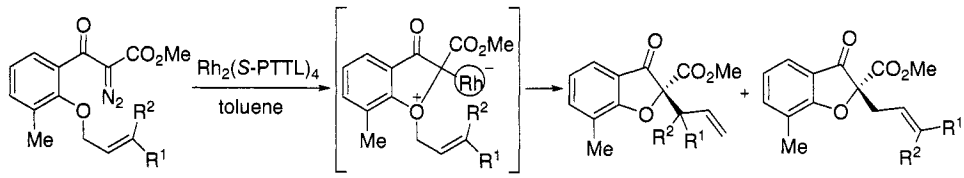
The treatment of alkynyliodonium salts **50** with mild nucleophilie *p*-toluene-sulfinate resulted in Stevens 1,2-shift of R within the ylide **52** to afford 2,3-disubstituted dihydrofurans **53** and **54**.[37, 38]



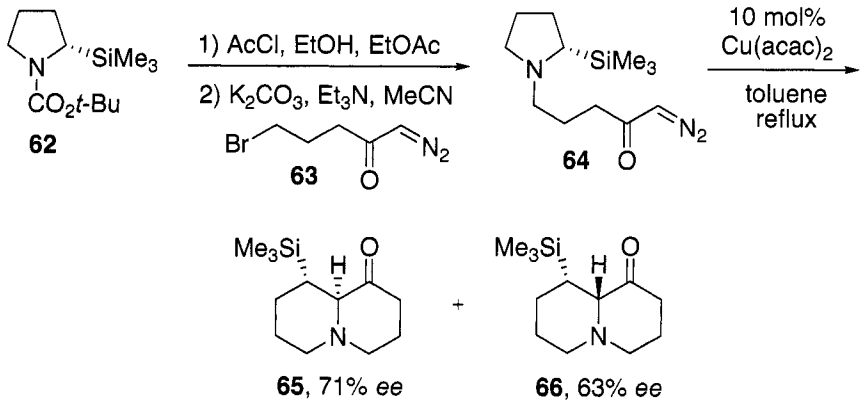
The $Cu(acac)_2$-catalyzed decomposition of the diazo ketone **55** afforded the ring-expanded 5,7-fused benzazepine **57** via the initial formation of ammonium ylide **56** followed by Stevens rearrangement of the benzylic carbon atom.[39]



Kitagaki *et al.*[40] reported an enantioselective formation of benzofuran-3-ones. The reaction of **58a–c** with chiral dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] in toluene afforded a mixture of [2,3]-sigmatropic rearrangement products **60** and [1,2]-Stevens rearrangement products **61**, with the former being favored. This reaction presumably proceeds through the allylic oxonium ylide intermediates **59**.

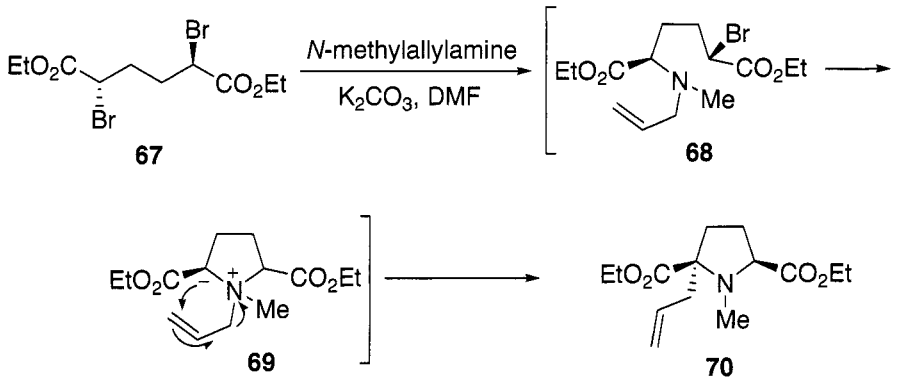


(*S*)-*N*-Boc-2-trimethylsilylpyrrolidine **62** was deprotected and alkylated with bromide **63** to afford the diazoketone **64**, which underwent Stevens rearrangement upon treatment with $Cu(acac)_2$ at reflux furnishing quinolizidines **65** and **66** in 58% yield.[41]

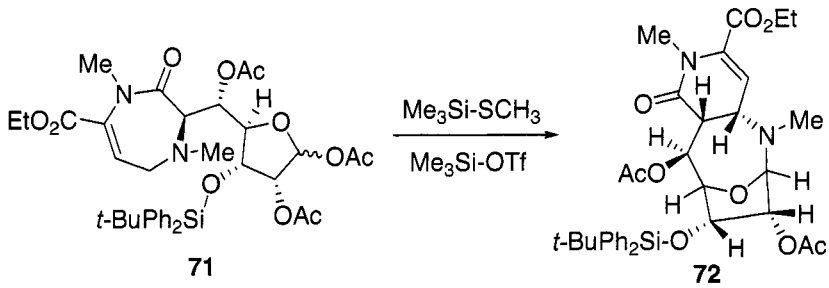


Treatment of the dibromide **67** with *N*-methylallylamine gave the [2,3]-Stevens rearranged product **70** in one pot via the intermediates **68** and

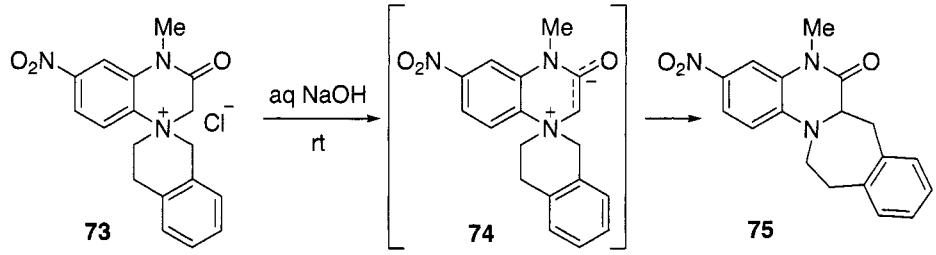
69.[42] It has been found that the reaction proceeds rapidly and at lower temperature than via the quaternisation route.



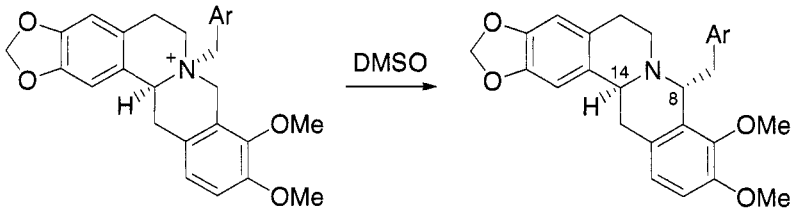
The Stevens rearrangement of the diazepanone **71** in the presence of $Me_3Si\text{-}SCH_3$ and $Me_3Si\text{-}OTf$ led to the formation of the diacetate **72**.[43]



The Stevens rearrangement of carbonyl stabilized ylide **73** with aqueous sodium hydroxide at room temperature afforded the quinoxalinone **75** through the migration of the benzyl moiety of the intermediate ylide **74**.[44]



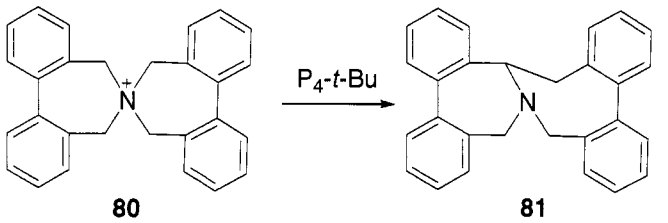
The reaction of *cis*-(8-arylmethyl)canadinium salts (*cis*-**76** or **77**) with dimsylsodium in DMSO afforded the 8-arylmethylcanadine **78** and **79** derivative stereoselectively with a *cis*-configuration between H-14 and the substituent at C-8.[45]



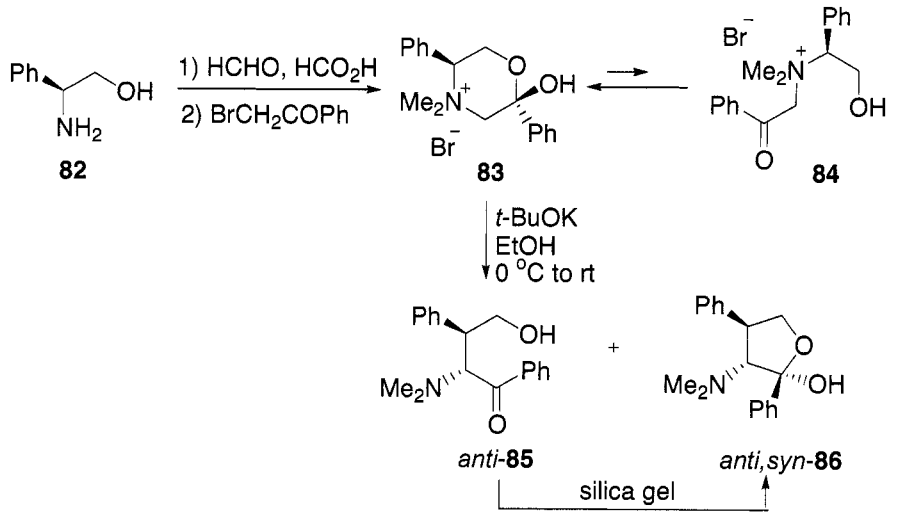
76 *cis* Ar = Ph
77 *cis* Ar = 4-MeO-C_6H_4

78 *cis* Ar = Ph
79 *cis* Ar = 4-MeO-C_6H_4

Stevens rearrangement of highly symmetric spirobi[dibenzazepinium] cation **80** in the presence of P_4-*t*-Bu furnished exclusively the ring-expanded tertiary amine **81**.[46]



80 **81**

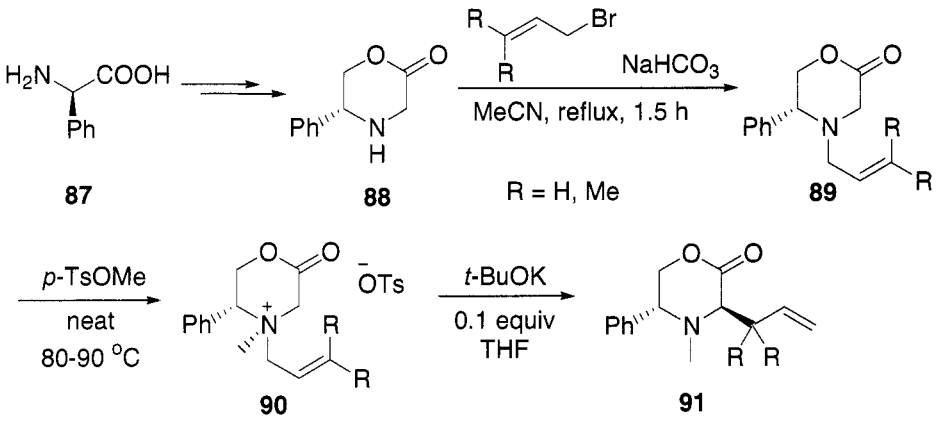


82 **83** **84**

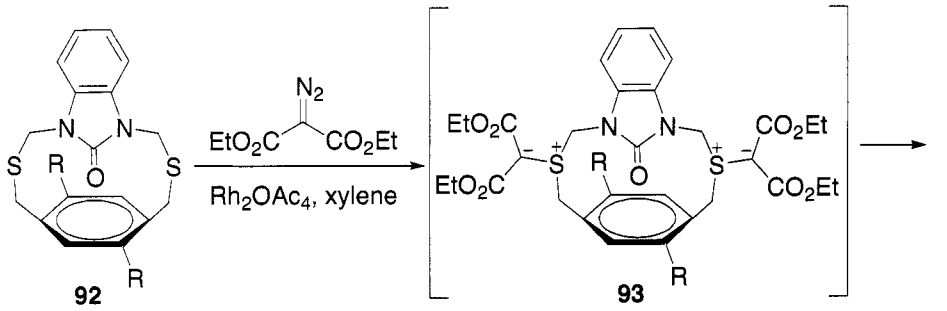
anti-**85** *anti,syn*-**86**

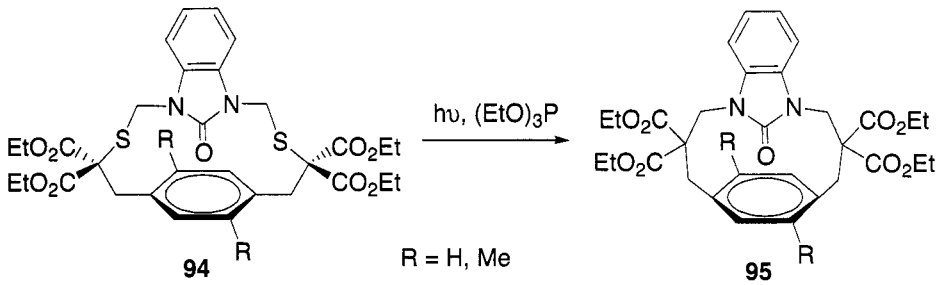
The racemic ammonium salt **83** was prepared from phenylglycinol **82** in two steps *viz.* *N*-methylation followed by treatment with bromoacetophenone. From NMR studies, it is confirmed that the salt **83** exists predominantly in a cyclic hemiacetal form. The Stevens rearrangement of **83** with potassium *tert*-butoxide in ethanol afforded the hydroxyl ketone **85** as a single diastereomer along with a hemiacetal **86**.[47] Also it was shown that the ketone **85** tautomerized to **86** on silica gel.

The 1,4-oxazin-2-one **88** was obtained from *D*-phenylglycine in two steps, which upon *N*-allylation afforded **89**. Further reaction of **89** with *p*-TsOMe furnished the epimeric mixture of *trans*- and *cis*-**90**. Treatment of this epimeric mixture with *t*-BuOK afforded the Stevens rearranged product **91** [(3*R*)- and (3*S*)- **91**] in 30 % yield as a 7:1 mixture of stereoisomers.[48]



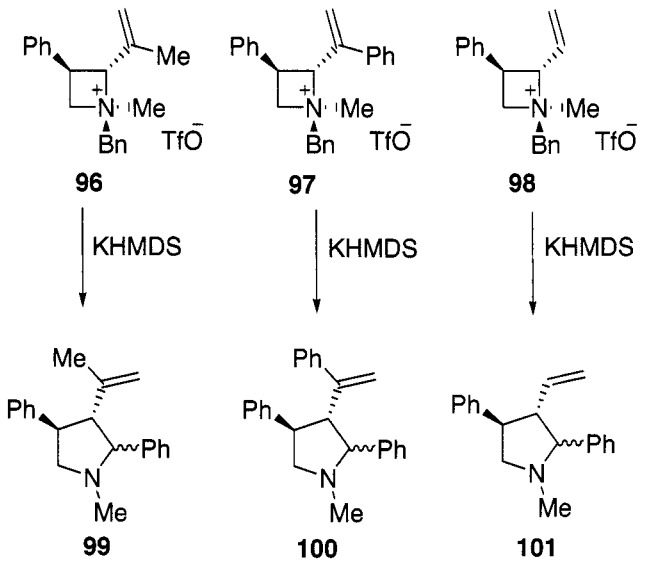
A rhodium(II)-catalyzed double Stevens rearrangement of cyclophanes **92** led to ring expansion affording benzimidazolidinone cyclophanes **94** via the sulfonium intermediates **93**.[49] Irradiation of **93** in triethyl phosphite resulted in extrusion of the bridging sulfur atoms to give ring-contracted [3.3]heterophanes.





94 95

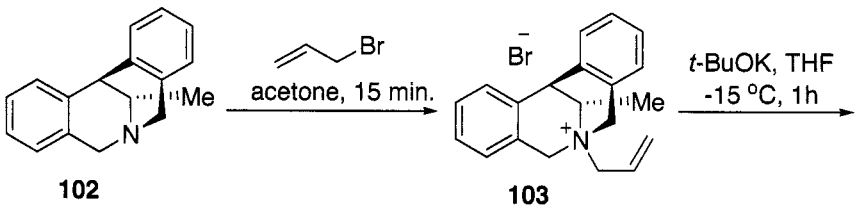
The Stevens rearrangement of azetidinium trifluoromethanesulfonate salts **96–98** possessing a methyl and benzyl group on the nitrogen in the presence of KHMDS afforded 3-alkenylpyrrolidines **99–101** regioselectively.[50]



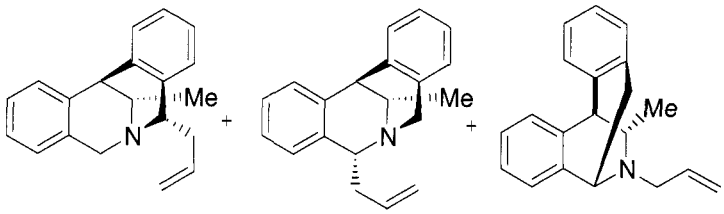
96 97 98

99 100 101

The reaction of **102** with allyl bromide in refluxing acetone led to the quaternary salt **103**. Treatment of **103** with *t*-BuOK gave a mixture of **104** as major (55%), **105** (5%) along with the Stevens rearranged product **106** (5%).[51]

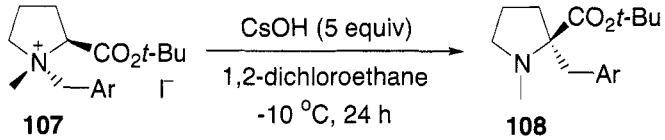


102 103



104, (5*S*, 12*S*) **105**, (5*R*, 12*R*) **106**

The Stevens rearrangement of *N*-(arylmethyl)proline ammonium salts **107** in the presence of cesium hydroxide in 1,2-dichloroethane afforded the corresponding α-(arylmethyl)proline *t*-butyl esters **108** with 84–90% *ee*.[52]



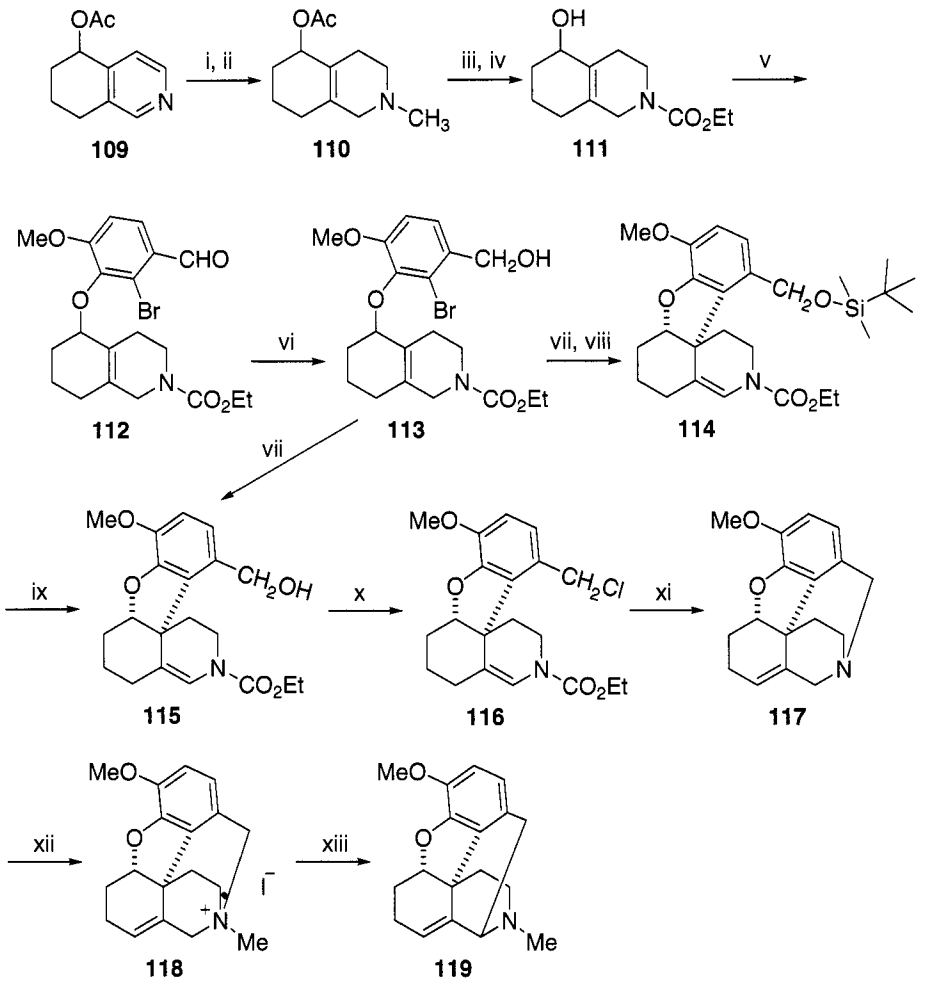
107 **108**

Ar = 4-Me-Ph, 4-MeO-Ph, 4-F-Ph

1.3.8.5 Synthetic Utility

Total synthesis of (±)–desoxycodeine.

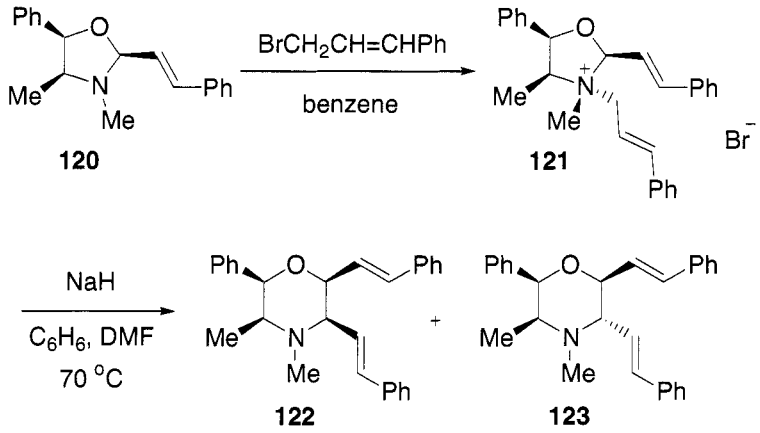
The reaction of 5-acetoxy-5,6,7,8-tetrahydroisoquinoline **109** with MeI followed by reduction afforded the octahydroisoquinoline **110**, which upon treatment with ethyl chloroformate followed by hydrolysis gave **111**. The condensation of **111** with 2-bromoisovanillin afforded **112**, which was reduced to give the benzyl alcohol intermediate **113**. Heck reaction of **113** led to the formation of O-ring affording **115**. The yield of the above intramolecular cyclization was increased significantly via prior protection of the alcohol in **113** as silyl ether **114**. Conversion of **115** to benzyl chloride **116** was achieved via the treatment with NCS and triphenylphosphine. Further, Heck reaction of **116** afforded the tertiary amine **117** via an intramolecular *N*-benzylation. The amine **117** was converted into the corresponding *N*-methylammonium iodide **118**, which was then subjected to Stevens rearrangement with PhLi to afford (±)–desoxycodeine **119** in 83 % yield.[54]



i) MeI, CH_2Cl_2, rt; ii) $NaBH_4$, MeOH, 0 °C; iii) EtOOCCl, $KHCO_3$, $ClCH_2CH_2Cl$, reflux
iv) NaOH, MeOH, 0 °C; v) 2-bromoisovanillin, DEAD, $(n\text{-}C_4H_9)_3P$, THF;
vi) $NaBH_4$, MeOH, 0 °C vii) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, 120-130 °C;
viii) TBDMSCl, imidazole, THF; ix) $(n\text{-}C_4H_9)_4N^+F^-$, THF, rt; x) NCS, PPh_3, THF, rt;
xi) $Pd(PPh_3)_4$, Et_3N, MeCN, 120-130 °C; xii) MeI, CH_2Cl_2, rt; xiii) PhLi, ether, 0 °C

Synthesis of enantiopure morpholines.

The reaction of oxazolidines **120** with an excess of cinnamyl bromide afforded oxazolidinium bromide **121** as a mixture of diastereoisomers at the nitrogen center. Treatment of **121** with NaH in DMF furnished a mixture of diastereomeric morpholines **122** and **123**.[55]



1.3.8.6 Experimental

General procedure for the synthesis of ***99–101***

A solution of KHMDS (0.5 M in toluene, 2.4 mL, 1.2 mmol) was added dropwise at –78 °C to a solution of 2-alkenylazetidinium salt (1 mmol) in THF (6 mL). The temperature was slowly raised to –30 °C and the mixture was hydrolysed at this temperature by the addition of a saturated aqueous solution of ammonium chloride (5 mL). The resulting oil was further purified by flash chromatography to afford **99–101**.[50]

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Name Reactions for Homologations
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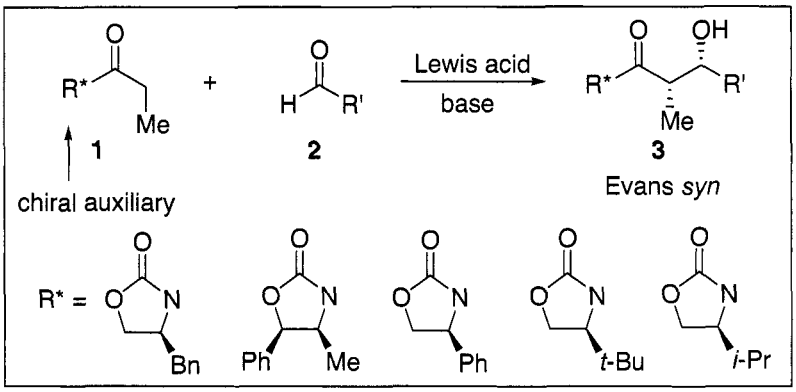
Chapter 2. Asymmetric C–C bond formation

2.1 Evans aldol reaction

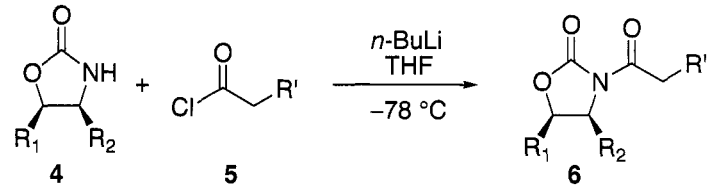
Ji Zhang

2.1.1 Description

The aldol reaction is an important carbon–carbon bond formation reaction. The general concept of the reaction involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β-hydroxy ketone, or "aldol", a structural unit found in many naturally occurring molecules and pharmaceuticals. Since the aldol addition reaction creates two new stereocenters, up to four stereoisomers may result. The Evans aldol reaction[1] performs a diasteroselective aldol transformation using an Evans's acyl oxazolidinone (also known as Evans chiral auxiliary), a chiral carbonyl compound that creates a temporary chiral enolate for the aldol addition. Upon subsequent removal of the auxiliary, the desired aldol stereoisomer is revealed.[2]

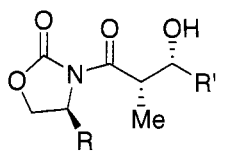


The *N*-acyloxazolidinone derivatives **6**, are easily prepared by acylation of commonly available chiral oxazolidinones **4** (both enantiomeric forms) with acyl chlorides **5**.[3]

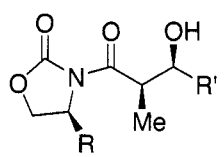


2.1.2 Historical Perspective

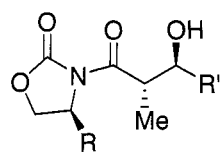
The use of a chiral auxiliary for the asymmetric aldol addition was first reported by Evans and co-workers in 1981, wherein dibutylboron enolates of *N*-acyl oxazolidinones were employed to afford the *syn*-aldol (Evans *syn*, **3′**) adducts with virtually complete stereocontrol.[1a] This reaction is general for a wide range of aldehydes and imide enolates. It was found that titanium (IV) enolates of propionyloxazolidinones also undergo the aldol addition under chelation control, high selectivities are observed although two or more equivalents of amine base are required. The study by Thornton and co-workers in 1986 found diethyl ether provides a nearly a fivefold increase in diasterofacial selectivity as compared to THF for titanium enolates.[4] In 1991, Heathcock extended the scope of the Evans asymmetric aldol reactions through the judicious selection of Lewis acid and reaction conditions. It was demonstrated that the selective generation of either "non-Evans" *syn* aldol adduct **7** or anti adduct **8** could be achieved.[5] This discovery considerably amplified the synthetic utility of Evans aldol reaction.[6] In 1997, Crimmins and co-workers further developed the Evans aldol reaction by using titanium enolates of thiazolidinethione chiral auxiliaries.[7] Either the "Evans" or "non-Evans" *syn* aldol adducts can be prepared in high diastereomeric purity by simply changing the stoichiometry of the Lewis acid relative to the starting material and the nature of the amine base.[8] A significant advantage of the thiazolidinethiones is that they are more readily cleavable auxiliaries in comparison to the oxazolidinones or oxazolidinethiones.[9] Since the pioneering work of Evans,[10] this synthetic methodology has become widely used by the synthetic community for the stereoselective synthesis of natural products and pharmaceutical targets.[11]



3′
Evans *syn*



7
non-Evans *syn*

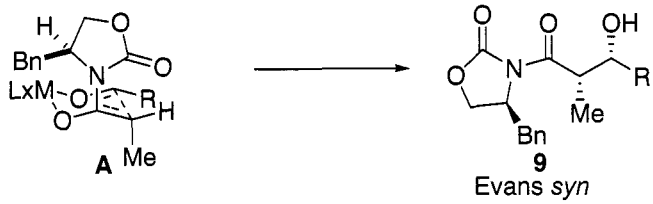


8
anti

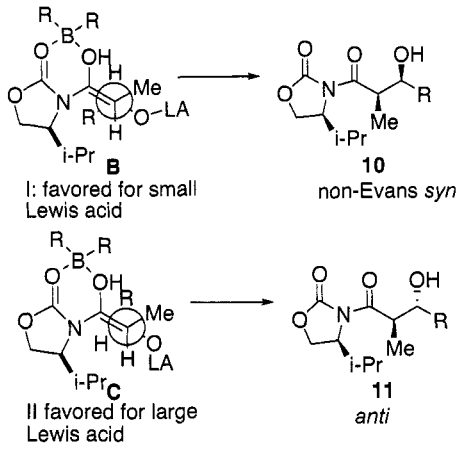
2.1.3 Mechanism

The boron-mediated aldol reaction of an Evans's acyl oxazolidinone with an aldehyde affords the Evans-*syn* aldol adduct **9**. The process proceeds *via* formation of the *Z*-enolate that reacts with the aldehyde, presumably through a well ordered six-membered, chair-shaped "Zimmerman–Traxler" model

A,[12] to afford essentially a single diastereomeric aldol product out of four possible isomers.

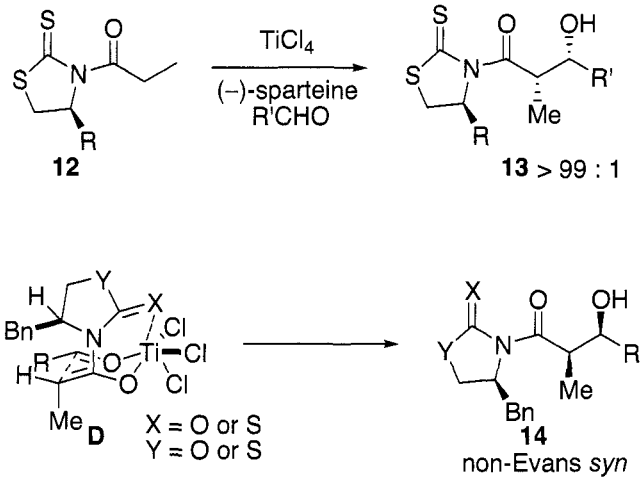


Either the *syn*- or *anti*-aldol adducts can be obtained from the Evans reagent, or from imide-derived enolates under Lewis acid catalysis to give anti or "non-Evans" *syn* aldol adducts. Depending upon the specific reaction conditions (the size of Lewis acid), the stereochemical outcome of the diastereoselective aldol reaction is rationalized via formation of the open transition states.[5] *syn* aldol **10** and *anti* aldol **11** are given from transition states **B** and **C** respectively. If the Lewis acid is small, transition state **B** is preferred because it minimizes gauche interactions about the bond formation. However, in the case of a large Lewis acid, transition state **C** becomes competitive because of the methyl-Lewis acid interaction in **B**. For example, Et_2AlCl which is considered a bulky Lewis acid gives the *anti*-isomer because the O–Al bond is short and ligands are relatively large.



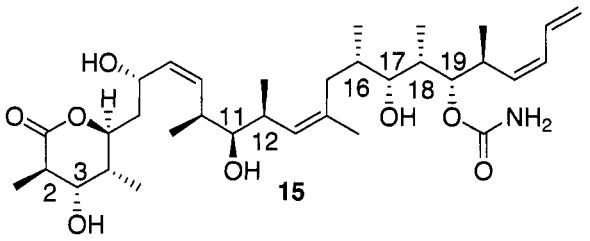
A proposed highly ordered chelated transition states for aldol additions using titanium enolates of thiazolidinethiones has been proposed by Crimmins.[8,9] Crimmins's thiazoldinethione aldol proceeds with high diasteroselectivity for the "Evans" or "non-Evans" *syn*-product depending on the stoichiometry of the Lewis acid as well as the nature and amount of the

amine base used. When 2 equivalents of (–)-sparteine or TMEDA as the base and 1 equivalent of $TiCl_4$ were used, selectivities between 97 : 3 and > 99 : 1 were obtained for the Evans *syn* product. Alternatively, when the ratio is inverted to use 1 equivalent of amine base, such as DIEA, TMEDA or (–)-sparteine and 2 equivalents of $TiCl_4$, the non-Evans *syn* aldol was generated. The change in facial selectivity is considered as the result of switching of mechanistic pathways between chelated and nonchelated transition states.[8]



2.1.4 *Reaction Types and Synthetic Utility*

Evans aldol reactions are well understood in terms of reaction mechanism and have a board substrate scope. An optimum chiral auxiliary often exerts powerful control over the stereochemical course of the reaction in a predictable manner. The popular use of these readily available and inexpensive chiral auxiliaries has had a great impact on the asymmetric synthesis of complex natural products as well as novel active pharmaceutical ingredients.[11] Evans chiral oxazolidinone mediated *syn* propionate aldol reactions have proven to be both reliable and practical and received widespread application in API synthesis on multi-kilogram scales. One impressive application is in large-scale synthesis of the anti-cancer marine natural product (+)-discodermolide **15** by Novatis.[13] After evaluating all reported synthesis of discodermolide and its fragments, they decided to utilize two benzyl oxazolidinone-based aldol reactions to install 8 out of the 13 stereocenters embedded in discodermolide at C2–C3, C11–C12, C16–C17, and C18–C19.



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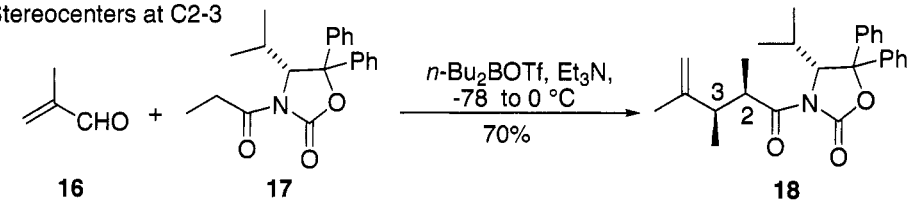
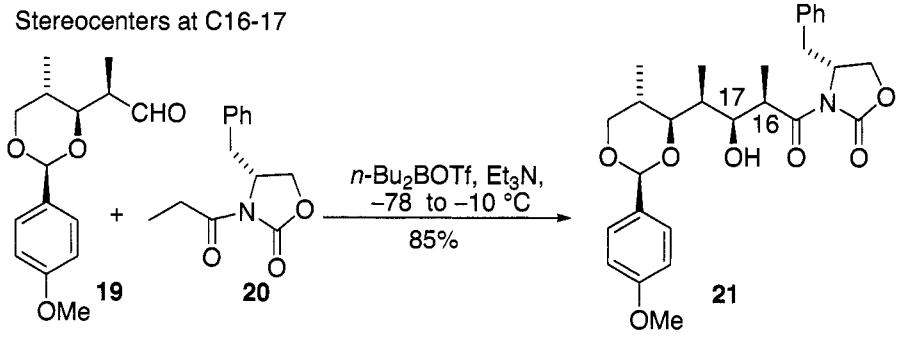
Stereocenters at C2-3



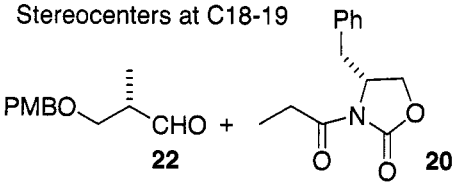
16 17 18

Stereocenters at C16-17



19 20 21

Stereocenters at C18-19



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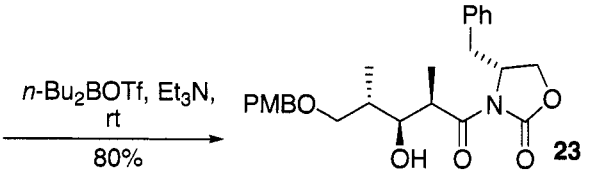
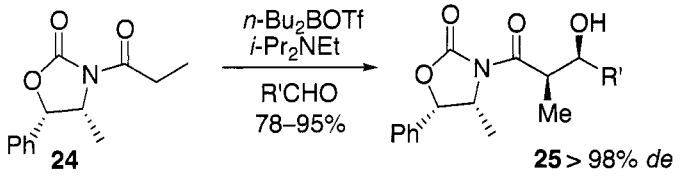
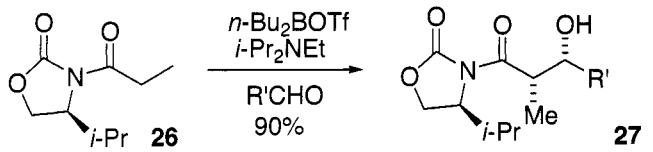


23

Propionate Aldol Reactions

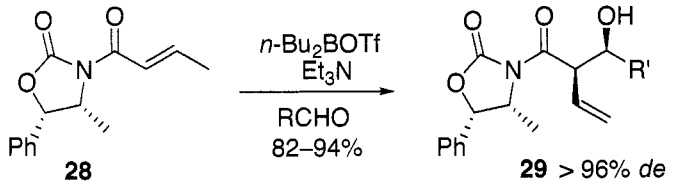
The boron-mediated aldol reaction of **24** (or **26**) with aldehydes to give the *syn* aldol adduct **25** (or **27**) is one of the most reliable aldol bond formations.[1a, 14]





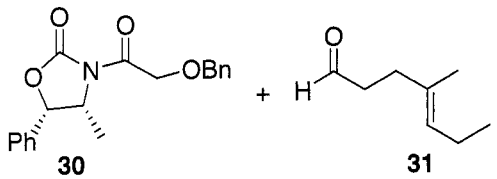
Crotonyl Enolate Aldol Reactions

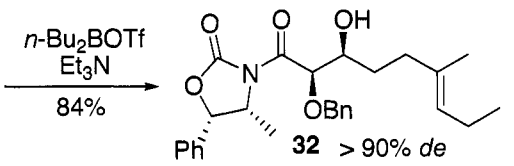
Boron enolates of the *N*-crotonyloxazolidinones have been shown to afford the *syn*-aldol adducts.[15]



α-Alkoxyacetate Aldol Reactions

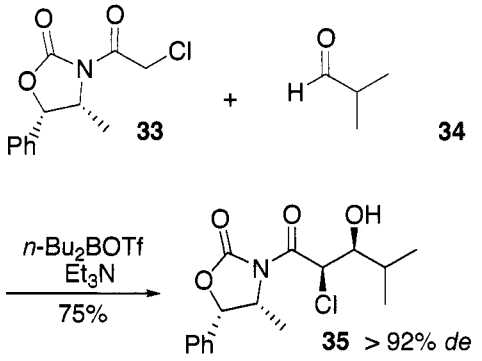
The enolates derived from *N*-α-alkoxyacetyloxazolidinones provide *syn* aldol adducts in good yield and selectivity.[16]





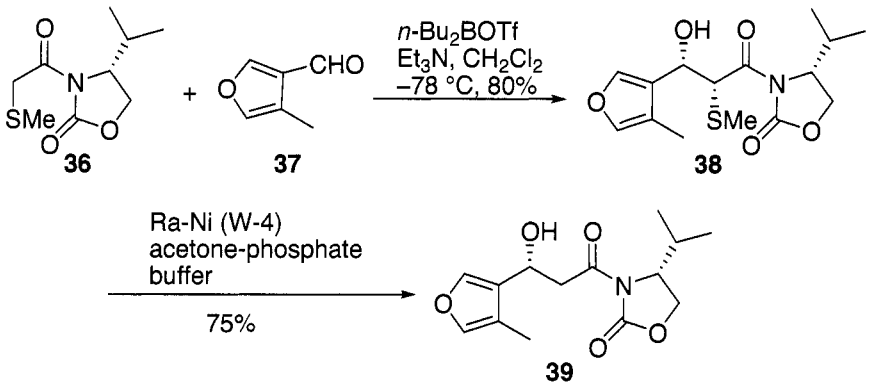
Haloacetyl Aldol Reactions

N-Haloacetyl oxazolidinones form suitable enolate partners in aldol reactions, although complete aldehyde conversion requires the use of a slight excess of imide. Nucleophilic azide displacement of α-halo-β-hydroxy *syn* aldol adducts affords the corresponding anti α-amino-β-hydroxy compounds.[17]



Acetate Aldol Equivalents

Unlike α-substituted dibutylboryl imide enolates that provide for a highly stereoselective transformation, boron enolates derived from *N*-acetyloxazolidinones gave a statistical mixture of aldol adducts under the same reaction conditions. Acetate enolate equivalents may be obtained from enolates bearing a removable α-substituent. For example, thiomethyl-, thioethyl- and haloacetyloxazolidinones can be used for highly selective boron-mediated aldol reactions.[18]



Crimmins Oxazolidinethione and Thiazoldinethione Aldol Reaction[8]

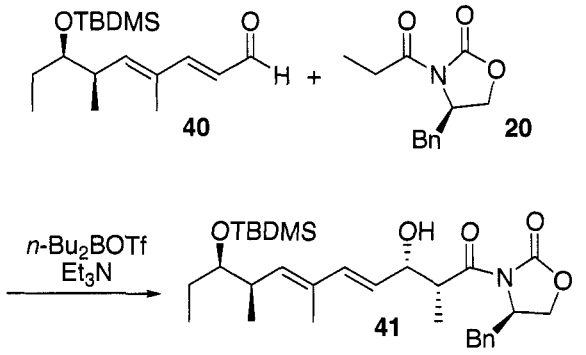
An interesting feature of the Crimmins thiazoldinethione is that either the "Evans" *syn* or "non-Evans" syn adducts can be prepared through a variation in the amount of (–)-sparteine (or other diamine bases, such as DIEA and TMEDA) utilized. The yields, diastereoselectivities and enantioselectivities of the reaction are generally high and can be used in the acetate aldol reaction.[19]

Synthetically the use of oxazolidinethione or thiazolidinethione auxiliaries offers the advantage that they are easily removed under mild conditions. Efficient reductive removal to give the diol is readily achieved in high yield with inexpensive and easily handle $NaBH_4$. Alternatively the auxiliaries can be transformed into the versatile Weinreb's amide by simply stirring in the presence of imidazole and the hydroxylamine salt. Most importantly, direct conversion to the aldehyde using *i*-Bu_2AlH was achieved directly.[7, 9]

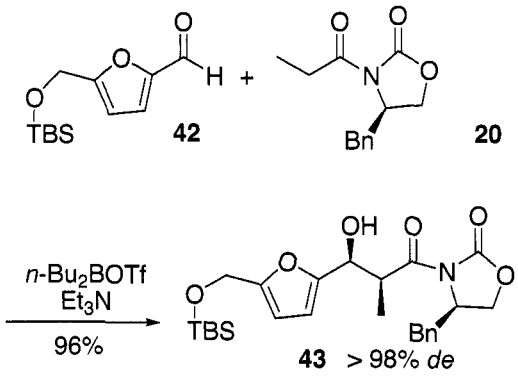
Due to the relatively high cost of these chiral auxiliaries, the development of an efficient means for chiral auxiliary removal and their recovery upon completion of the reaction is critical. Manipulating the relatively high acidity of the thiazolidinethione, allows the liberated auxiliary to be removed from the reaction mixture via a basic wash by using 1 M NaOH and subsequently recovered by acidification. The ability to separate the auxiliary from the cleavage products by simple extraction is a distinct advantage of both the oxazolidinethione and thiazolidinethione auxiliaries.

Applications in Natural Product Synthesis

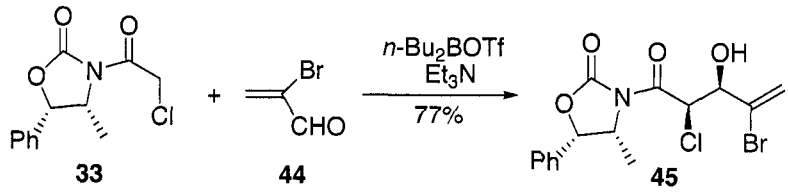
In the study of biosynthesis of polyketide antibiotics, Cane and Luo applied the Evans aldol reaction to prepare a key intermediate **41** from aldehyde **40** and Evans reagent **20**.[20]



In the first formal asymmetric synthesis of phorbol, a tigliane diterpene, Wender and co-workers utilized a chiral oxazolidinone-based asymmetric aldol reaction to produce chiral alcohol **43**, a non-Evans *syn* product as a single diastereomer in 96% yield.[21]

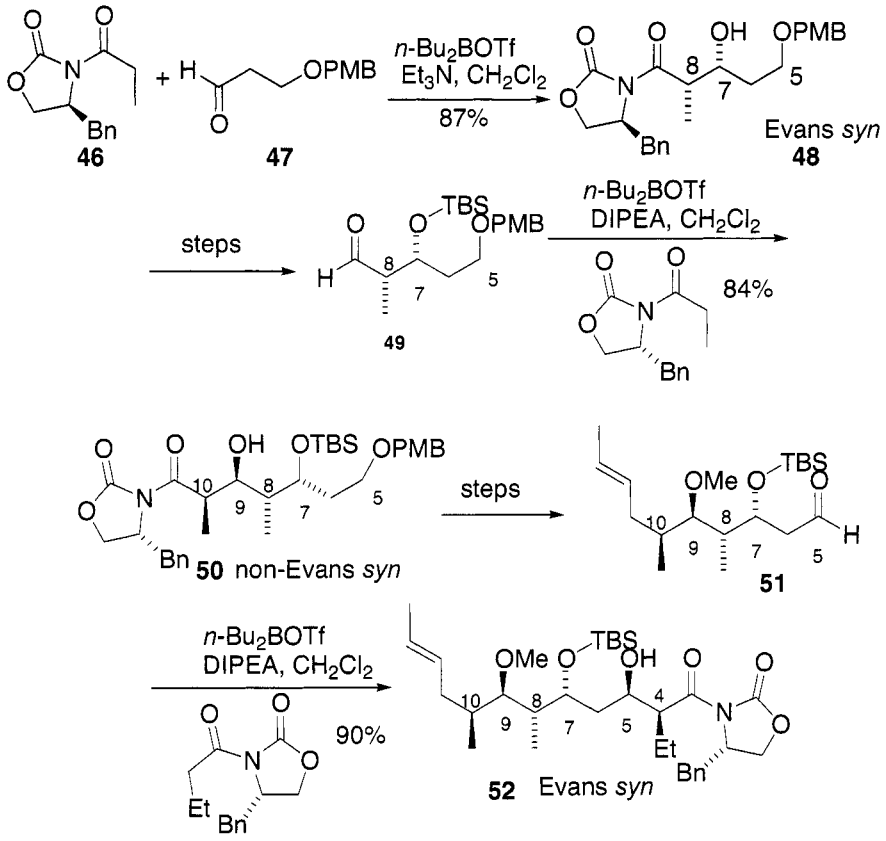


Two Evans aldol reactions were used to create the C5 and C7 stereocenters in the asymmetric synthesis of a Taxol C-ring with chloroacetyl oxazolidinone **33**, giving the Evans *syn*-aldol **45** as a single diastereomer in 77% yield.[22]

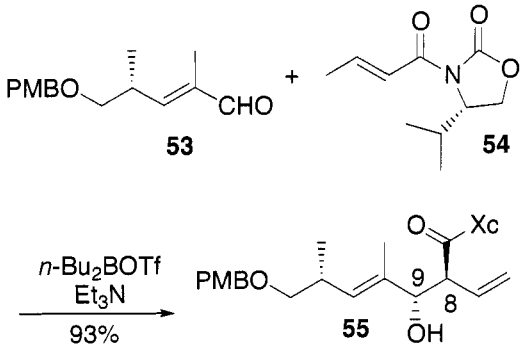


In the total synthesis of (–)-pironetin, an unsaturated lactone derivative with antitumor activities. Dias and co-workers developed a novel

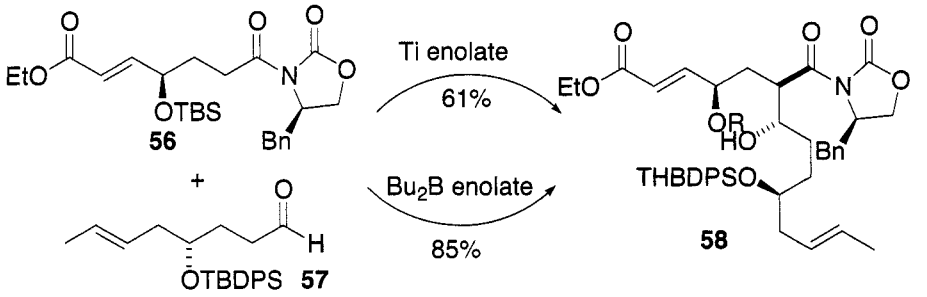
approach that involves the use of highly efficient Evans aldol reaction three times to establish the stereocenters at C4, C5, C7, C8, C9, and C10.[23]



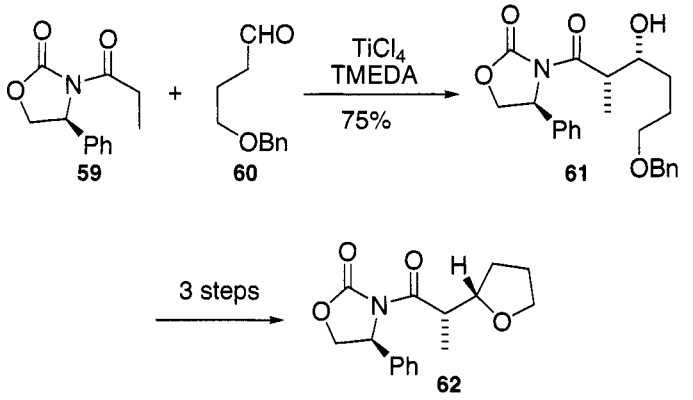
Total synthesis of myriaporones had been completed by Taylor wherein the Evans aldol reaction was used to set the C8 and C9 stereocenters in high yield and with excellent diasteroselectivity.[24]



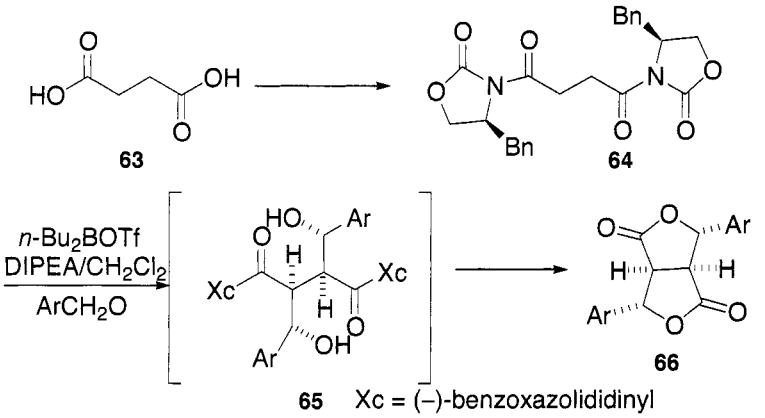
In the synthesis of (–)-amphidinolide K fragment **58**, the C14 and C15 stereocenters were established by an Evans aldol reaction. Application of two enolization protocols to **56** and aldehyde **57** provided **58** as a single diastereomer in 61% yield under $TiCl_4$/DIPEA conditions, and 85% yield when Bu_2BOTf/Et_3N conditions were utilized.[25]



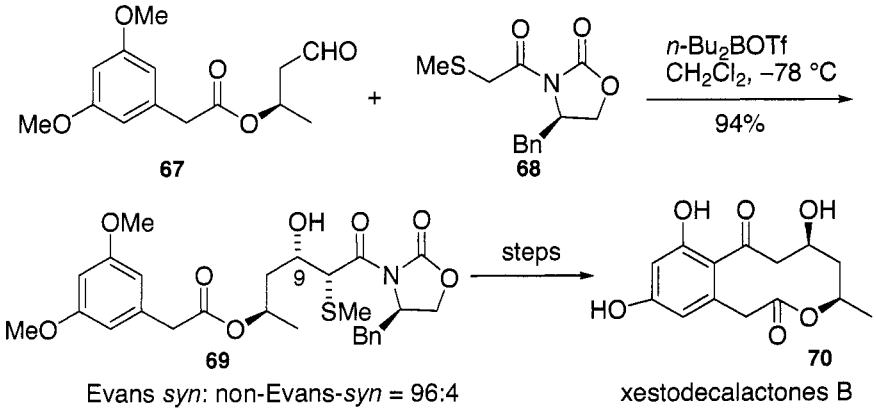
An efficient enantioselective route to nonactin using a novel β-inversion of an Evans *syn* aldol to construct the THF ring **62** is reported.[26] Condensation of aldehyde **60** with imide **59** under the Crimmins conditions led to *syn* aldol **61** in 75% isolated yield.[26]



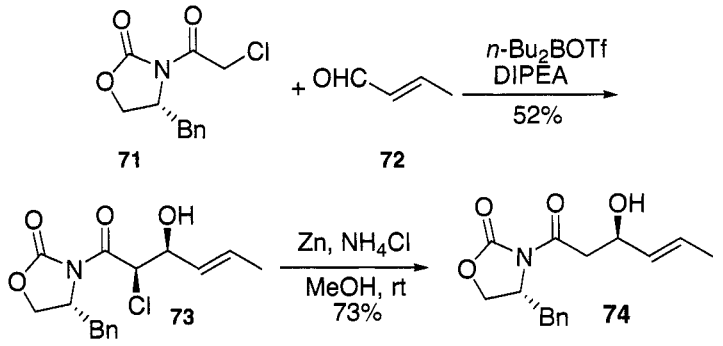
Park and co-workers developed a highly stereoselective method to generated the core skeleton of furofuran rings in the synthesis of furofuran lignans **66** by utilizing an Evans aldol reaction. Among known approaches to (+)-eudesmin, (–)-eudesmin, (+)-yangambin and (–)-yangambin, this is the shortest and highly efficient way to establish four stereocenters in only one step (**64** to **65**) by using double Evans aldol reaction.[27]



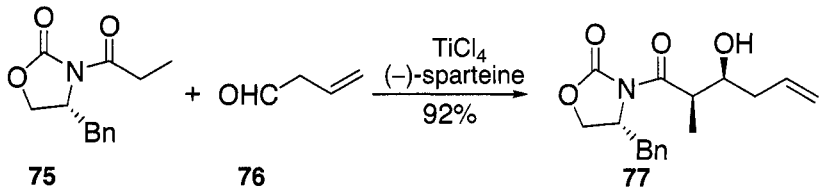
The first asymmetric total synthesis of xestodecalactone B and C was recently accomplished in 10 steps with an overall yield of 22%.[28] The key step involves the use of Evans aldol reaction to establish the C-9 configuration. Initial attempts to use an *N*-acetyloxazolidinone boryl enolate afforded the corresponding aldol product as a nearly 1:1 ratio of diastereomers. A switch to the boryl enolate of thiomethylacetyloxazolidinone **68**, which is an acetate aldol equivalent, generated the product **69** with high diastereoselectivity (92% *de*). Subsequent desulfurization with *n*-Bu_3SnH and AIBN was required to remove the thiol functionality.

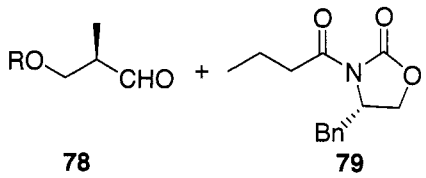


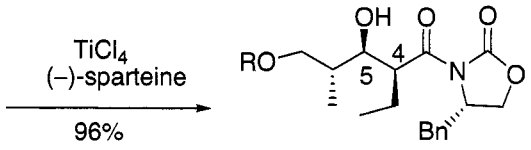
Chiral alcohol **73** was synthesized using the Evans aldol reaction and provided the *syn*-selective aldol adduct (95:5) in 52% yield in the haloacetyl aldol reaction during the total synthesis of (–)-clavosolide B.[29] The chlorine atom was removed by treatment of Zn/NH_4Cl in methanol, providing an additional example of an acetate aldol equivalent.

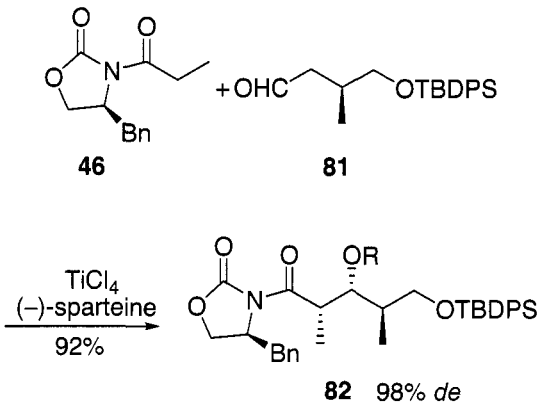


In the synthesis of the C1–C12 fragment of amphidinolide T1, *syn* aldol adduct **77** was prepared in 92% yield as a single diastereomer by the Crimmins modified Evan's strategy ($TiCl_4$ with (–)-sparteine).[30] This protocol was also used to install the stereocenters at the C4 and C5 in **80** with excellent diastereoselectivity (96% *de*) in the total synthesis of (–)-bitungolide F.[31] In the total synthesis of cruentaren B, the Crimmins modified condition was used in the Evans *syn* aldol reaction, giving adduct **82** in excellent yield and diastereoselectivity (92%, 98% *de*).[32]





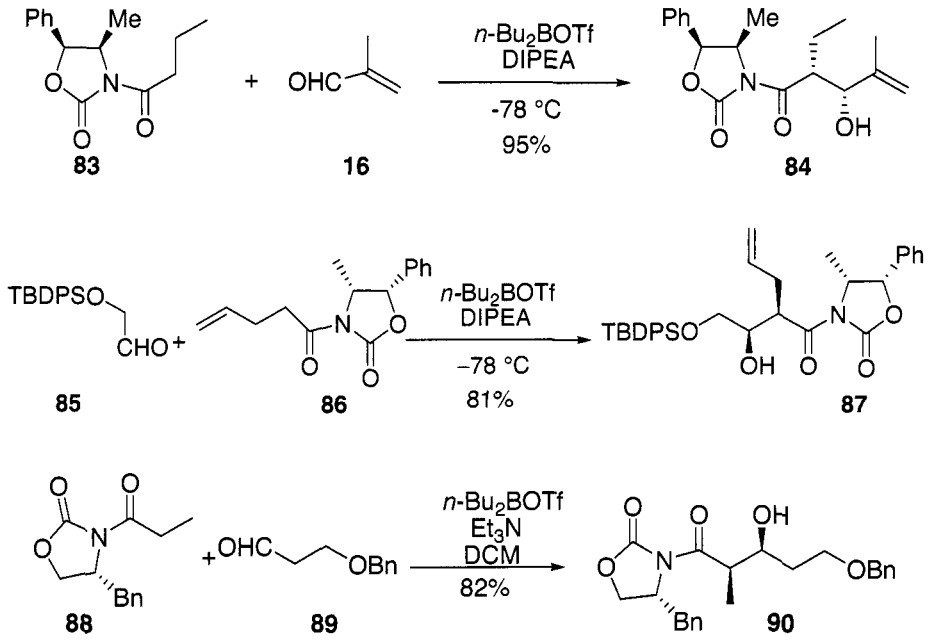




46 81

82 98% *de*

In a study on the biosynthesis of the polyether antibiotic lasalocid A, a *syn*-selective Evans aldol reaction of **83** with methacrolein gave **84** in 95% isolated yield.[33] In the total synthesis of the antitumor sesquiterpenoid (+)-eremantholide A, an Evans aldol reaction was used to deliver a single *syn*-aldol adduct **87** in 81% yield.[34] Yadav and co-workers used the Evans *syn* aldol to access key intermediate **90** in the synthesis of prelactones and *epi*-prelactones V and E.[35]



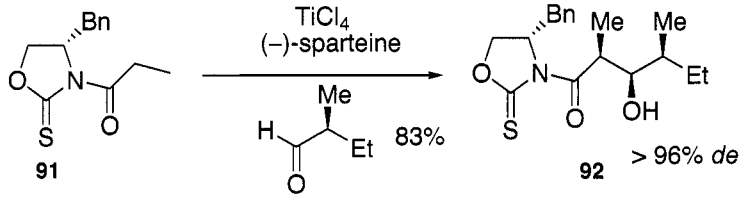
83 16 84

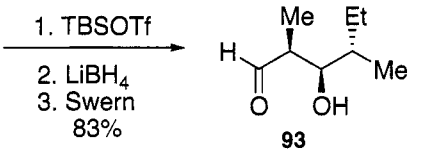
85 86 87

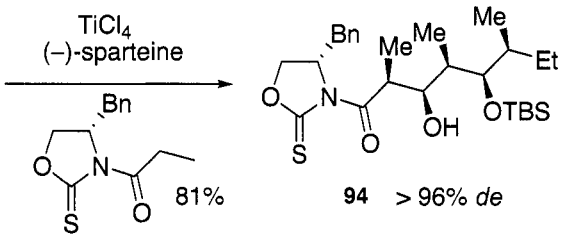
88 89 90

Crimmins used the thiazoldinethione aldol twice in the total synthesis of callystatin A. The chiral titanium enolates were generated by the use of

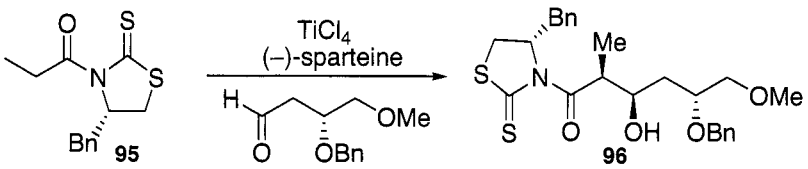
$TiCl_4$ and (–)-sparteine; the reaction of the enolate of **91** with chiral aldehyde gave the *syn*-aldol adduct **92** with an excellent selectivity (96% *de*). Execution of the second asymmetric aldol, under the same condition, yielded the *syn*-aldol adduct **94** (96% *de*).[36]





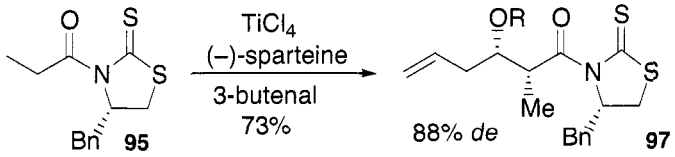


Thiazolidinethione chiral auxiliaries were utilized in the enantioselective synthesis of apoptolidinone. The enolate of thiazolidinethione **95** was formed by treatment with 1 equivalent each of $TiCl_4$ and (–)-sparteine. Addition of chiral aldehyde to the enolate solution generated aldol adduct **96** with excellent selectivity (96% *de*) for the Evans *syn* product.[37]

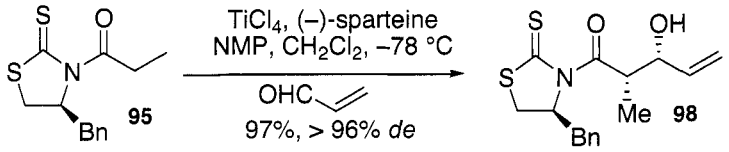


In the enantioselective total synthesis of FD-891, a 16-membered macrolide, the fragment **97** is generated from the aldol reaction between 3-

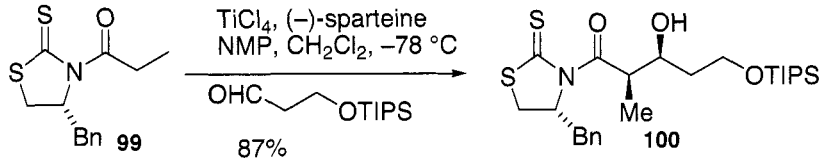
butenal and the enolate of thiazolidinethione **95** under Crimmins conditions, giving the non-Evans *syn* aldol adduct **97** in 73% yield (88% *de*).[38]



Enantioselective total synthesis of (+)-SCH 351448 has been completed recently by Crimmins and Vanier. Addition of acrolein to a solution of the chlorotitanium enolate of *N*-propionyl thiazolidinethione **95** provided the aldol adduct **98** in 97% yield (96% de).[39]

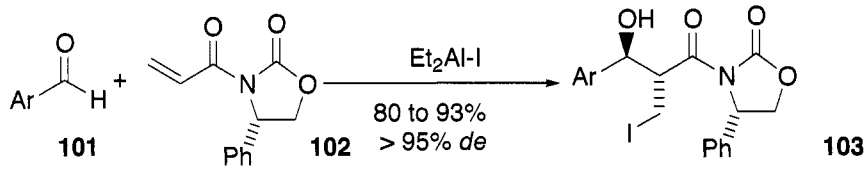


In the enantioselective total synthesis of Bistramide A, Crimmins and DeBaillie utilized their procedure for the synthesis of a key fragment **100**. Exposure of the aldehyde to the chlorotitanium enolate of *N*-propionyl thiazolidinethione **99** proceeded smoothly with excellent diastereoselectivity (> 96% *de*).[40]

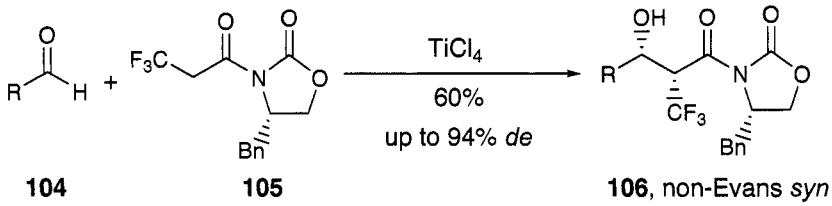


2.1.5 Variations and Improvements

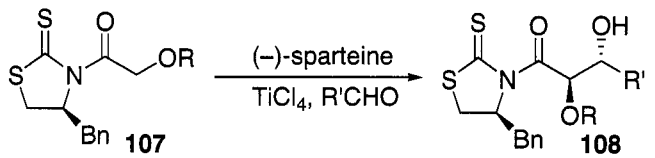
Li and co-workers developed a novel asymmetric halo aldol reaction using Evans oxazolidinones as chiral auxiliaries for tandem I–C/C–C bond formations. This reaction provides a practical approach to a variety of halo aldols of a non-Evans type that cannot be easily prepared by other methods. Excellent diastereoselectivity (> 95% *de*) and yields (80–93%) have been obtained.[41] This reaction can be considered as a Lewis acid (Et_2Al–I)-promoted Morita–Baylis–Hillman (MBH) process.



The growing interest in trifluoromethylated organic compounds as pharmaceuticals has led to a new focus on the development of facile methods for introducing a CF_3 group into useful optically intermediate. Ishihara and co-workers developed a $TiCl_4$-catalyzed Evans-aldol reaction, giving the non-Evans *syn* product, α-trifluoromethyl-β-hydroxycarboxylic acid derivatives **106** stereoselectively.[42]

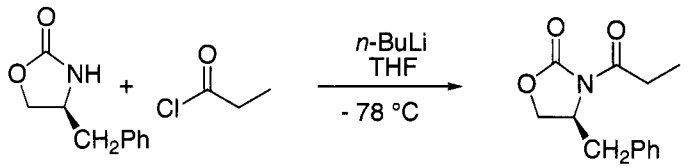


A highly diastereoselective *anti* aldol addition utilizing a variety of *N*-glycolyloxazolidinethiones has been developed by Crimmins.[43] Enolization of an *N*-glycolyoxazlidinethione with titanium(IV) chloride and (–)-sparteine followed by the addition of an aldehyde activated with additional $TiCl_4$ resulted in highly *anti*-selective aldol additions, typically with no observable *syn* isomers.

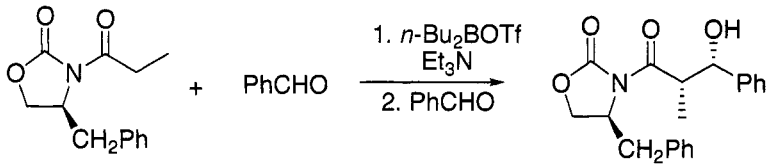


2.1.6 Experimental

A. Synthesis of (S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone[44]



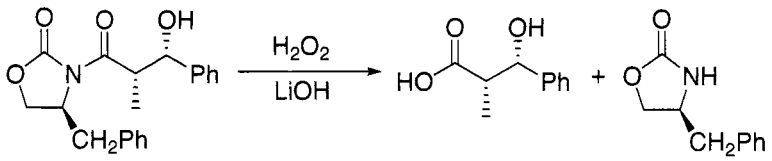
A dry, 500 mL flask equipped with a magnetic stirring bar is charged with 17.7 g (0.100 mol) of (*S*)-4-(phenylmethyl)-2-oxazolidinone, capped with a rubber septum, and flushed with nitrogen. Anhydrous tetrahydrofuran, 300 mL, is then added to the flask via cannula, and the resulting solution is cooled to −78 °C in an acetone–dry ice bath. A solution of 68.3 mL (0.101 mol) of 1.47 M butyllithium in hexane is transferred via cannula first to a dry, septum-stoppered, 100 mL graduated cylinder with a ground-glass joint, and then to the reaction flask over a 10-min period. The solution may turn yellow and slightly cloudy. Freshly distilled propionyl chloride (9.6 mL, 0.11 mol), is added in one portion by syringe after completion of the addition of butyllithium. The resulting clear, nearly colorless solution is stirred for 30 min at −78 °C, then allowed to warm to ambient temperature over a 30-min period. Excess propionyl chloride is quenched by the addition of 60 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotary evaporator (bath temp. ca. 25–30 °C), and the resulting slurry is extracted with two 80 mL portions of dichloromethane. The combined organic extracts are washed with 75 mL of an aqueous 1 M sodium hydroxide solution and 75 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation, and the residue, a light-yellow oil, is placed in a refrigerator overnight to crystallize. The resulting crystalline solid is pulverized and triturated with a minimum quantity of cold hexane. After filtration and drying 21.2–22.3 g (91–96%) of the desired product is obtained as a colorless crystalline solid, mp 44–46 °C.



B. The boron aldol reaction.

Into a dry, 2-L flask equipped with a large magnetic stirring bar is introduced 21.2 g (0.091 mol) of the acylated oxazolidinone. The flask is sealed with a rubber septum and swept with nitrogen. The solid is dissolved in 200 mL of anhydrous dichloromethane, which is introduced via syringe. A thermometer is inserted through the rubber septum, and the contents of the flask are cooled to 0 °C with an ice bath. To this cooled solution is added via syringe 27 mL (0.107 mol) of dibutylboron triflate followed by 16.7 mL (0.120 mol) of triethylamine dropwise at such a rate as to keep the internal temperature below +3 °C. The solution may turn slightly yellow or green during the dibutylboron triflate addition, and then to light yellow when triethylamine is added. The ice bath is then replaced with a dry ice–acetone bath. When the internal temperature drops below −65 °C, 10.3 mL (0.101 mol) of freshly

distilled benzaldehyde is added over a 5-min period via syringe. The solution is stirred for 20 min in the dry ice–acetone bath, then for 1 hr at ice-bath temperature. The reaction mixture is quenched by the addition of 100 mL of a pH 7 aqueous phosphate buffer and 300 mL of methanol. To this cloudy solution is added by syringe 300 mL of 2 : 1 methanol–30% aqueous hydrogen peroxide at such a rate as to keep the internal temperature below +10 °C. After the solution is stirred for an additional 1 hr, the volatile material is removed on a rotary evaporator at a bath temperature of 25–30 °C. The resulting slurry is extracted with three 500 *mL* portions of diethyl ether. The combined organic extracts are washed with 500 mL of 5% aqueous sodium bicarbonate and 500 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, to afford 35–36 g of a white solid. The unpurified aldol adduct has a diastereomeric purity of > 97% as determined by gas chromatography. The solid is recrystallized from ca. 500 mL of 1 : 2 ethyl acetate–hexane to yield 25.8 g (84%) of the desired aldol adduct, mp 92–93 °C.

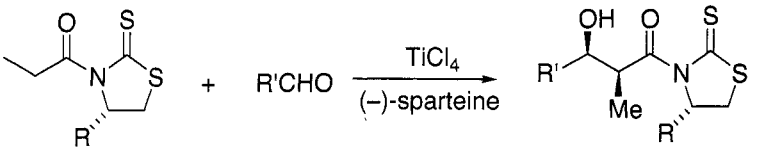


C. Chiral auxiliary removal.

A 500 mL flask fitted with a magnetic stirring bar is charged with 8.48 g (0.025 mol) of the aldol adduct and 125 mL of 4 : 1 tetrahydrofuran–distilled water. The flask is sealed with a rubber septum, purged with nitrogen, and cooled to 0 °C in an ice bath. To this solution is added via syringe 10.2 mL (0.100 mol) of 30% aqueous hydrogen peroxide over a 5-min period, followed by 0.96 g (0.040 mol) of lithium hydroxide in 50 mL of distilled water. Some gas evolves from the clear solution. After the solution is stirred for 1 hr, the septum is removed, and 12.6 g (0.100 mol) of sodium sulfite in 75 mL of distilled water is added. The bulk of the tetrahydrofuran is removed on a rotary evaporator at a bath temperature of 25–30 °C, and the resulting mixture (pH 12–13) is extracted with three 100 mL portions of dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer is cooled in an ice bath and acidified to pH 1 by the addition of an aqueous 6 M hydrochloric acid solution. The resulting cloudy solution containing the β-hydroxy acid is then extracted with five 100 mL portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated, affording 5.1 g of a white crystalline solid, which is dissolved in approximately 200 mL of an aqueous 5% sodium bicarbonate solution. This solution is extracted with two 100 mL portions of

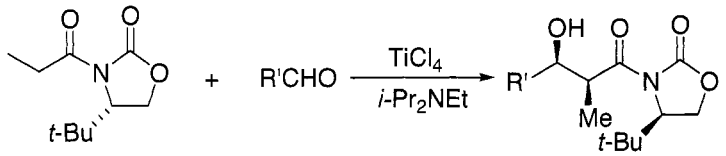
dichloromethane and then acidified and extracted with ethyl acetate as before. The combined dichloromethane extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 4.35 g (99%) of the oxazolidinone auxiliary as a white crystalline solid. This solid is recrystallized from 50 mL of 2 : 1 ethyl acetate–hexane to give 3.95 g (89%) of the recovered oxazolidinone as white crystals, mp 85–87 °C. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 4.50 g (100%) of the desired hydroxy acid as a white crystalline solid, which is recrystallized from ca. 20 mL of carbon tetrachloride to give 4.00–4.03 g (89–90%) of pure (2*S**,3*S**)-3-hydroxy-3-hydroxy-3-phenyl-2-methylpropanoic acid, mp 89.5–90 °C.

Crimmins procedure[9]



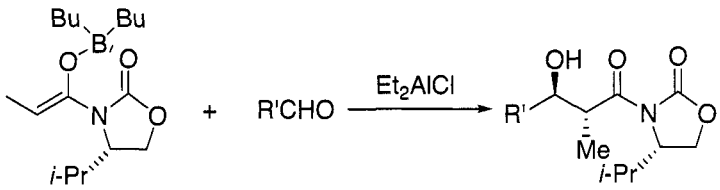
To a dry round-bottom flask under nitrogen was added 233 mg (1.0 mmol) of the thiazolidinethione in 5 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium(IV) chloride (0.121 mL, 1.1 mmol) was added dropwise, and the solution was allowed to stir for 5 minutes. To the red suspension was added (–)-sparteine (0.572 mL, 2mmol). The dark red enolate was stirred for 20 minutes at 0 °C. Freshly distilled aldehyde (1.1 mmol) was added dropwise and the resulting mixture stirred for 1 h at 0 °C. The reaction was quenched with half-saturated ammonium chloride, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated. HPLC analysis of the unpurified product revealed the isomer ratios. Purification by flash column column chromatography afforded the major diastereomer (Evans *syn* adduct). Note: Using 1.0 equiv of diamine gave selective formation of the non-Evans *syn* product, while using 1.5 equiv of diamine gave selective formation of the Evans *syn* product, but 2 equiv results in better selectivity.

Preparation of "non-Evans" syn aldols (Heathcock procedure)[5]



To a solution of 199 mg (1.00 mmol) of imide in 2.00 mL of CH_2Cl_2 at 0 °C were added 0.20 mL (148 mg, 1.15 mmol) of *i*-Pr_2NEt and 0.30 mL (330 mg, 1.20 mmol) of Bu_2BOTf. After 45 min at 0 °C the solution was cooled to –78 °C and 1.10 mL of $TiCl_4$ (0.92 M in CH_2Cl_2) was added. The aldehyde (1.00 mmol) was added dropwise over 30 min. After 3–5 h the reaction was quenched with a 5:1 mixture of MeOH/30% H_2O_2. Stirring was continued at –78 °C for another 10 min after which the solution was allowed to warm to 0 °C and stirred an additional 30 min. Water was added, and the layers were separated. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic layers were washed with dilute $NaHCO_3$ and brines then dried ($MgSO_4$). After filtration and evaporation of the solvent the crude product was chromatographed on SiO_2 (230–400 mesh), using 3:1–4:1 hexanes/EtOAc.

Preparation of anti aldols (Heathcock procedure)[5]



The boron enolate was generated as above method and cooled to –78 °C. In a separated flask the aldehyde (1.5 mmol) was added to a solution of 3.00 mL of Et_2AlCl (1.0 M in hexanes) in 2.00 mL of CH_2Cl_2. After being stirred for 5 min the cooled enolate was added by cannula, using an additional 1.00 mL of CH_2Cl_2 to aid the transfer. After 3–5 h the reaction was quenched and the mixture worked up as above method.[5]

2.1.7 References

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Chapter 2.2 Hajos–Wiechert Reaction

Daniel P. Christen

2.2.1 *Description*

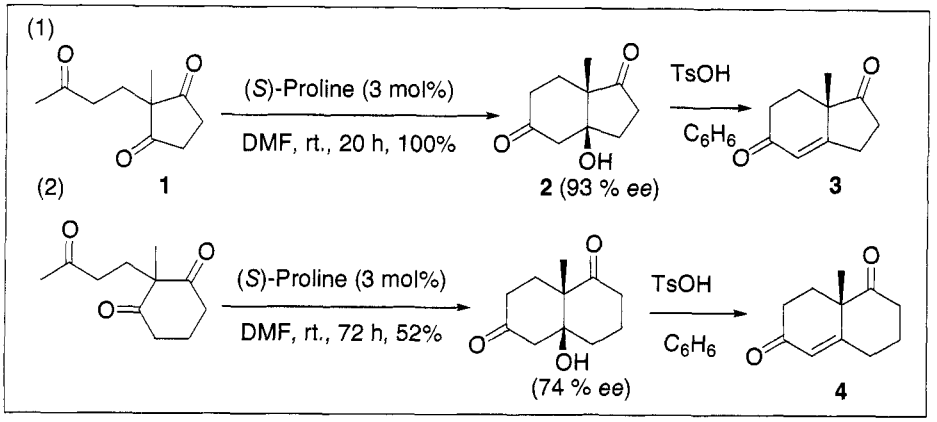
The study of steroids has had a profound impact on the evolution of biological and chemical research during the last sixty years. Steroids function primarily as sex hormones, but participate in many other significant biological pathways as well.

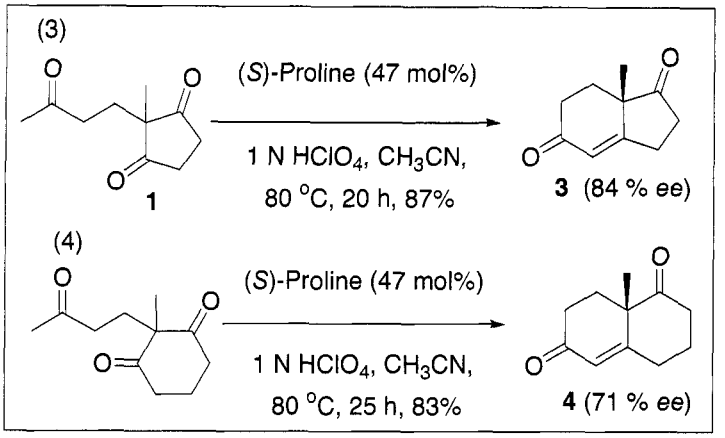
In medicinal chemistry, birth control pills and the use of HMG-CoA reductase inhibitors to control cholesterol biosynthesis have led to tremendous developments in organic and biological chemistry. Not surprisingly, the organic chemistry community has had a long-standing fascination with the structure and synthesis of steroids. Initially focused on understanding the structure and conformational chemistry of the steroids, this work eventually turned to the industrial preparation of estrogen-related steroids for use as contraceptives. This research, which has used all common approaches in total synthesis, has led to the development of many named reactions and processes.[1] The Marker process, Torgov synthesis, *etc.* are just a few of many examples.

In the late 1960s, independent work by research groups at Hoffman LaRoche and Schering AG led to the discovery of the proline mediated asymmetric Robinson annulation known as the Hajos–Wiechert reaction. This reaction, one of the earliest and most important organocatalytic processes developed, remains very useful today for the preparation of Wielend-Miescher ketone and related building blocks; these building blocks have become important parts of the "chiral pool" for the synthesis of steroids and other natural products. This reaction was one of the first asymmetric produce concise, elegant solutions for direct aldol and Mannich reactions. Ongoing research on proline mediated organocatalysis is one of the main research frontiers in organic chemistry.[2]

Reactions 1 and 2 show the initial work by Hajos and Parrish.[3] After an initial Michael reaction, usually with methyl vinyl ketone, starting material **1** was obtained in quantitative yield. Compound **1** was treated with 3 mol% proline in DMF at room temperature to give intermediate **2**; upon further reaction with toluenesulfonic acid, the dehydrated product **3** is obtained. In an analogous manner, enantioenriched Wieland–Miescher ketone **4** was obtained in a lesser optical yield. Reactions 3 and 4 show the one-pot reaction discovered by Eder, Sauer and Wiechert.[4] The yields and optical purity of the compounds obtained were similar to those of Hajos and

Parrish. Crystallisation is commonly used to further purify the final products in order to increase their optical purity.



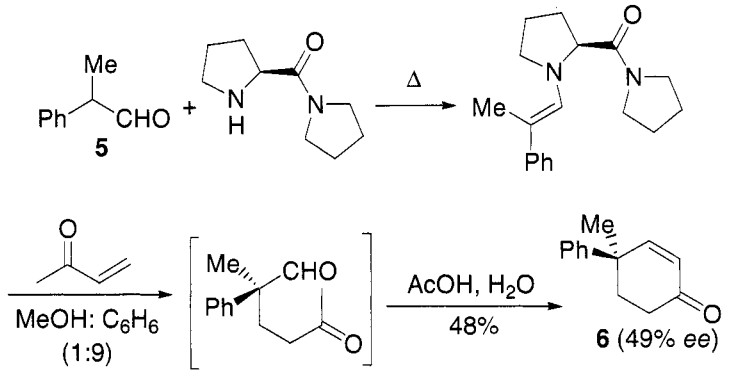


Overall, this annulation method delivers a quick entry into 6–5 and 6–6 bicyclic chiral building blocks that can be readily modified as needed. The predictable absolute stereochemistry of the reaction is further expanded in utility by using the readily available enantiomers of the amino acid catalysts to prepare either of the two enantiomeric products. The reaction can be run on kilo scale if needed.

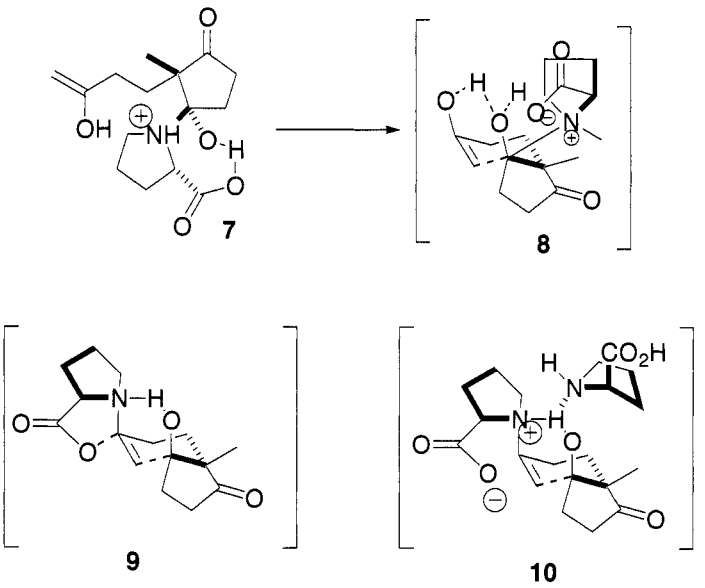
2.2.2 *Historical Perspective*

This reaction was one of the first asymmetric produce concise, elegant solutions for the direct aldol and Mannich reactions. The most closely related work reported in the literature at the time is a single report by

Yamada and Otani on a proline derived ring formation.[5] Cyclohexenone **6** was obtained in 48% yield from aldehyde **5** and 3-buten-2-one.



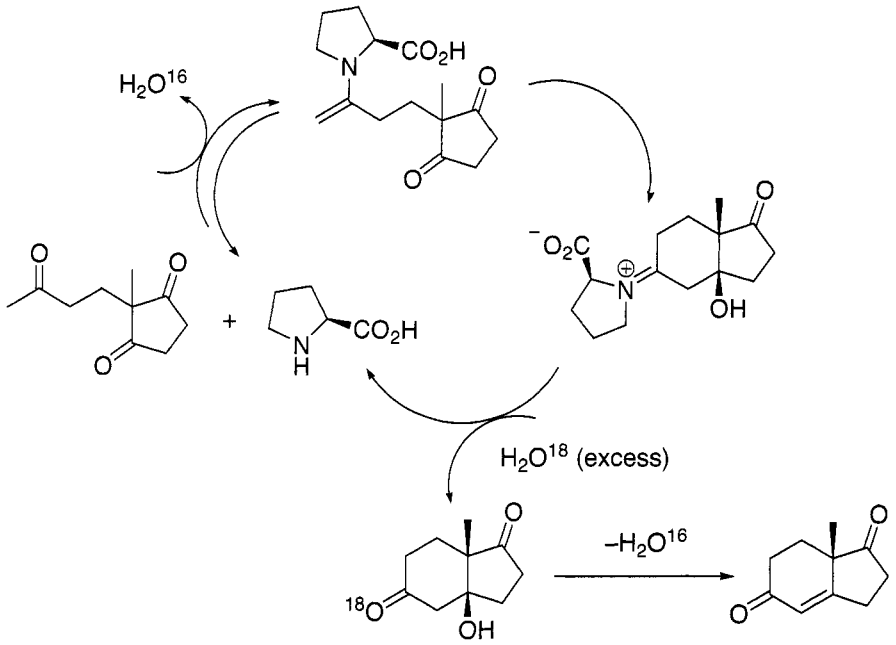
2.2.3 *Mechanism*



The mechanism of the Hajos–Wiechert reaction has not been without controversy. The original paper by Hajos and Parrish proposed two possible mechanisms.[3] The first, via the carbinolamine **7**, proposed addition of proline to a ketone, followed by a nucleophilic attack of the pendant, remote enol [transition state **8**]. Calculations by Houk and Clemente show that this is one of the higher energy pathways.[6] The second proposed mechanistic pathway proceeded via an enamine intermediate, followed by carbon–carbon bond formation via transition state **9** and a hydrogen transfer between nitrogen and

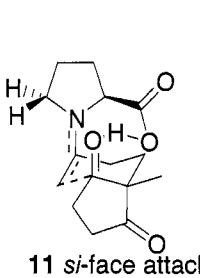
oxygen. Based on the lack of incorporation of labelled oxygen from H_2O^{18}, Hajos and Parrish favoured the first mechanism. However, more recent work by List *et al.* clearly showed greater than 90% incorporation of labelled oxygen, thus supporting the enamine mechanism.[7] To make things even more complicated, dilution experiments by Agami and co-workers led to the proposal of a third possible mechanistic pathway involving two prolines.[8] Transition state **10** shows a possible arrangement of the two prolines.

More recently, several groups have taken another look at the mechanism. Extensive experimental studies were carried out by List and his co-workers, while Houk's group took a detailed look at the transition states and mechanisms of the major proposed reaction pathways using computational methods.[9] The experimental studies by List's group found no nonlinear effect or dilution effect; in addition, they found extensive incorporation of labelled oxygen if the reaction was carried out in the presence of H_2O^{18}. Houk's computational work suggests that the enamine pathway via an intermediate initially proposed by Jung is energetically most favorable.[10] Based on this data, the mechanistic scheme shown below is proposed as a plausible mechanism for the Hajos–Wiechert reaction.

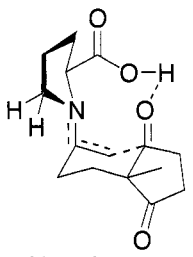


Based on the product shown in the mechanism, the enamine preferentially adds to the *si*-carbonyl. The proposed transition states for the two potential modes of attack are summarised below as structures **11** and **12**. The transition state for *si* face attack places the iminium double bond into an

almost planar position, whereas the iminium double bond is slightly more bent for the *re* transition state. The hydrogen bond between the carboxylic acid hydrogen and the reacting carbonyl appears to be more favourable in the *si* transition state as well. Bahmanyar and Houk reported that the transition state for *re*-face attack is 3.4 kcal/mol higher using a HF 6-31G calculation.[11]



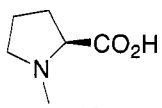
11 *si*-face attack



12 *re*-face attack

2.2.4 *Variations*

The Hajos and Wiechert research groups looked at a number of other potential proline based catalysts for their intramolecular Robinson annulation. (*S*)-(–)-Hygrinic acid, *N*-methylproline **13**, was examined, but only the racemic intermediate ketol product **2** was obtained. In a similar manner, the proline methyl ester **14** also produced the racemic ketol intermediate. No reaction was observed with the piperidine analog **15**. The homo-proline analog **16** gave the enantiomeric product. An explanation for this change in selectivity has not been provided yet. Please note that the use of (*R*)-proline provides the enantiomeric product.



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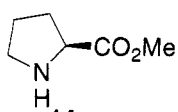
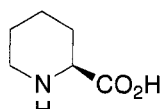


14



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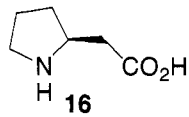
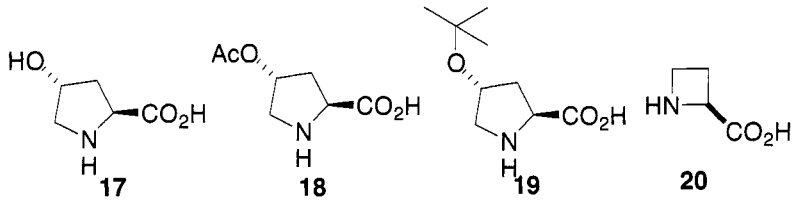
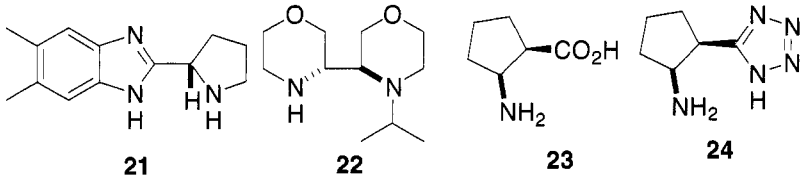


16

Recently, Barbas and Bui looked at the one-pot proline-catalysed Robinson annulation sequence to see if proline can catalyse the entire reaction sequence; they found that substituted hydroxyproline derivatives **17**–**19** were viable catalysts for the reaction, producing the desired products in 60 to 70% *ee*.[12] The corresponding smaller analog **20** gave the product in less than 10% *ee*. Additional work looked at analogs in which the carboxylic acid was reduced or replaced by other functional groups; these compounds, which are not shown, were not viable catalysts for the entire reaction sequence. Instead, the intermediate Michael adduct or cyclized, but not dehydrated, intermediates were observed.



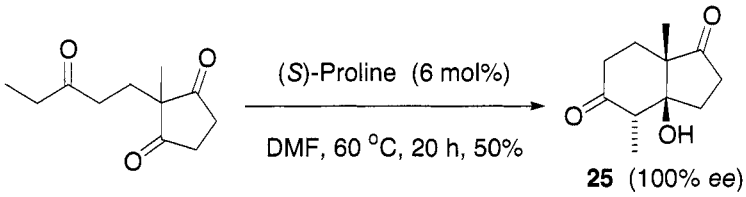
Several other groups have looked at other modified "proline" analogs to find novel catalysts for the Hajos–Wiechert reaction. While these compounds produce the desired products in yields that approach or even slightly surpass (*L*)-proline, additional work is often required to prepare the catalysts. The benzimidazole-pyrrolidine proline surrogate **21** (10 mol%), as the corresponding trifluoroacetate salt, provided **3** in quantitative yield with an 86% *ee*.[13] The unusual bismorpholine trifluoroacetate salt **22** (5 mol%) provided Wieland–Miescher ketone **4** or bicycle **3** in 50 to 90% yield in *ee*'s of up to 95%.[14] Lastly, (1*R*,2*S*)-cispentacin **23** (30 mol%) provided alcohol **2** in quantitative yield after 48 h; further reaction with toluenesulfonic acid provided the enantiomer of **3** in 90% *ee*. Interestingly, the tetrazole analog of cispentacin (**24**) produced the racemic alcohol intermediate **2**.[15]



Additional research with other amino acids, in particular phenylalanine, showed that other amino acids were viable catalysts for the reaction as well. In some cases, phenylalanine can be superior to proline. Some examples using phenylalanine will be seen later in this review.

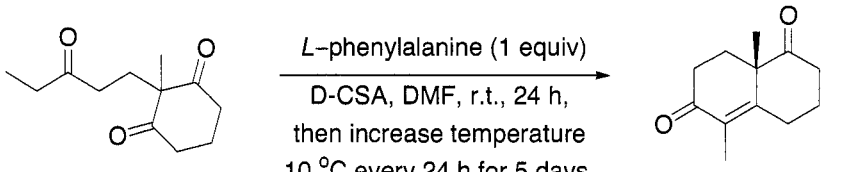
The preparation of Wieland–Miescher ketone has sparked additional interest since the Hajos–Wiechert reaction provides it in lesser purity than the corresponding hydrindane derivative. The groups of Furst and Harada have reported two crystallization protocols for Wieland–Miescher ketone based on recrystallization from ether or a 10:1 ether/ethyl acetate blend; these protocols, although time consuming, appear to be scaleable.[16,17]

Occasionally, more substituted derivatives of **3** are needed to prepare steroid analogs. Medarde and co-workers found that the classical proline reaction conditions for the preparation of **25** are very slow, requiring 10 or more days. Increasing the temperature of the reaction to 60 °C decreased the reaction time to 5 days, but started to produce by-products at higher temperatures. Interestingly, the addition of piperidine led to a decrease in reaction time.[18]



25 (100% *ee*)

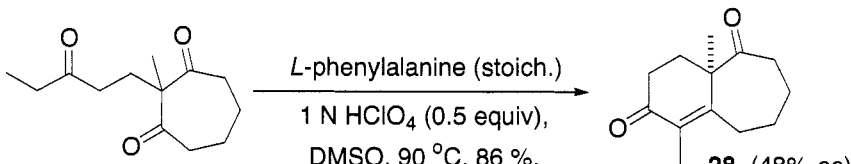
The most useful variation of the standard Hajos–Wiechert reaction protocol was developed by Hagiwara and Uda.[19] In this approach, a stoichiometric amount of *L*- or *D*-phenylalanine and 0.5 equiv of D-CSA were stirred together with precursor **26** at room temperature for 24 h; the temperature was then increased by 10 degrees every 24 h for 4 days. Compound **27** was obtained in 79% yield with an *ee* of 91% after column chromatography.



26

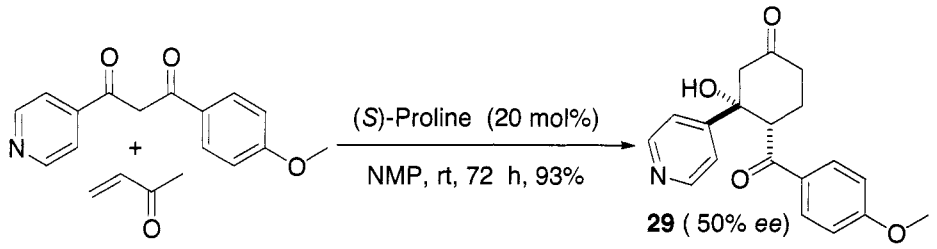
27 (91% *ee*)

Paquette and co-workers were interested in using the Hajos–Wiechert reaction to prepare 6–7 fused ring system analogs such as **28**.[20] After screening several amino acids, the best yield was obtained with *L*-phenylalanine (86% yield, 48% *ee*). The methyl group stereochemistry at the ring junction was inverted from that typically observed in the preparation of the fused 5,5- or 5,6-bicyclic analogs.



28 (48% *ee*)

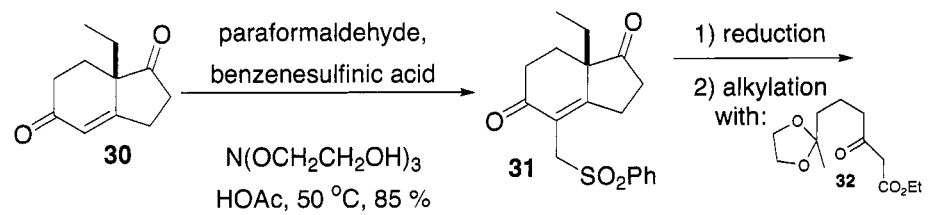
More recently, Gryko reported an isolated example of a proline mediated cyclization of non-cyclic triketones.[21] The reaction followed a domino Michael–Aldol pathway in the preparation of compound **29**. The yields and % *ee* of these reactions are very solvent dependent and much lower than those reported for the Hajos–Wiechert reaction. Typically, the best results were obtained in NMP.

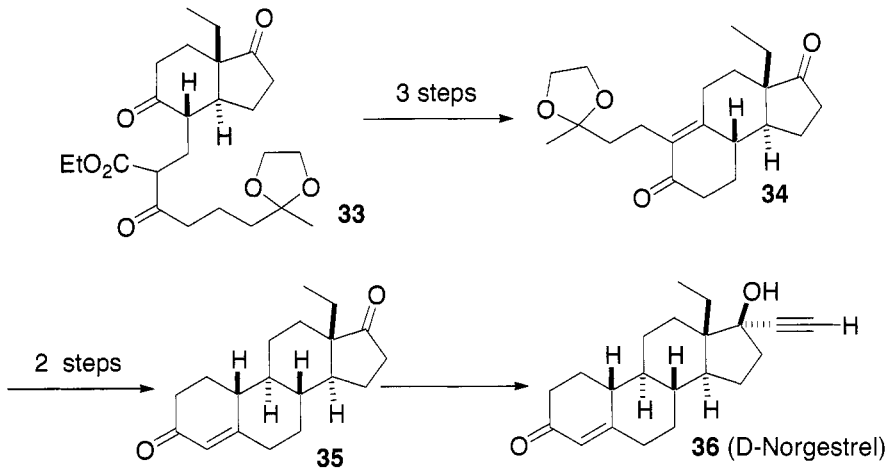


2.2.5 *Applications in total synthesis*

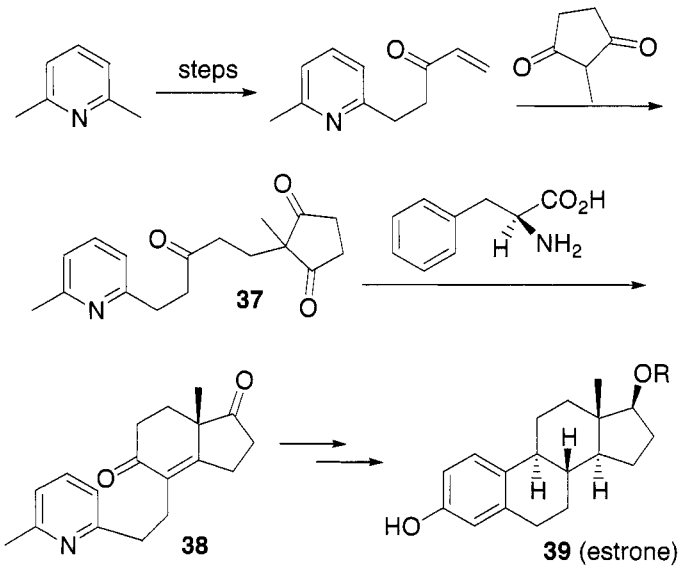
The total synthesis of enantiopure natural products has been one of the key developments of the modern era of asymmetric synthesis. Since the Hajos–Wiechert reaction allows ready access to useful chiral bicyclic building blocks, the reaction has been widely employed to construct a variety of precursors for the synthesis of steroids, vitamin D derivatives, and other natural products. The remainder of the review will look at select examples from the total synthesis literature to illustrate this point.

One of the earliest applications of the Hajos–Wiechert reaction in steroid total synthesis came from Wiechert's group at Schering.[22] The ethyl analog of **3** was used in a straightforward synthesis of 17a-ethynyl-18-methyl-19-nortestosterone (*D*-Norgestrel), a clinically useful steroid inhibitor of ovulation. Reaction of enedione **30** with paraformaldehyde and benzenesulfinic acid gave sulfone **31** in 85% yield. Selective reduction of the double bond was followed by displacement of the sulfonyl leaving group by the sodium salt of 7,7-ethylenedioxy-3-oxooctanoate (**32**) to give intermediate **33**, which was then cyclized, hydrolysed and decarboxylated to yield compound **34**. After reduction of the double bond, deprotection of the ketal was followed by another aldol cyclization to give 18-methyl-19-norandrostenedione **35** in 35% overall yield from the starting material. Addition of acetylide then yielded *D*-Norgestrel (**36**). This approach proved useful for Crabbé in the preparation of dinordrin and analogs thereof as well.[23]

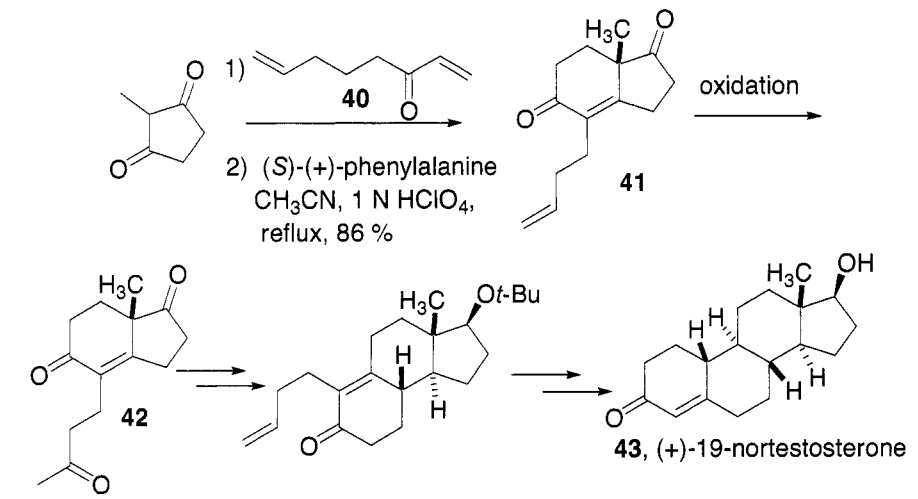


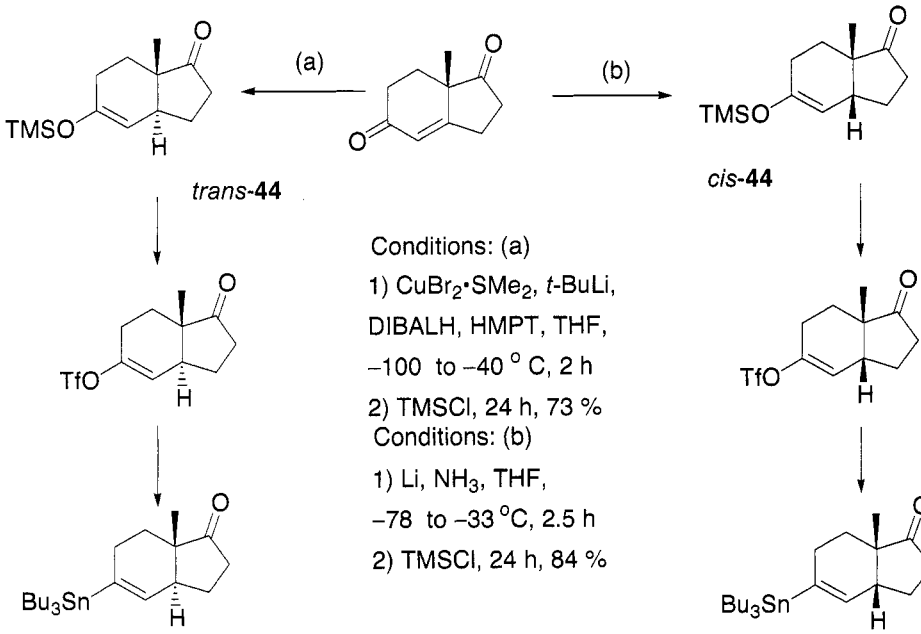


Danishefsky and his co-workers have used the Hajos–Wiechert reaction several times during total synthesis projects; one of the first such applications was in a nice synthesis of estrone that employed a substituted 6-α-picoline moiety as a masked cyclohexenone.[24] 2,6-Lutidine was converted into the cyclization precursor **37**; attempted cyclization under the standard Hajos–Parrish conditions with proline as the catalyst gave unsatisfactory levels of enantioselection, but additional work showed that *L*-phenylalanine gave the desired compound **38** in 86% *ee*. Several additional steps converted the intermediate **38** into (+)-estrone. This methodology was employed for the synthesis of a number of 19-norsteroids as well.



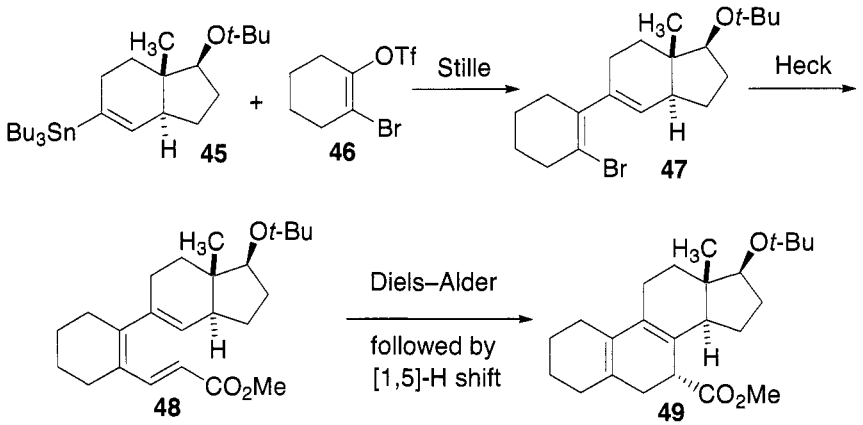
Tsuji and co-workers completed a total synthesis of (+)-19-nortestosterone by using a key intermediate prepared using the Hajos–Wiechert reaction of **40** with stoichiometric (*S*)-phenylalanine following the Wiechert protocol.[25] This approach was the best among approximately twenty conditions that were tried; the resulting product **41** was oxidized to the known crystalline compound **42** to determine that the Hajos–Wiechert reaction occurred in 76% *ee*. A series of alkylation and annulation reactions was used to convert **42** into (+)-19-nortestosterone (**43**).



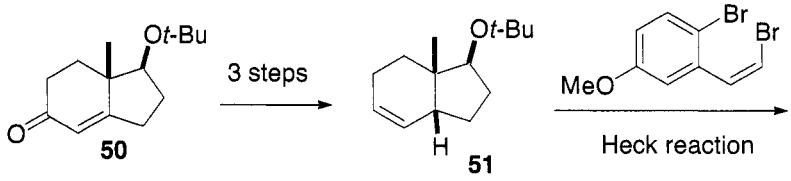


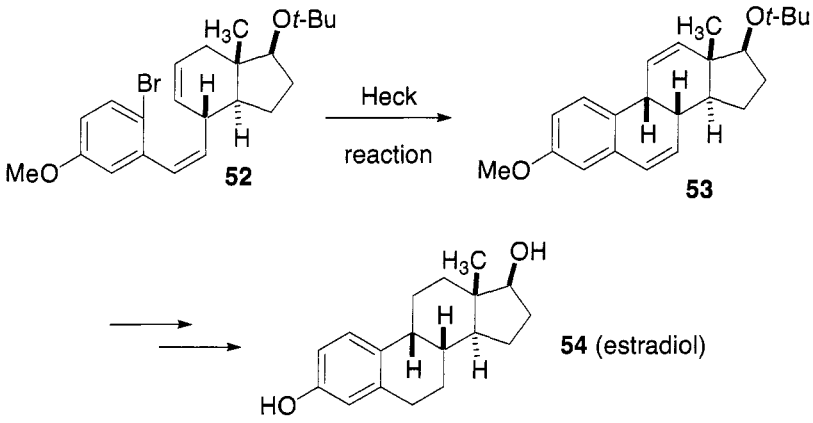
More recently, de Meijere and co-workers employed a Stille–Heck coupling reaction of a modified Hajos–Wiechert reaction product, followed by an intramolecular Diels–Alder reaction, to gain entry into new classes of steroid skeletons.[26] The Stille–Heck precursors were prepared as shown below. Interestingly, reduction of the building block with lithium in liquid ammonia gave the enol silyl ether after trapping the intermediate enolate with TMSCl, while the corresponding *trans*-diastereomer was obtained using an *in situ* generated lithium hydridocuprate. *cis*-**44** and *trans*-**44** were then elaborated into the corresponding vinyl stannanes as shown.

The completion of the steroid skeleton proceeded as follows. After Stille coupling of the vinyl stannanes **45** with the more reactive triflate **46**, the resulting vinyl bromide product **47** was converted into the Diels–Alder precursor **48** via a Heck reaction. A quick Diels–Alder reaction gave steroid intermediate **49**. Significant alterations of this analog and other steroid skeleta were carried out to produce novel steroids for biological testing.



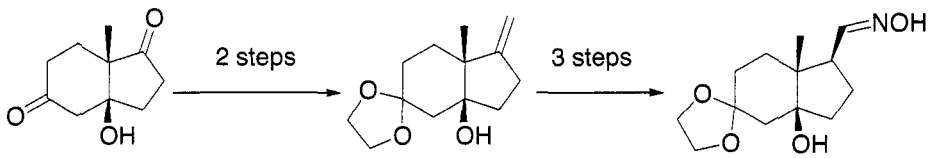
Tietze and his co-workers prepared estradiol and a number of other steroid derivatives using a compact sequential Heck reaction approach.[27] Compound **51** was obtained from the known Hajos–Wiechert ketone derivative **50** in 3 steps. Heck reaction with palladium(II) acetate in the presence of triphenylphosphine gave intermediate **52**, the precursor of the second Heck reaction. Additional steps converted steroid analog **53** into estradiol (**54**).





Cardiac glycosides, steroids of plant origin with a carbohydrate moiety at the 3β position, are a mainstay treatment for congestive heart failure. As such, there has been an ongoing interest in the synthesis of natural products related to digoxin and the preparation of analogs of the most bioactive compounds. This work has encompassed the preparation of parts of the parent steroids and unexpectedly modified hydroindene derivatives.

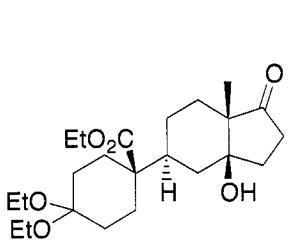
Medarde and co-workers have prepared a number of truncated cardenolide analogs; these compounds incorporate the C–D rings of the steroid skeleton.[28] This work began with modifications of the readily available Hajos–Parrish ketone **2** or the dehydrated analog thereof. A summary of the preparation of an oxime analog **55** is shown below. In addition to the protected carbonyl compound shown, the corresponding keto analog was also prepared. The aldehyde intermediate obtained after hydroboration–oxidation was converted into other derivatives (not shown) as well.



2, Hajos–Parrish ketone **55**

Medarde and co-workers prepared modified Hajos–Parrish ketones **56** and **57** as simple cardenolide analogs.[29]

Cerri and his co-workers looked at a different class of truncated analogs; these compounds were prepared in multi-step syntheses from Hajos–Parrish ketone.[30] The inspiration for the oxime substitution in this series came from a series of novel, highly active oxime substituted steroid analogs prepared in the same laboratory. While the truncated compound **58**



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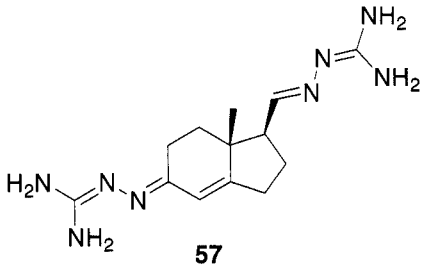

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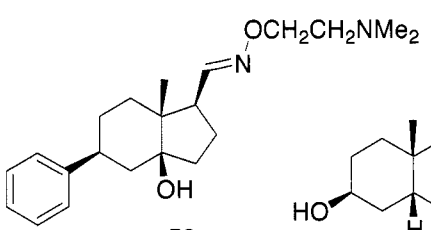
exhibited Na^+,K^+-ATPase activity in the micromolar range, this was not as potent as the modified steroid **59**, which showed nanomolar potency.



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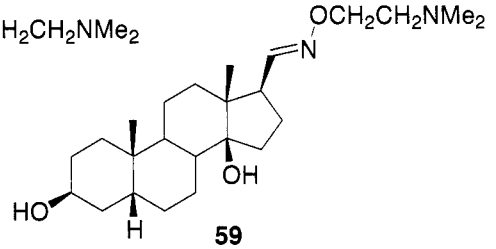
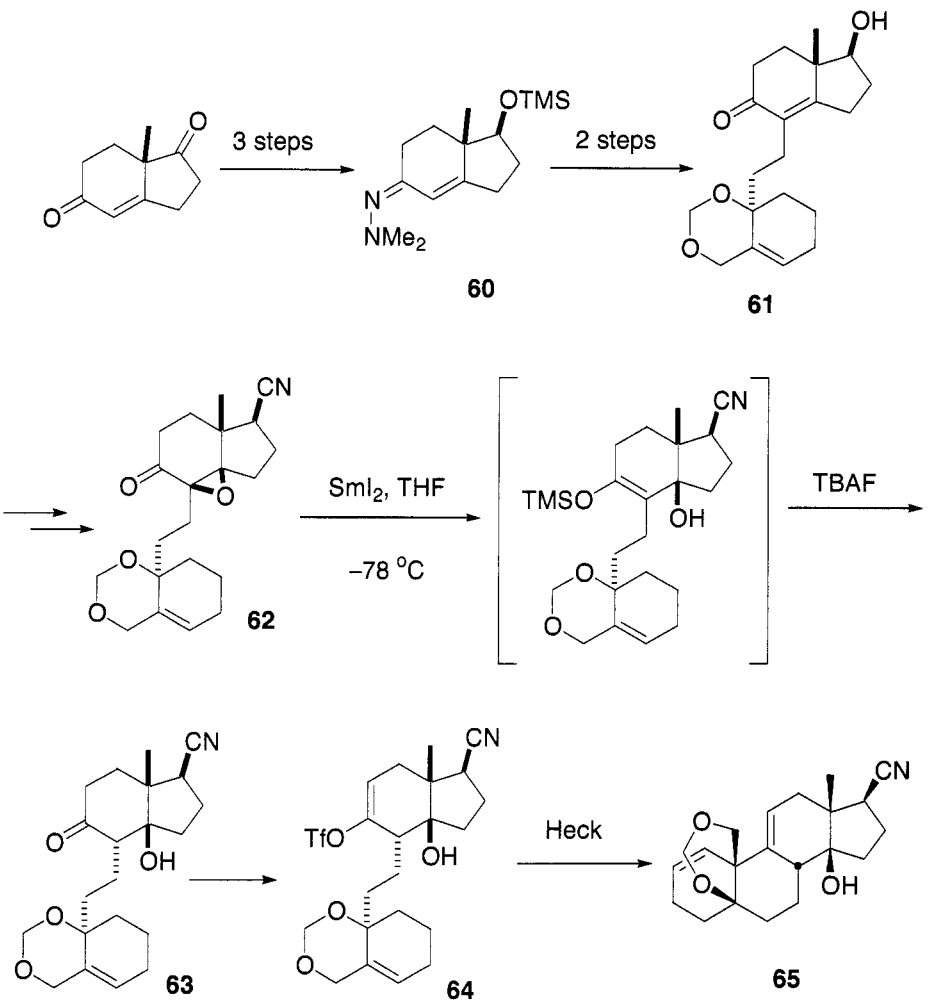
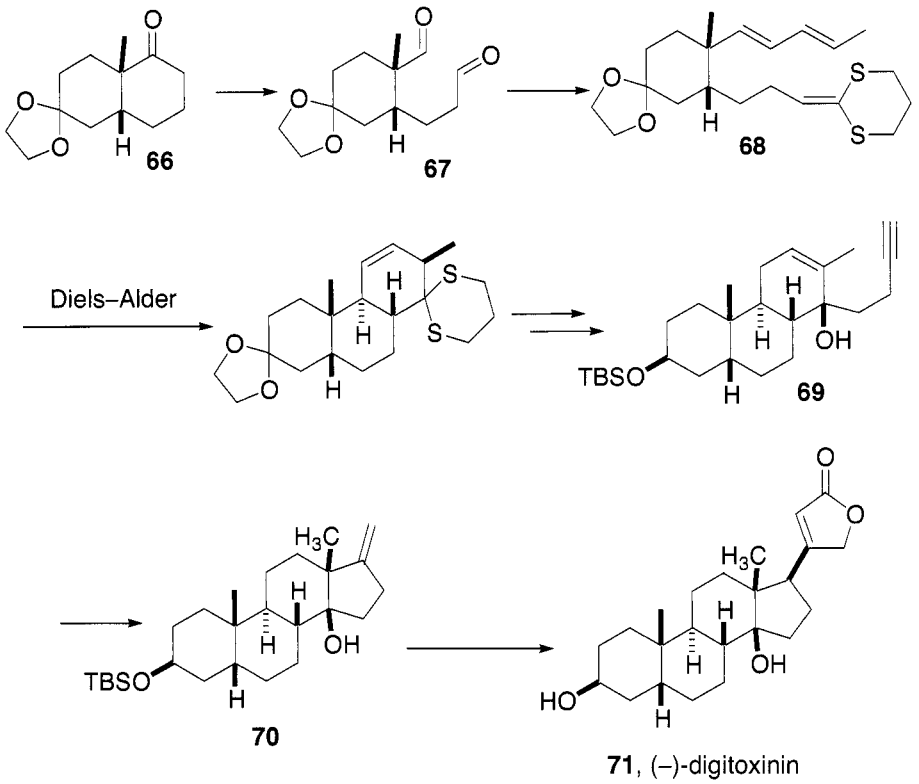


59

Overman and his co-workers developed an elegant entry into the cardenolide steroid skeleton utilizing an intramolecular Heck reaction; since this reaction favours the formation of *cis*-substituted polycycles, it is well suited for establishing the stereochemistry at the A/B ring junction.[31] Hajos–Parrish ketone was converted into **60** using three standard steps. Intermediate **60** was converted into its lithium salt and reacted with a suitable iodide to provide **61** after deprotection. After conversion of the alcohol into the cyano group, the C-14 hydroxyl was installed following a Luche reduction, directed epoxidation, and oxidation (with TPAP) to the ketone. Reductive opening of the epoxide **62** in the presence of TMS-imidazole gave the bracketed intermediate, which was selectively protonated from the β face upon treatment with TBAF and silica gel. Conversion of ketone intermediate **63** into the corresponding vinyl triflate **64** was followed by the intramolecular Heck reaction to give the cardenolide steroid skeleton **65**. A more concise second generation approach took advantage of much of the chemistry shown below to produce a slightly more functionalised cardenolide.



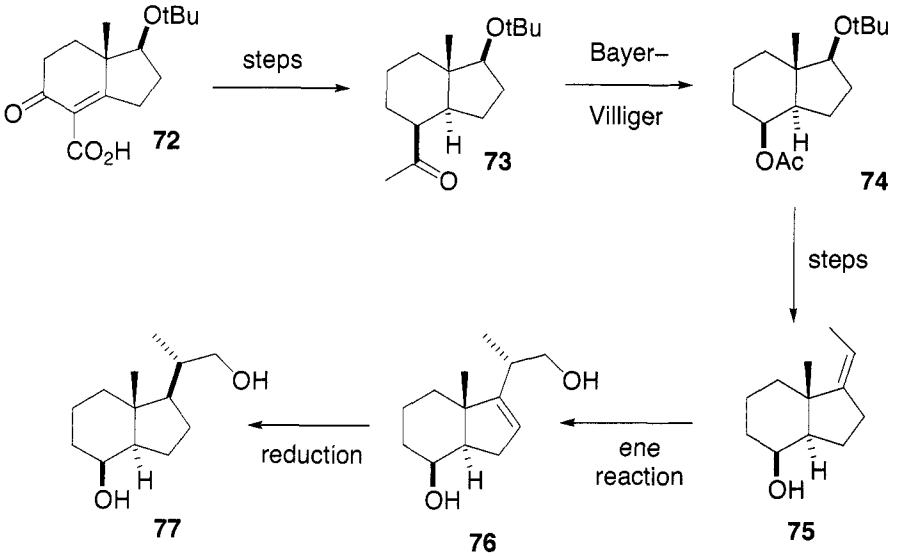
A section on cardenolides would not be complete without mentioning the total synthesis of (+)-digitoxinin by Stork and his co-workers.[32] Protected Wieland–Miescher ketone **66** was converted into compound **67** via formation of the trimethylsilyl enol ether; ozonolysis of the enol ether gave a mixture of hydroxyketones, which was reduced to the corresponding diol and then cleaved with sodium periodate to yield dialdehyde intermediate **67**. Compound **67** was then elaborated into Diels–Alder precursor **68** in two steps. After completion of the Diels–Alder reaction, four additional steps led to the preparation of intermediate **69**, which was ideally set up for a vinyl radical cyclization. Key intermediate **70** was then elegantly converted into (+)-digitoxinin (**71**).



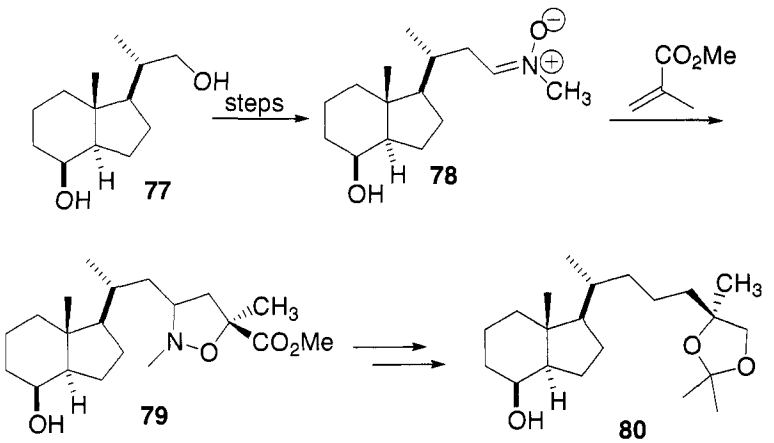
Vitamin D, an essential steroid hormone required for bone growth and maintenance, is converted into the biologically active 1,25-dihydroxyvitamin D (calcitriol) via metabolism in the liver and kidneys.[33] Vitamin D receptors are widely expressed throughout the body and play important roles in the regulation of cell proliferation and differentiation. The many useful biological properties of Vitamin D and its derivatives have led to an active research effort to explain which part of the molecule contributes to what function and if it is possible to make analogs that selectively function in the calcium homeostasis pathway or the regulatory pathways. Since vitamin D contains a chiral bicyclic 5–6 membered ring system, the Hajos–Wiechert reaction is ideally suited for the preparation of the basic ring system or substituted variations thereof. Not surprisingly, a number of research groups have used the reaction exactly for that purpose.

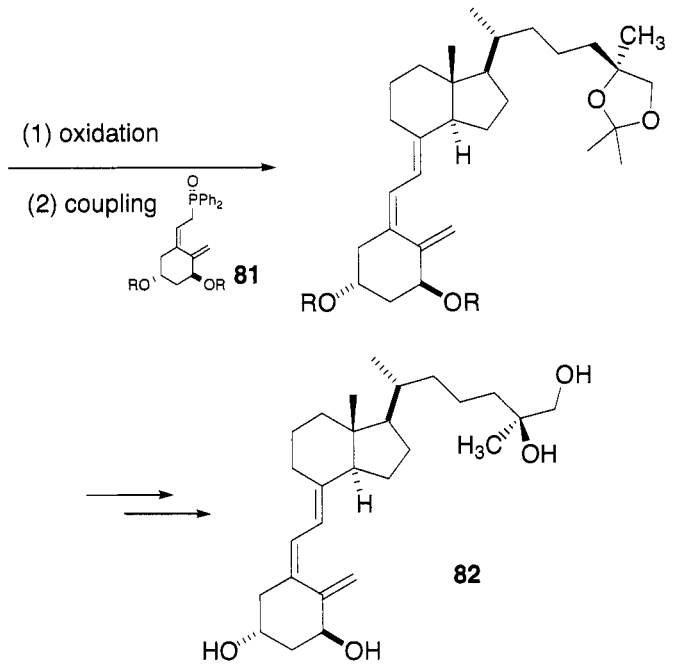
One of the first applications of the Hajos–Wiechert reaction in the vitamin D area was undertaken by Uskoković's group at Hoffman LaRoche.[34] The starting point of a synthesis of 1a,25*S*,26-trihydroxy-cholecalciferol was the known acid derivative **72**. After five steps, intermediate **73** was converted into the acetate **74** via the Bayer–Villiger oxidation. Following a deprotection, oxidation and acetate removal step, the

resulting intermediate ketone was converted into alkene **75** using ethylidine triphenylphosphorane. Intermediate **75** underwent an ene reaction with *para*-formaldehyde in the presence of boron trifluoride etherate to give compound **76**. Reduction produced the known diol **77**.

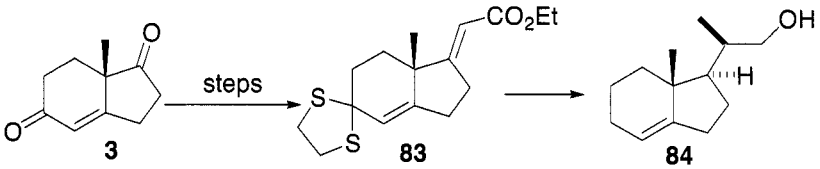


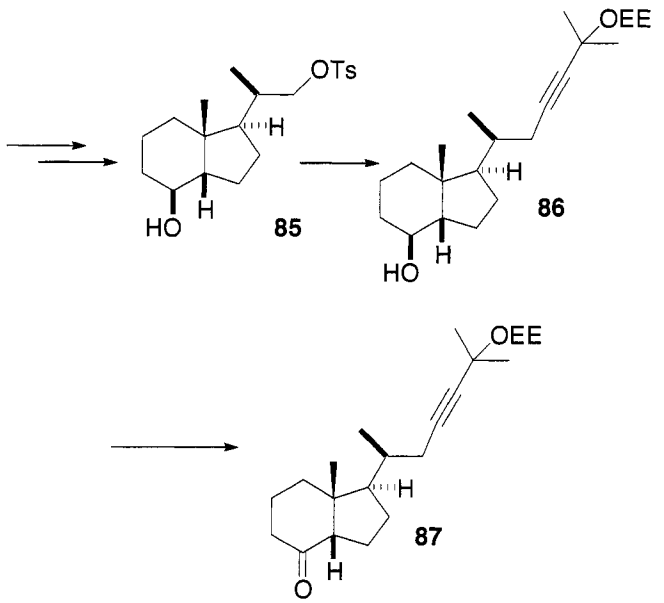
The completion of the synthesis continues with conversion of diol **77** into nitrone **78**. A cycloaddtion reaction with methyl methacrylate produced intermediate **79**, which was further elaborated into compound **80**. Oxidation of **80** with 2,2′-bipyridinium chromate is followed by coupling with the anion of **81**. Deprotection gave the desired vitamin D metabolite 1α,25*S*,26-trihydroxycholecalciferol (**82**).

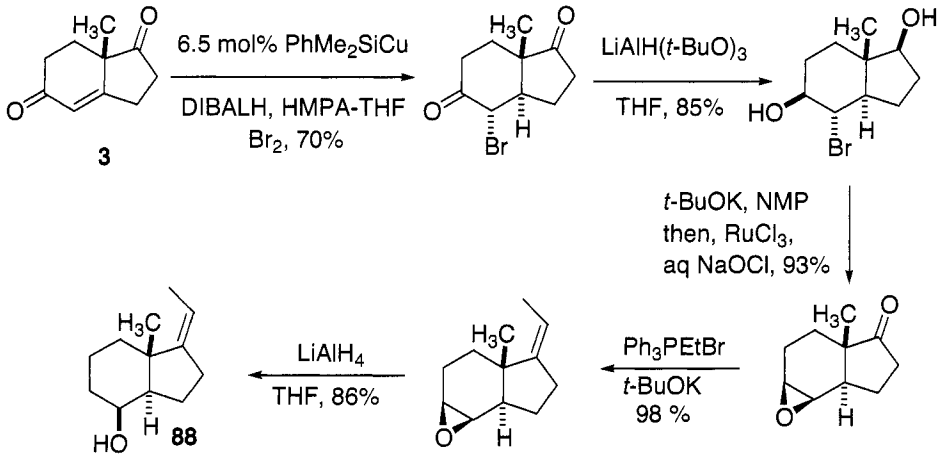




Maurits Vanderwalle and his group have explored vitamin D derivatives for many years. Some of the group's more recent research has focused on variations within the CD ring and its pendant alkyl group.[35] After formation of the dithioacetal of **3**, the remaining ketone was converted into an alkene via a Horner–Wadsworth–Emmons reaction to give intermediate **83**. In a complex one-pot procedure, **83** was converted into **84**. The dithioacetal was reductively removed with lithium; concomitant reduction of the exocyclic double bond gave an intermediate anion that was alkylated in-situ with methyl iodide; lastly, the ester was reduced to the corresponding alcohol to give **84**. After conversion of the alcohol into the corresponding tosylate, hydroboration–oxidation of the double bond gave the *cis*-CD ring bicycle **85**; this compound was then reacted with an anionic acetylide to give intermediate **86**. After oxidation of the secondary alcohol to the ketone, a viable coupling intermediate (**87**) to prepare a novel vitamin D derivative was obtained. In a related reaction sequence, Vanderwalle's group also prepared related CD analogs containing two cojoined six membered rings derived from Wieland–Miescher ketone.

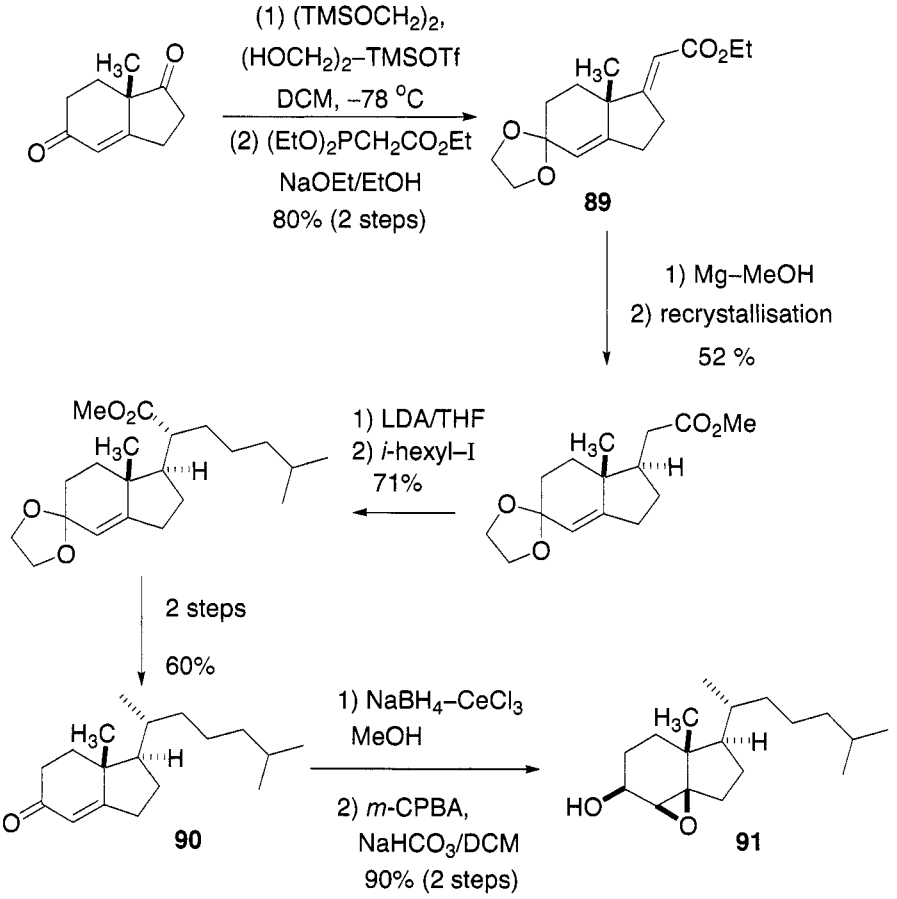




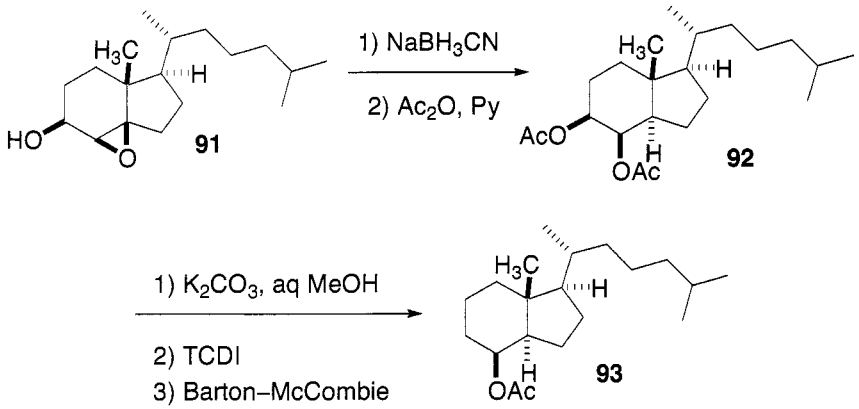


One of the most challenging vitamin D precursors to prepare is (3a*R*,4*S*,7a*S*)-(Z)-ethylidene-7a-methyloctahydro-1*H*-4-indenol (**88**). Many possible approaches to this key intermediate were reviewed recently. Since then, ongoing work at Hoffman–LaRoche has produced an updated route starting from Hajos dione **3**. One of the key problems in the original approach was the thermal instability of *tert*-butyl copper hydride used in the reduction of the double bond. Replacement of *t*-BuCu with dimethylphenylsilyl copper gave a better yield than that obtained with the former reagent. The remaining steps of the synthesis of **88** are shown below.

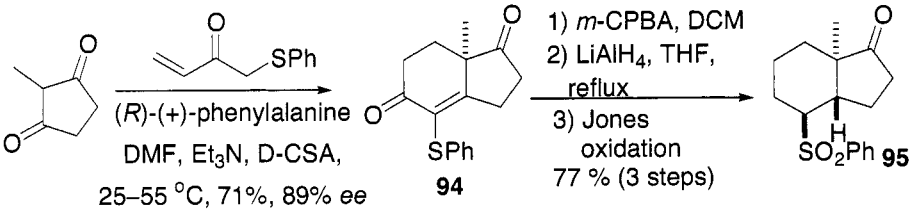
Wicha and his group in Poland have actively pursued the synthesis of vitamin D and its derivatives for many years. As such, his group has been at the forefront of developing new methodology to prepare key building blocks for the synthesis of new vitamin D analogs. One of the most recent contributions of the group focused on a new approach to the basic CD building block of vitamin D.[37] After the traditional protection–Horner–Emmons sequence, the exocyclic double bond of **89** was reduced with magnesium in methanol; the ethyl ester was also converted to the corresponding methyl ester in this step. Stereoselective alkylation with *i*-hexyl iodide introduced the alkyl sidechain in 71% yield. Conversion of the ester into the methyl group was followed by deprotection to obtain intermediate **90**, which was then selectively reduced to the alpha hydroxyl using a Luche reduction reduction; directed epoxidation then gave intermediate **91**.



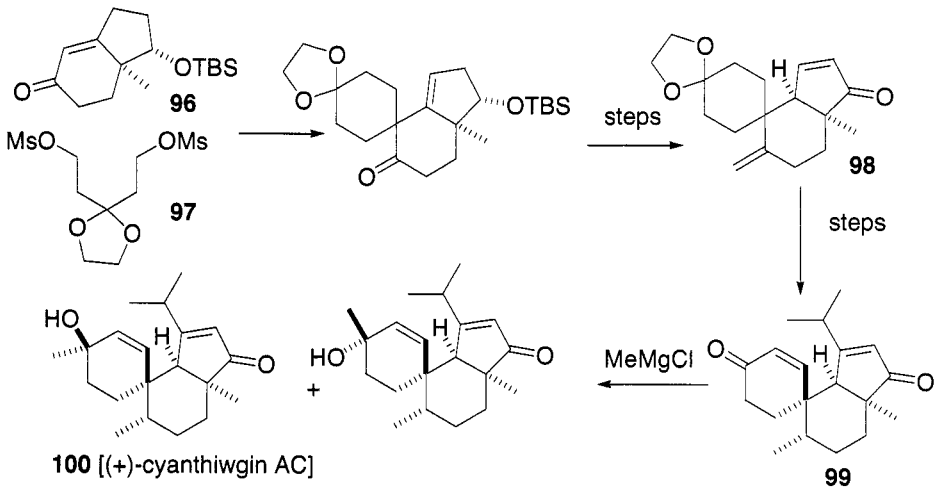
The preparation of the CD building block was continued as follows. After reductive opening of the epoxide **91** with sodium cyanoborohydride, the resulting diol was converted into the bis-acetyl ester **92**. Selective hydrolysis of the less sterically hindered ester was followed by conversion of the unprotected alcohol into the thiocarbonate. After deoxygenation via a Barton–McCombie reaction, the ensuing product **93** is set up for deprotection and oxidation to a key chiral CD intermediate for vitamin D synthesis.



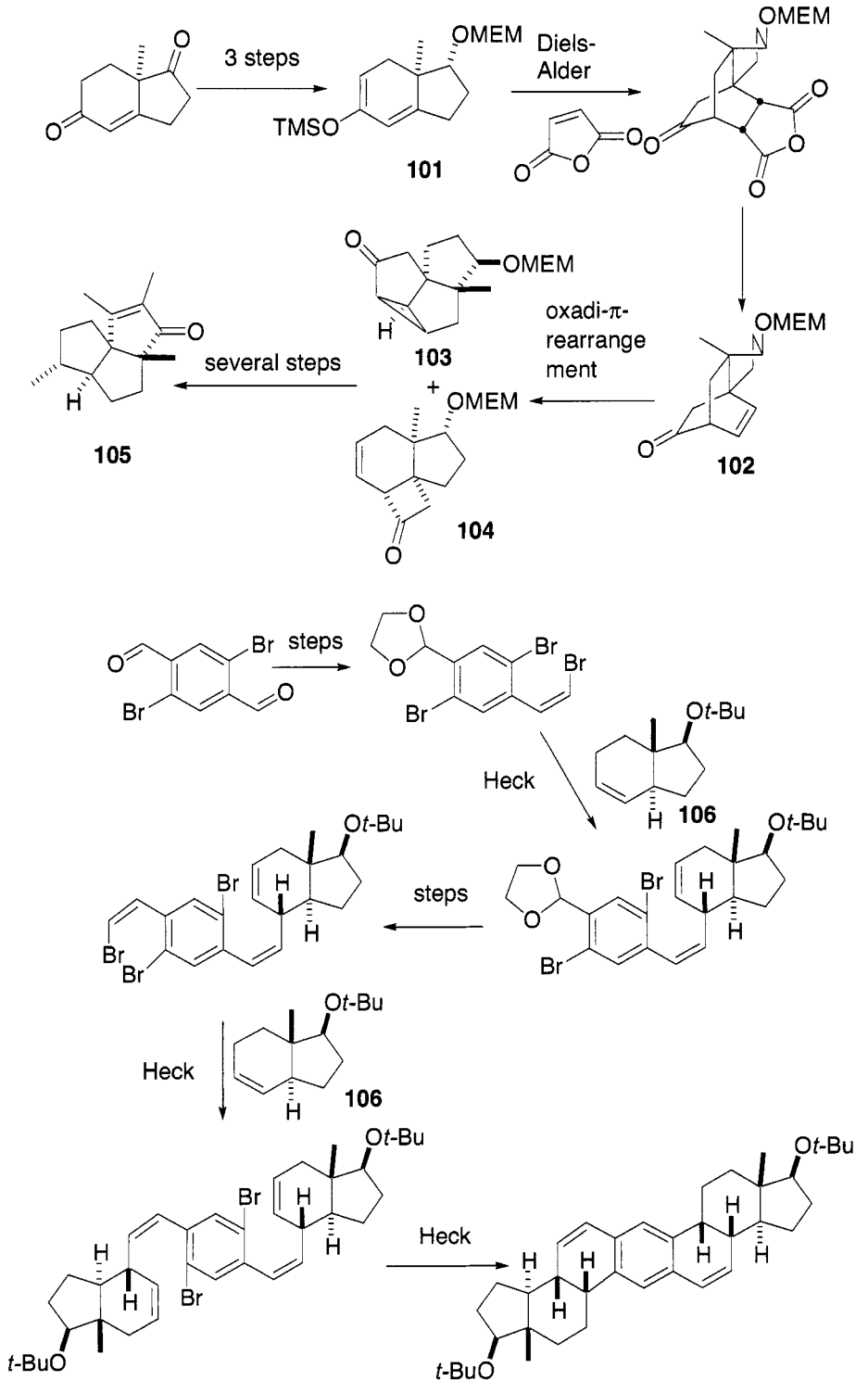
As already mentioned, the Hajos–Wiechert reaction allows entry into both enantiomers of the CD ring system. Wicha and co-workers employed the Hagiwara–Uda procedure using (*R*)-phenylalanine to produce the thiophenyl substituted CD ring system precursor **94** in 71% yield with 89% *ee*. After oxidation of the thiophenyl substituent into the corresponding sulfone with *m*-CPBA, the resulting intermediate was reduced with $LiAlH_4$ in refluxing THF to remove the ketone adjacent to the sulfone and to reduce the double bond and the other ketone. Oxidation of the intermediate alcohol with Jones reagent then gave keto-sulfone intermediate **95**. This sequence was accomplished in an overall yield of 77%. Sulfone **95** was subsequently converted into a CD ring coupling partner suitable for a modified Julia–Kocienski reaction with a lower half aldehyde fragment to yield an 1α, 25-dihydroxyvitamin D_3 diastereomer.



The last section in this chapter covers the application of intermediates obtained from the Hajos–Wiechert reaction in the total synthesis of terpenes and other natural products. Reddy and his group at Merck–Frost completed a total synthesis of (+)-cyanthiwigin, a novel diterpene isolated from the marine sponge *Epipolasis reiswigi* that exhibits cytotoxicity against *Mycobacterium tuberculosis*.[38] This total synthesis, accomplished in 13 steps from (+)-Hajos–Parrish ketone derivative **96**, commences with a carefully optimised alkylation of biselectrophile **97**. After conversion of the ketone into the corresponding methylene, the ensuing intermediate was converted into **98**. Following the stereoselective addition of a vinyl cuprate, the ensuing product was further manipulated to obtain the penultimate intermediate **99**. Low temperature Grignard reaction provided a mixture of 2-methyl adducts, favouring the desired natural product **100** in a 2:1 ratio. The pivalate protected enantiomer of **96** was used by Molander *et al.* in work towards the total synthesis of variecolin.[39]

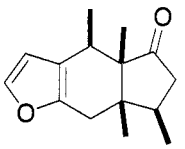


Denmuth and his group developed a novel approach to prepare linear and angular triquinanes using an efficient triplet-sensitised oxadi-π-methane rearrangement.[40] The enantiomeric synthesis of (–)-silphiperfol-6-en-5-one starting from **3** is outlined below. Diketone **3** was converted into Diels–Alder precursor **101** via a reduction, protection (MEMCl) and enol silyl ether formation sequence. After Diels–Alder reaction with maleic anhydride, the resulting adduct was converted to olefin **102**, which underwent the triplet-sensitised oxadi-π-methane rearrangement to give products **103** and **104**. Intermediate **103** was then converted into (–)-silphiperfol-6-en-5-one (**105**) in several additional steps.

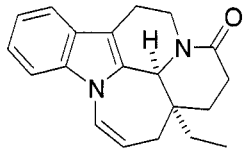

3 steps
TMSO
OMEM
101
Diels-
Alder
OMEM
oxadi-π-
rearrange
ment
OMEM
102
OMEM
103
+
OMEM
104
several steps
105
Br
steps
Br
Br
Br
Heck
Ot-Bu
106
Ot-Bu
steps
Heck
Ot-Bu
106
Ot-Bu
Heck
Ot-Bu
t-BuO
t-BuO

The cephalostatins are a group of cytotoxic dimeric steroid derivatives from the marine worm *Cephalodiscus gilchristi.* Tietze and Krahnert prepared a group of natural product analogs using multiple Heck reactions using derivative **106** obtained from the Hajos–Wiechert reaction; their approach is outlined below.[41]

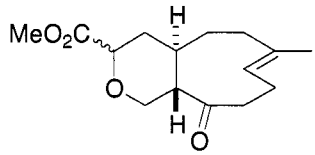
Lastly, the figure below lists a number of other natural products for which Hajos–Parrish ketone and other derivatives from the Hajos–Wiechert reaction were employed as chiral building blocks to achieve partial or complete total syntheses.



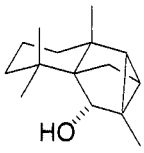
Pinguisone
Jommi *et al.*[42]



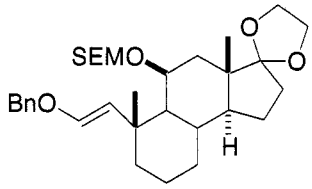
Vincamine intermediate
formal total synthesis
Takano *et al.*[43]



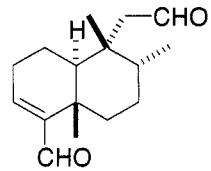
Xenicane intermediate
Pfander *et al.*[44]



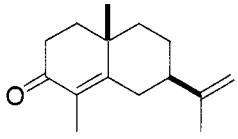
(+)-Cycloyltaylan-5α-ol
Hagiwara *et al.*[45]



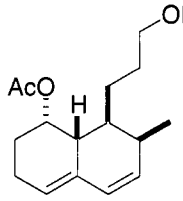
(+)- Wortmannin intermediate
Ohshima and Shibasaki *et al.*[46]



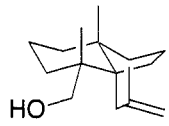
Cleoricidin intermediate
Kim Almstead *et al.*[47]



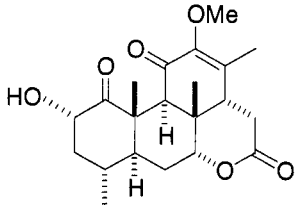
α-Cyperone
Agami *et al.*[48]



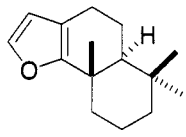
Compactin intermediate
Daniewski and Uskokovic[49]



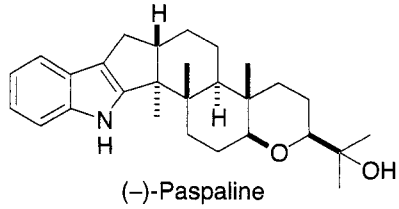
(–)-myltaylenol
Winterfeldt *et al.*[50]



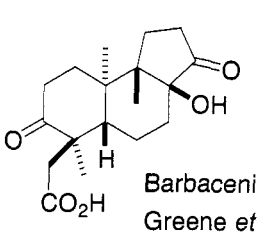
(–)-Picrasin B
Watt *et al.*[51]



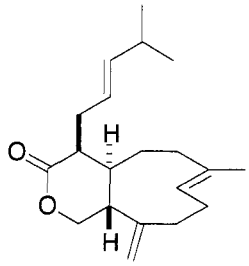
(+)-Pallescensin
Smith and Meshaw[52]



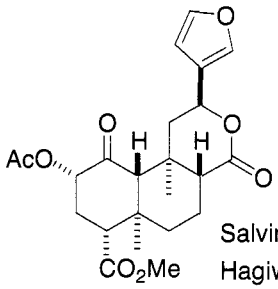
(–)-Paspaline
Smith *et al.*[53]



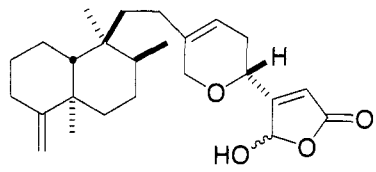
Barbacenic Acid
Greene *et al.*[54]



Coraxeniolide-A
Leumann *et al.*[55]
Larianov & Corey[56]



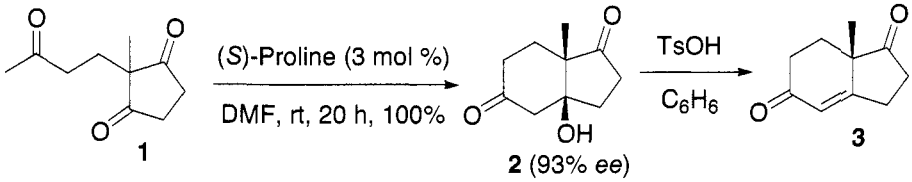
Salvinorin A
Hagiwara *et al.*[57]



(+)-Cacospongionolide B
Snapper *et al.*[57]

2.2.6. *Experimental*

The experimental procedures in this section are based on two *Organic Synthesis* reports. The first one involves the preparation of **3**, whereas the second outlines the synthesis of Wieland–Miescher ketone **4**.



*Preparation of (7aS)-7a-Methyl-2,3,7,7a-tetrahydro-7a-methyl-1-H-indene-1,5-(6H)-dione (**3**).*[59]

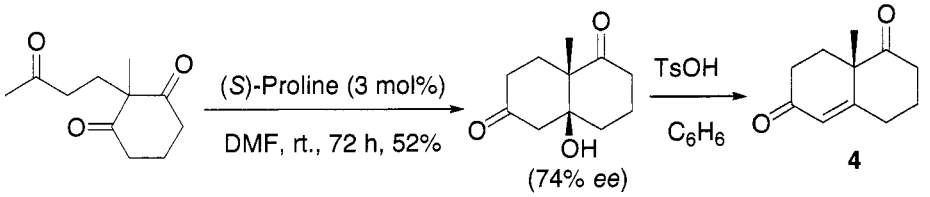
Starting material **1** is prepared as follows from 2-methyl-1,3-cyclopentanedione and methyl vinyl ketone (MVK). The reaction is carried out in a 1.0 L three neck round-bottom flask equipped with a condenser and an internal thermometer. The dione (112.1 g. 1.0 mol) and MVK (140 mL, 120.96 g, 1.72 mol) are suspended in 230 ml deionised water and 3.0 mL of glacial acetic acid is added. The reaction is heated at 70 °C until judged complete by GLC (typically 1–2 h). After cooling down, the reaction is worked up by extracting the reaction mixture three times with dichloromethane. The combined extracts are washed with brine (2 ×). After two extractions of the brine wash with dichloromethane (2 × 100 mL), the

combined organic extracts are dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue is further dried on a rotary evaporator for an additional 16 h. The triketone **1** was obtained as an orange oil in quantitative yield (181.8 g).

Intermediate **2** [(+)-(3a*S*,7a*S*)-2,3-3a,4,7,7a-hexahydro-3a-hydroxyl-7a-methyl-1*H*-indene-1,5(6H)-dione] was prepared as follows. *S*-(–)-proline (863 mg, 7.5 mmol) and 188 mL of freshly distilled DMF were placed into a 500 mL 3-neck flask with a nitrogen inlet. After degassing the solution four times by alternative evacuation and flushing with nitrogen, the flask was wrapped in aluminium foil and cooled to 15 °C. 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (45.5 g, 0.25 mol) was added to the flask. An additional 62.5 mL of DMF was used to ensure complete transfer of the starting material. After repeating the degassing procedure, the suspension was stirred for 48–72 h at 15 °C. The reaction turned brown as the reaction proceeded. Once the reaction was judged complete by TLC, the solution of the intermediate ketol **2** was used directly in the preparation of **3**.

A 3-neck flask fitted with a pressure-equalizing addition funnel is filled with 50 mL of DMF and cooled to –20 °C. Concentrated sulfuric acid (2.70 mL, 4.97 g, 48.6 mmol) was added over 5 to 10 min at a rate that maintained a temperature between –15 and –20 °C. The flask containing ketol **2** is placed in an oil bath and heated to 95 °C. At approximately 70 °C internal temperature, an 18.8 mL aliquot of the sulfuric acid solution is added as one batch. The reaction mixture is heated for 3 h at 95 °C; an additional batch of sulfuric acid solution (7.5 mL) was added after 1 h. After the reaction is judged complete by GLC, the solvent is removed at 0.3 mm pressure to give a brown oil. The residue is dissolved in 375 mL dichloromethane, washed with two portions of sodium chloride saturated 2.0 N aqueous sulfuric acid (190 mL each), two portions of sodium chloride saturated aqueous sodium bicarbonate solution (190 mL each) and finally one 190 mL portion of brine. Each aqueous wash is back extracted twice with the same 190 mL portion of dichloromethane. The combined organic extracts are dried over sodium sulfate, filtered and concentrated *in vacuo* to yield approximately 39 g of an oily, brown semisolid. The residue is taken up in 78 mL of ethyl acetate and directly loaded onto a silica gel column (78 g); after elution with 600 mL of ethyl acetate, the column fractions are concentrated to yield 37.2 to 38.8 g of a tan crystalline solid. The solid is further purified by bulb-to-bulb distillation (120–135 °C, 0.1 mm) and recrystallisation. The approximately 36 g of yellow cream solid are dissolved in refluxing ether (74 mL). After addition of hexanes (19 mL), the resulting turbid suspension is cooled to room temperature, seeded and then placed into a 17 °C water ice bath for 30 min. The precipitate is collected on

a medium porosity frit, washed with ice-cold 1:1 ether/hexanes and then dried to obtain 28.7–31.3 g (70–76% yield) of a white crystalline solid.



Preparation of Wieland–Miescher ketone **4** *(2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione)*

2-Methyl-1,3-cyclohexanedione (126.1 g, 1.0 mol) and 300 mL distilled water are placed into a 1 liter round-bottomed flask fitted with a reflux condenser and a thermometer. Acetic acid (3.0 mL), hydroquinone (1.1 g) and methyl vinyl ketone (142 g, 167 mL, 2 mol, freshly distilled) are added and the resulting mixture is heated for 1 h at 75 °C. After cooling to room temperature, the reaction mixture is saturated with 103 g of sodium chloride and poured into 400 mL of ethyl acetate. After separation of the layers, the aqueous phase is twice extracted with ethyl acetate (150 mL each). The combined organic extracts are washed with two 200 mL portions of brine solution, dried over sodium sulfate, filtered, and then concentrated *in vacuo* to yield 210.8 g of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione as a pale yellow oil.

Proline (5.75 g, 0.05 mol, finely ground), 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (210.8 g crude material) and 1 L of anhydrous DMSO are added to a 3 L round-bottomed flask. After stirring for 120 h at room temperature, the reaction mixture is concentrated *in vacuo* (65 °C, 1.0 mm) to give 206.9 g of a reddish-violet oil. The oil, dissolved in 100 mL toluene, is loaded directly onto a hexanes wetted silica gel column (9 cm × 60 cm, 1.5 kg 70–230 mesh silica gel) and eluted with 1 L of hexanes/ethyl acetate (5:1) and then hexanes/ethyl acetate (3:2). After collecting approx. 5 L of eluent as 300 mL fractions, the product begins to elute. The fractions containing product are combined, concentrated *in vacuo* and then placed under high vacuum to obtain 154.2 g of an orange colored oil. The material, which may solidify, is dissolved in 535 mL of ether, filtered and then combined with the ether wash. After cooling to 3 °C, the solution is seeded and the mixture is left undisturbed at –20 °C for 18 h. After careful decantation of the supernatant, the crystals are collected and rinsed with ice-cold 1:1 hexanes/ether. After drying under high vacuum, a first crop 85.9 g of white crystals is obtained. If desired, a second crop of material can be obtained by concentrating all filtrate down to an orange oil (67.1 g). The solid is dissolved in 604 mL ether, cooled to 3 °C, seeded with racemic **4**, and then

stored for 18 h at –20 °C. After careful filtration, 36.3 g of wet solid, racemic **4** are obtained. After concentration of the filtrate to 30.6 g of an oil, the oil is dissolved in 100 mL ether. The flask is rinsed with 114 mL ether and the combined filtrates are cooled to 3 °C, seeded with the (*S*)-enantiomer of **4** and then stored overnight at –20 °C. After filtration and washing, an additional crop of 15.3 g of (*S*)-enedione **4** is obtained. Total yield: 101.2 g (56.8%).

2.2.6 References

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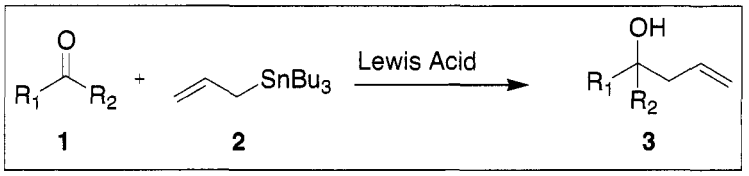
2.3 Keck allylation reaction

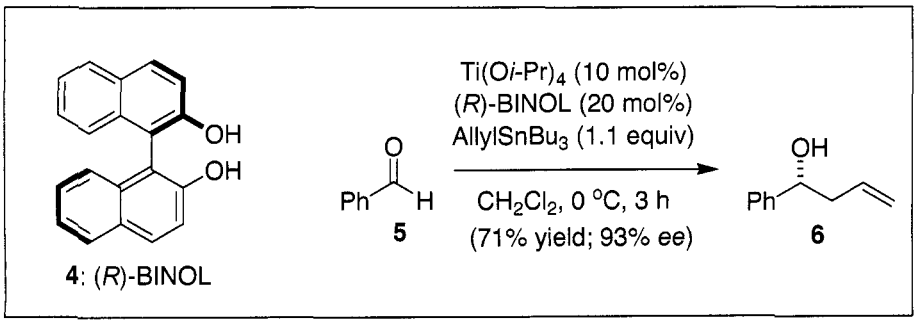
Marco A. Biamonte and Thomas A. Wynn

2.3.1 Description

The Keck reaction is the allylation of a carbonyl compound performed with an allylstannane and mediated by a Lewis acid. The reaction product is a homoallylic alcohol.



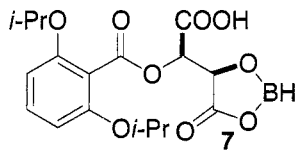
To be accurate, the definition should be restricted to asymmetric reactions catalyzed by a combination of 1,1′-binaphthalene-2,2′-diol (BINOL, **4**) and Ti(O*i*-Pr)$_4$. Nonetheless, this chapter will give some background on non-chiral Lewis acid promoters, and include other asymmetric catalytic systems. We will not discuss the allylations that are promoted by Lewis bases, which are reviewed elsewhere,[1] nor cover the reactions with other electrophiles. Excellent reviews already exist on: "*Selective Reactions Using Allylic Metals*",[2] and "Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones",[3] as well as in the comprehensive monograph "*Modern Carbonyl Chemistry*".[4] The use of BINOL-based catalysts in other fields of organic synthesis has also been reviewed.[5,6]



Caution: Stanannes are notoriously toxic, and should be treated with care. In rodents, tributyltins damage the bile duct, and induce immunotoxicity and tumors of endocrine origin.[7]

2.3.2 Historical Perspective

The reaction of allylstannanes with carbonyl compounds (**1** + **2** → **3**) was first published by Neumann in 1967.[8] The reaction was performed thermally, and required high temperatures (T = 150–200 °C). It took nearly a decade to realize that the reaction could be performed at lower temperatures (T= –78 °C) by using Lewis acids, as found by Maruyama in 1978.[9] The Lewis acids were used in stoichiometric amounts and, strictly speaking, the acids acted as promoters rather than catalysts. The reaction quickly gained in popularity, in part thanks to the efforts of Yamamoto, who investigated the stereochemical issues of said transformation.[10] In parallel, Yamamoto also developed a series of chiral Lewis acids: the tartrate-derived acyloxyboranes (*e.g.,* **7**). Surprisingly, the application of Yamamoto's catalyst to the reaction of allylstannannes with aldehydes was published by another investigator, Marshall.[11] The chiral promoter still had to be used in stoichiometric amounts, but one year later, in 1993, the first chiral catalysts emerged. Three groups, led respectively by Mikami and Nakai,[12] Umani–Ronchi and Tagliavini,[13] and Keck,[14–16] independently reported that combinations of BINOL (**4**) with a source of Ti(IV) led to useful levels of stereoinduction. More recently, BINOL/Zr catalysts[17–19] and BINOL/In catalysts[20] have also been reported, but to date the BINOL/Ti catalysts remain the most popular ones.



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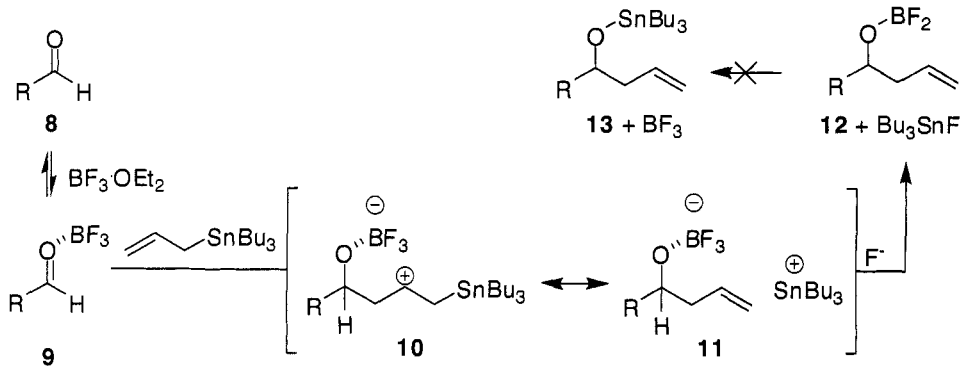
The differences between promoters of the BINOL/Ti family lie in the details. Mikami and Nakai, as well as Umani–Ronchi and Tagliavini, used (i-PrO)$_2$TiCl$_2$ as titanium source, in a 1:1 ratio with BINOL. The best results were obtained with thoroughly dried 4 Å molecular sieves (250 °C, 0.1 Torr, 12 h).[13] Keck used (i-PrO)$_4$Ti and BINOL, initially in a 1:1 or 1:2 ratio, with molecular sieves and catalytic CF_3COOH or CF_3SO_3H.[14] He then advocated the 1:2 ratio, and found the acid and molecular sieves to be superfluous.[15] Dichloromethane can be replaced with toluene or pentane, a modification claimed to improve the reproducibility of the reaction, and which bypasses

the need for molecular sieves.[21] The BINOL/Ti catalysts are poorly stable towards air and moisture, and degrade over a few hours at room temperature.

A modern trend is to investigate as many chiral ligands as possible to extend the scope of the asymmetric Keck reaction. The ligands include BINAP, salen, and pybox-based system, and will be discussed later. Another goal is to simplify the reaction conditions by developing water-tolerant Lewis acids. The hydrate $GdCl_3 \cdot 6H_2O$ can be used in catalytic amounts in acetonitrile at room temperature to affect the allylation of aldehydes.[22] Stoichiometric amounts of $ZnCl_2$,[23] or catalytic amounts of $Sc(OTf)_3$[24] allow to perform allylations in water-acetonitrile solutions. As for asymmetric catalysts, BINOL/$InCl_3$ tolerates adventitious moisture, and in fact performs best with 2 equivalents of water.[20] Alternatively the BINAP/$AgNO_3$ complex developed by Loh and Zhou is able to work in a water–ethanol mixture.[25]

2.3.3 *Mechanism*

We first illustrate the putative mechanism of the Keck reaction with $BF_3 \cdot OEt_2$. Only a fraction of the BF_3 in the reaction forms the complex to the aldehyde **8** to form the activated complex **9**. Addition of the allylstannane presumably proceeds through a β-stannyl cation **10** that is stabilized by hyperconjugation, as represented by the mesomeric form **11**. The analysis of the Hammett parameters suggests that the addition proceeds via a polar nucleophilic process, rather than a single electron transfer mechanism (the latter takes place in the addition of allyllithium and allylmagnesium halides to benzaldehyde).[26] The subsequent elimination of the stannyl group generates a new double bond. The reaction stops at the boronic ester **12**, not at the tin ether **13**.[27] Therefore, BF_3 is not regenerated, and BF_3 cannot be used in catalytic amounts.



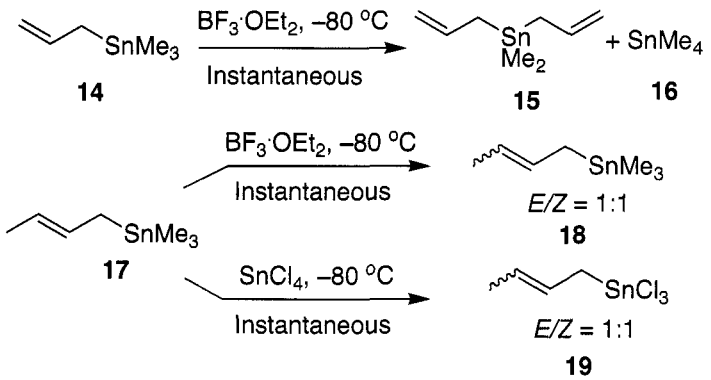
BF_3 binds to Et_2O more tightly than to aldehydes ($\Delta\Delta H$ = 1–2 kcal/mol, see Sakurai reaction more enthalpies of complexation), thus the

rate limiting step is the formation of the BF_3•aldehyde complex **9**. This is supported by the observation that electron-donating substituents on R somewhat accelerate the reaction.[28] However, if the Lewis acid is not buffered by Et_2O and can easily bind the aldehyde (*e.g.*, TMSOTf), the rate-limiting step becomes the nucleophilic addition of the allyl group. Consequently, the reaction is accelerated by electron-withdrawing groups on **8**.[29]

Equilibria between the aldehyde and its trimer (trioxane) can further complicate the picture. The BF_3-promoted Keck reaction is instantaneous at –80 °C with 4-*t*-BuC_6H_4CHO, and rapid with *t*-BuCHO, but does not take place with MeCHO at –80 °C. This is because MeCHO immediately trimerizes to *para*-acetaldehyde, which reacts only above –40 °C. Note that the desired reaction products tend to decompose if the reaction mixtures are warmed to room temperature.[27]

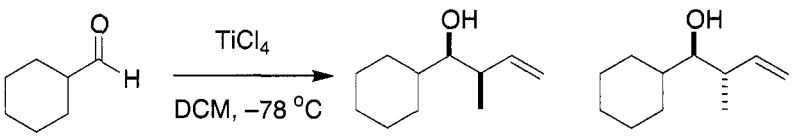
The Lewis acid

We have described the physical chemistry of Lewis acids in detail under the "Sakurai reaction", and we refer the reader to that chapter for further information. Briefly, for non-asymmetric reactions, the most popular Lewis acids are $TiCl_4$, BF_3, $SnCl_4$, and $MgBr_2$. BF_3 has only one coordination site, but $TiCl_4$, $SnCl_4$, and $MgBr_2$ have two coordination sites and form intramolecular chelates with α-alkoxyaldehydes. $MgBr_2$ is particularly effective at yielding high diastereoselectivities with alkoxyaldehydes. $TiCl_4$ can form 1 : 1 and 1 : 2 adducts with aldehydes, depending on the stoichiometry of $TiCl_4$, while $SnCl_4$ forms exclusively 1 : 2 complexes. The solvent of choice is CH_2Cl_2, with ethereal solvents (Et_2O, THF) being rarely used, because Lewis acids tend to bind more strongly to Et_2O and THF than to the aldehydes.



In the presence of BF_3•OEt_2 at –80 °C, allyltrimethylstannane (**14**) undergoes ligand redistribution: two molecules of allyltrimethylstannane (**14**) exchange their allyl group to provide diallylstannane **15** and tetramethylstannane **16** (and then tri, and tetraallylstannane).[30] *E*-Crotyltrimethylstannane **17** does not undergo such redistribution at –80 °C, but is immediately isomerized by BF_3•OEt_2 to a 1 : 1 mixture of *E* and *Z* isomers **18**.[27] With $SnCl_4$ at –80 °C, crotyltrimethylstannane **17** undergoes instantaneous and quantitative transmetallation to give, depending on the stoichiometry, crotyl$SnCl_3$ (**19**) or (crotyl)$_2SnCl_2$ which are likely the true allyl donors.[27]

This transmetallation is often faster than the addition to the aldehyde.[27] Hence the order of addition to a reaction is usually (1) aldehyde, (2) Lewis acid, and (3) stannane. Changing the order of addition can profoundly affect the course of the reaction. Keck provided a striking example,[31] wherein the "normal" sequence of addition (1) cyclohexylcarboxaldehyde **20**, (2) $TiCl_4$, and (3) crotyltributylstannane provides predominantly the *syn* adduct **21** (**21/22** = 93 : 7), while the "inverse" order (1) $TiCl_4$, (2) crotyltributylstannane, and (3) cyclohexylcarboxaldehyde provides the *anti* adduct **22** (**21/22**= 5 : 95). The inverse order probably results in a fast transmetallation to crotyl-$TiCl_3$, which unlike crotylstannanes can react via a cyclic transition state (Zimmerman–Traxler).

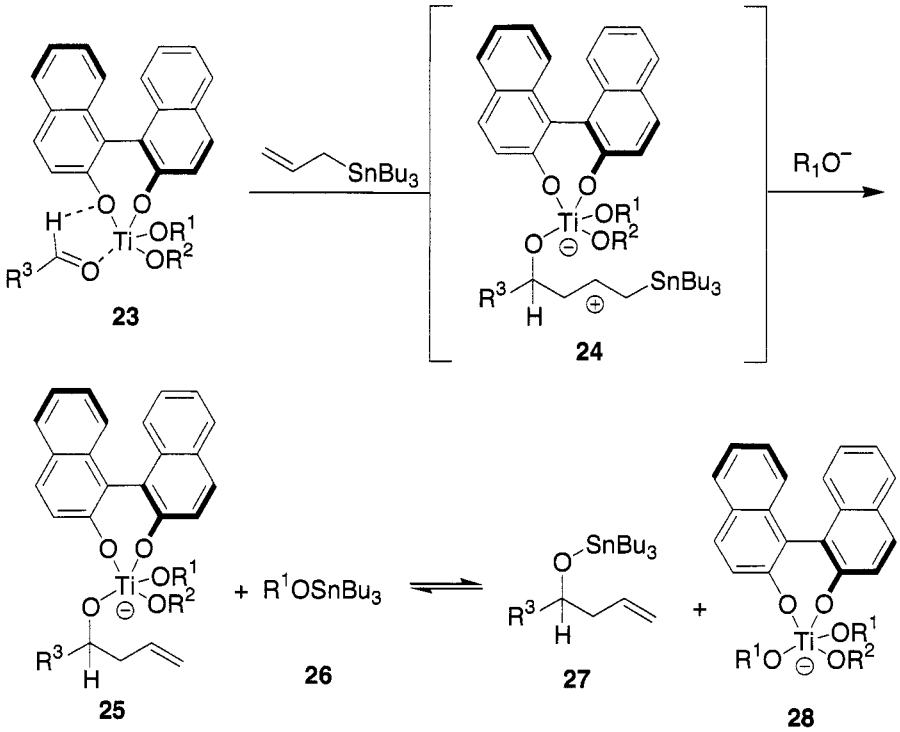


20 **21** **22**

Normal order of addition : **21:22**= 93:7
Inverse order of addition : **21:22**= 5:95

The exact nature of the BINOL/Ti catalytic species is not known. A 1 : 1 mixture of BINOL and either (*i*-PrO)$_2TiCl_2$ or (*i*-PrO)$_4$Ti in $CDCl_3$ gives (BINOL)Ti(O*i*-Pr)$_2$, which is dimeric in solution, and trimeric in the solid state.[32,33] Under strictly anhydrous conditions, (BINOL)Ti(O*i*-Pr)$_2$ is not an active as catalyst.[34] A 2 : 1 mixture of BINOL and (*i*-PrO)$_4$Ti in CD_2Cl_2 gives mixtures of uncharacterized clusters containing multiple Ti atoms.[34] Minute amounts of water are necessary for the reaction to proceed. This water can be brought by small amounts of unactivated molecular sieves, or large amounts of activated molecular sieves.[34] Whatever the catalytic species may be, it is likely to be dimeric to account for a non-linear relationship between the *ee* of the BINOL and the *ee* of the product (chiral amplification).[35]

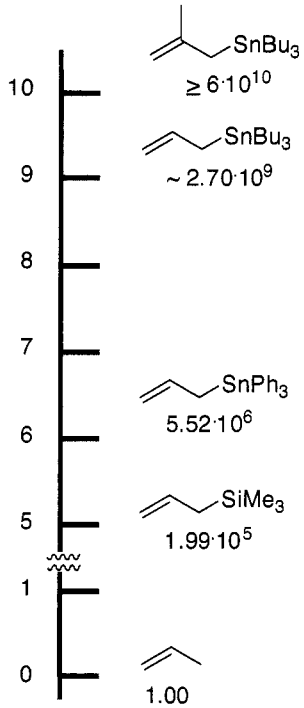
In addition, Corey has postulated a formyl hydrogen bond between the catalyst and aldehyde substrates, as in **23**, to rationalize the facial selectivity of the reaction.[36] The mechanism is thought to be similar to the one previously illustrated with BF_3, except that for the reaction to be catalytic, the titanium alkoxide **25** must eventually transmetallate to the tin alkoxide **27**, thus regenerating the catalyst (this transmetallation step does not occur with BF_3). Consequently, reactions with BINOL/Ti catalysts typically proceed at temperatures between –20 and + 20 °C.



The stannane

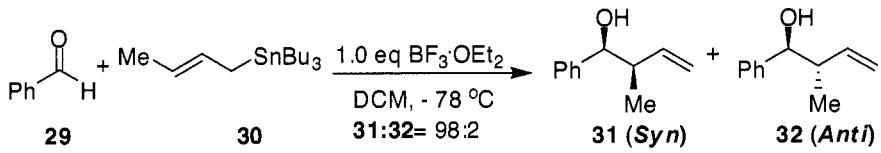
The reaction of allylstannanes with aldehydes is conceptually very close to the reaction of allylsilanes with aldehydes (Sakurai reaction). The major advantage of allylstannanes reagents is their high reactivity, a characteristic that has facilitated the development of the catalytic reactions. Allylstannanes are about 10,000 times more reactive than the corresponding allylsilanes, as measured by Mayr (Figure 1).[37] The stannyl group increases the reactivity of the double bond by a factor of 10^6–10^9 compared to H. Tributyl stannane is 10^3 times more nucleophilic than triphenyl stannane.

Figure 1: Relative Nucleophilicity of Stannanes



Stereochemistry of the transition state

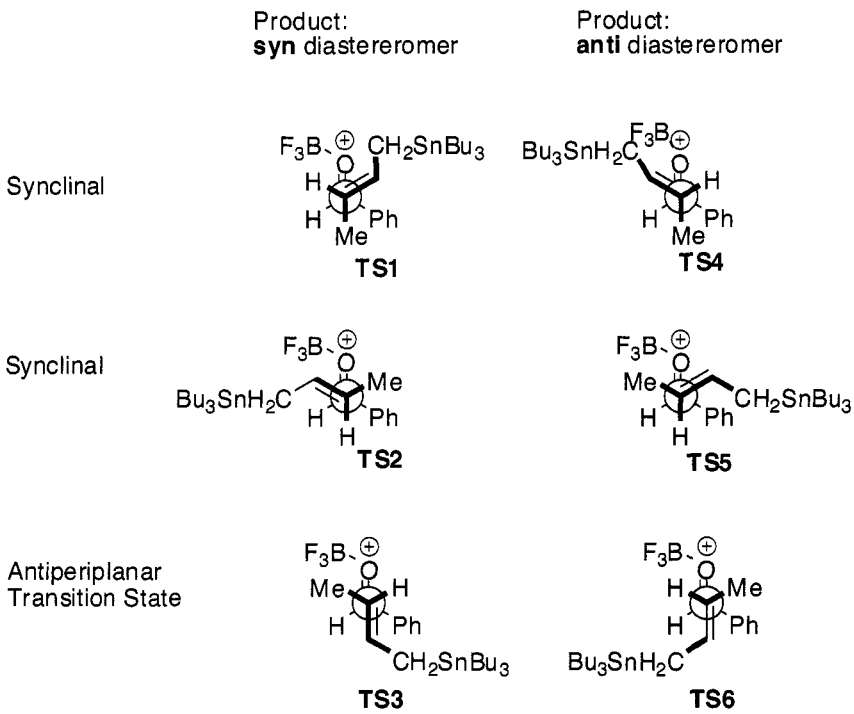
As will be discussed later, a useful feature of the Keck reaction is that both *E* and *Z*-crotylstannanes give predominantly *syn* adducts.



The reasons governing the selectivity are not obvious. Figure 2 depicts the possible transition states of the reaction between PhCHO•BF_3 and *E*-crotyltributylstannane. Based on the crystal structure of the PhCHO•BF_3 complex,[38] it is reasonable to assume that in solution, the BF_3 group coordinates *anti* to the phenyl group. The double bonds of the aldehyde and crotylstannane can be either in a synclinal or antiperiplanar arrangement, leading to 6 possible transition states (TS1–TS6). It is difficult to single out the most likely transition state. After an in-depth analysis,[39] Keck concluded that the synclincal transition state TS1 appears to best explain the results for

BF_3 promoted reactions. Keck also pointed out that the preferred transition state probably varies from one case to another owing to subtle changes in non-bonding interactions, a conclusion supported by computational studies performed with the analogous allylsilanes.[40]

Figure 2: Possible transitions states in the reaction of PhCHO•BF_3 with *E*-crotyltributylstannane



For intermolecular reactions, it is impossible to determine experimentally if the transition state is actually synclinal or antiperiplanar. However, it is possible to do so for intramolecular reactions. Denmark designed probe **33** to determine unambiguously if, in the case of an intramolecular reaction, the transition state involves a synclincal or antiperiplanar arrangement of the olefin.[3] Furthermore, the probe allows the analysis of whether the nucleofuge (Bu_3Sn group) is oriented towards (*syn*) or away (*anti*) from the oxygen atom in the olefin-yielding elimination step. The results reported in Table 1 show that the synclincal transition state is always favored ($\geq$ 86:14), regardless of the acid used. In the elimination step, the Bu_3Sn group is always oriented away from the oxygen atom.

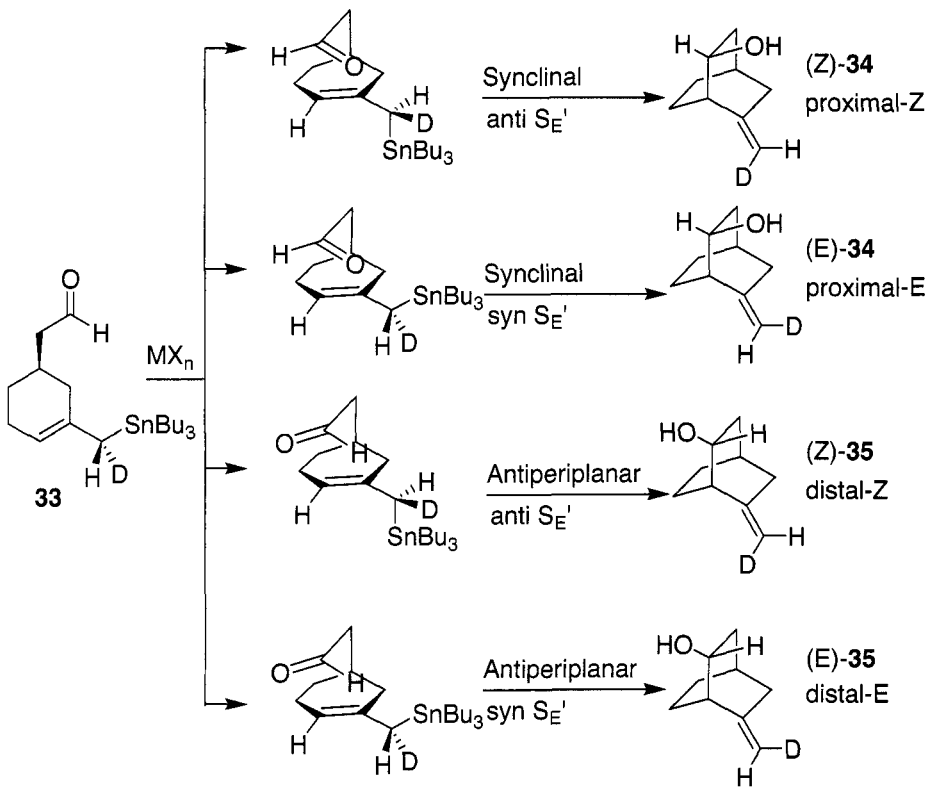


Table 1: Geometry of the transition state of the intramolecular allylation reaction with probe 33

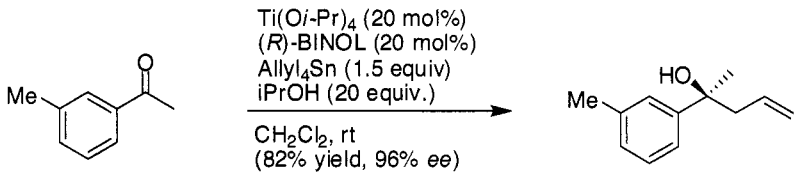
Entry	Lewis acid	Synclinal/ Antiperiplanar (**34**/**35**)	anti S_E'/ syn S_E' (*E*-**34**/*Z*-**34**)	anti S_E'/ syn S_E' (*E*-**35**/*Z*-**35**)
1	$TiCl_4$	88/12	89/11	95/5
2	$SnCl_4$	94/6	86/14	95/5
3	BF_3•OEt_2	86/14	92/8	95/5
4	CF_3SO_3H	97/3	93/7	
5	CF_3COOH	>99/1	93/7	

2.3.4 Variations and Improvements

Additives

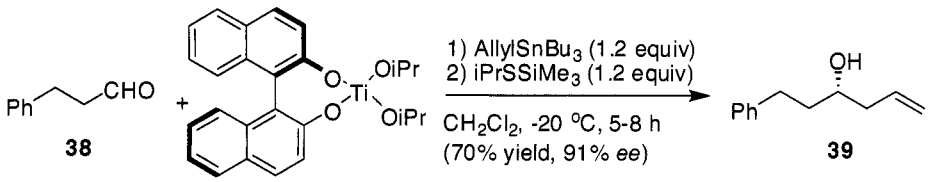
The Keck reaction can be accelerated by using additives, which facilitate the equilibria leading to the regeneration of the catalyst **28**. Walsh found that isopropanol increases the rate and the enantioselectivity of the allylation of

ketones catalyzed by BINOL/(i-PrO)$_4$Ti. For 3-acetophenone **36**, the *ee* increases from 51 to 96% upon addition of isopropanol.[32] Isopropanol can even be used without co-solvent, under highly concentrated conditions.[41] Notably, with these conditions, methyl ketones can be easily allylated.

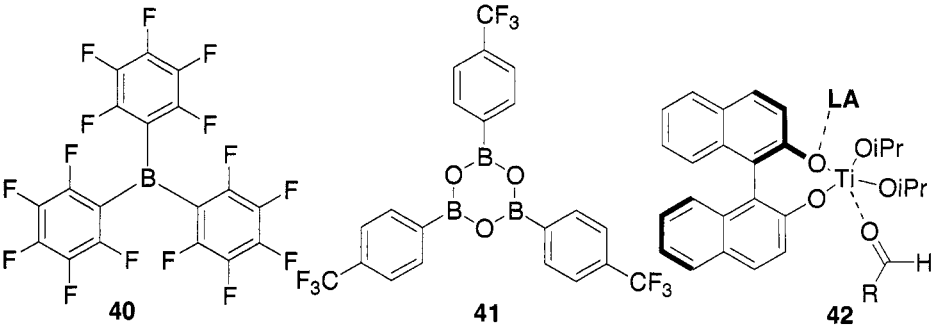


36 **37**

Yu has shown that i-PrSSiMe$_3$ enhances the reaction rate of the asymmetric Keck reaction, and allows the catalyst loading of BINOL/Ti to be decreased to 1–2 mol%. i-PrSSiMe$_3$ is prepared from (i-PrS)$_2$Pb and TMSCl, followed by distillation, and is added over several hours to a solution of the aldehyde, stannane, and catalyst at –20 °C. The additive is postulated to aid in regenerating the catalyst through the favorable formation of Sn–S and Si–O bonds.[42]

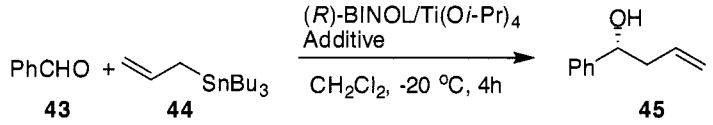


Yamamoto has shown that 1 mol% of *tris*(pentafluorophenyl)borane (**40**) or of 4-(trifluoromethyl)phenylboroxin (**41**), dramatically improve the reaction yields and enantiomeric excesses (Table 2). Yamamoto postulated that the accelerating effect may be due to an enhancement of the Lewis acidity of the titanium center via multimetallic complex **42**.[43]



40 **41** **42**

Table 2: Effect of borane and boroxin additives.[43]



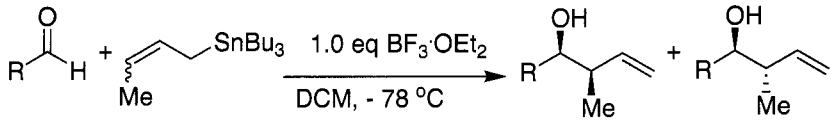
43 44 45

Entry	Additive	Yield [%]	%ee
1	None	5	51
2	$(C_6F_5)_3B$ (**40**)	77	89
3	$[4\text{-}(CF_3)C_6H_4BO]_3$ (**41**)	82	89

Diastereoselective reactions of crotylstannanes

Yamamoto recognized that the $BF_3{\cdot}OEt_2$ promoted reaction of aldehydes with crotylstannanes provides predominantly *syn* adducts irrespectively of the *E/Z* regiochemistry of the crotylstannane (Table 3).[10] The yields exceed 90% and, with *E*-crotyltributylstannane, the diastereomeric ratios are 94 : 6 or higher, which is better than for the corresponding Sakurai reaction of crotylsilanes. One exception is $PhCH{=}CHCH_2SnBu_3$, which provides *anti*, not *syn* adducts (not reported in Table 3).[44]

Table 3: Stereoselectivity in reactions of E/Z crotylstannanes with simple aldehydes.[39]

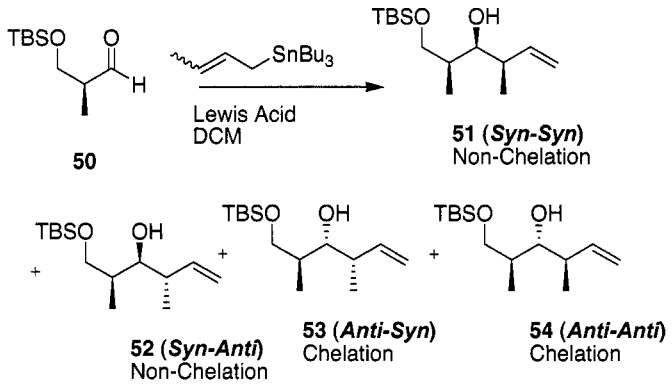


46 47 48 (*Syn*) 49 (*Anti*)

Entry	R	*Syn:anti* From *E*-stannane	*Syn:anti* From *Z*-stannane
1	*c*-C_6H_{11}–	94:6	58:42
2	Ph–	98:2	81:19
3	Ph–CH=CH–	98:2	82:18

If the aldehyde carries a chiral α-methyl group, as in **50**, the major product is the *syn–syn* adduct, in accordance with the Cram and Felkin–Anh model (Table 4). For a reminder of the Cram and Felkin–Anh rules, see "The Sakurai reaction".

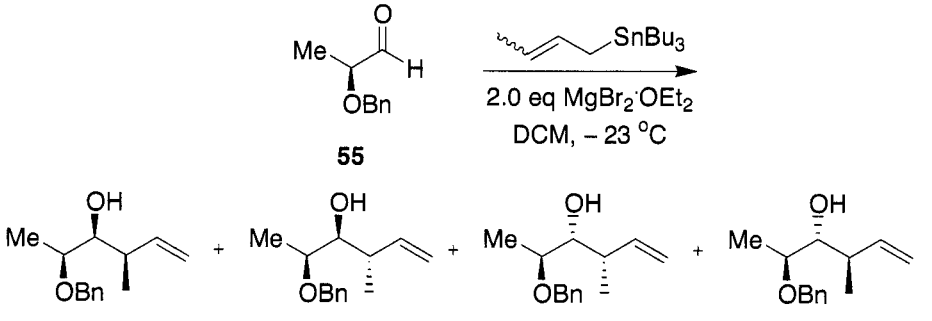
Table 4: BF_3-promoted reaction of an α-methylaldehyde with crotyltri-*n*-butylstannane in DCM at –78 °C.[39]



Entry	Stannane	Acid	*51*	*52*	*53*	*54*
1	*E*	BF_3•OEt_2	99	1	0	0
2	*Z*	BF_3•OEt_2	75	25	0	0

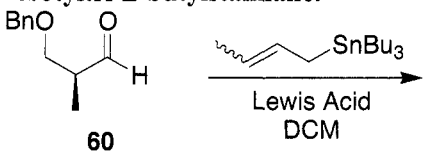
If the aldehyde carries a chiral α-alkoxy group, as in **55**, the major product is the *syn-syn* adduct, in accordance with the chelation model (Table 5). With a β-alkoxygroup, as in **60**, the major product is the *anti-syn* diasteromer (Table 6), also in accordance with the model for chelation control.

Table 5: $MgBr_2$-promoted reaction of 2-benzyloxypropanal with crotyltri-*n*-butylstannane in DCM at –23 °C.[39]

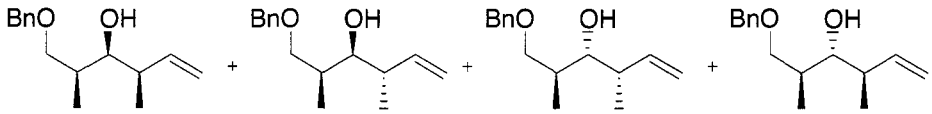


Entry	Stannane	Acid	*56*	*57*	*58*	*59*
1	*E*	$MgBr_2$•OEt_2	93	7	0	0
2	*Z*	$MgBr_2$•OEt_2	79	21	0	0

Table 6: Lewis-Acid promoted reaction of a 3-benzyloxymethylpropanal with crotyltri-*n*-butylstannane.[39]



60



61 (*Syn-Syn*) Non-Chelation | **62** (*Syn-Anti*) Non-Chelation | **63** (*Anti-Syn*) Chelation | **64** (*Anti-Anti*) Chelation

Entry	Stannane	Acid	*61*	*62*	*63*	*64*
1	*E*	$TiCl_4$	0	0	41	59
2	*Z*	$TiCl_4$	0	0	80	20
3	*E*	$MgBr_2 \cdot OEt_2$	9	5	73	13
4	*Z*	$MgBr_2 \cdot OEt_2$	5	0	87	8

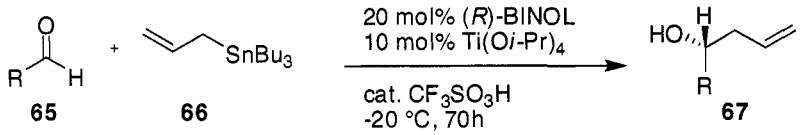
Catalytic asymmetric reactions

Since Keck's original disclosure in 1993 many groups have been interested in expanding the scope of the reaction with a variety of chiral catalysts. These catalytic systems have, in general, moderated the reaction conditions and increased enantioselectivity. This section attempts to present the scope and limitations of many of those systems in an effort to assist in choosing the best system for asymmetric allylation of a specific substrate.

BINOL/Titanium complexes

Many of the reports on the Keck reaction have centered on optimizing the original BINOL/Ti(O*i*-Pr)$_4$ system described by Keck (Table 7).[14] All of the BINOL/Ti systems rely on the *in situ* generation of the chiral Lewis acid and the method used in generating the catalyst does have an effect on the stereoinduction of the reaction. In his original report[14] Keck observed that not only were molecular sieves needed but the addition of a catalytic amount of trifluoromethyl sulfonic or trifluoroacetic acid was required to generate the catalytic system that achieved the highest enantioselectivities. He later found that the acid and molecular sieves can be omitted, and that the reaction can be conducted at room temperature instead of –20 °C, while still yielding comparable results.[15]

Table 7: Selected examples of (*R*)-BINOL/Ti(O*i*-Pr)$_4$ catalyzed reactions.[14]



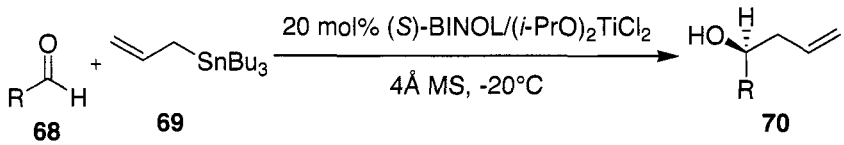
65 66 67

Entry	R	%Yield	%ee Config
1	C_6H_5-	98	92(*R*)
2	c-C_6H_{11}-	95	92(*R*)
3	(*E*) –C_6H_5CH=CH-	78	77(*R*)
4	$C_6H_5CH_2CH_2$-	98	96(*nd*)
5	*i*-C_3H_7-	97	87(*R*)
6	Furyl-	97	92(*nd*)

nd = not determined

In the same year Tagliavini and Umani-Ronchi published a similar system based on (*S*)-(BINOL/(*i*-PrO)$_2$TiCl$_2$ which had a similar substrate scope, yields and enantioselectivities (Table 8).[13] Note that all the examples of Table 8 give compound **70**, with the OH "up", but because of the Cahn–Ingold–Prelog nomenclature, the configuration can be *R* or *S* depending on the case in point.

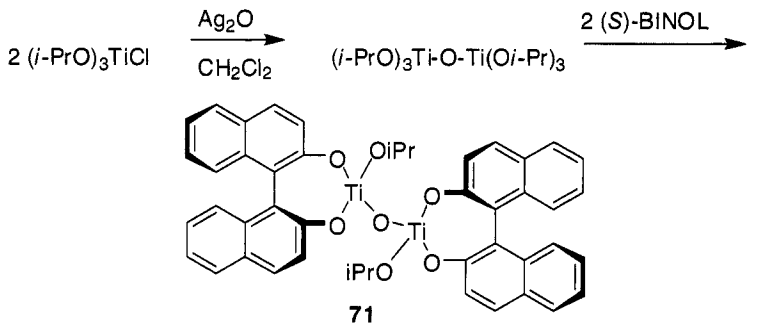
Table 8: Selected examples of (*S*)-(BINOL)/(*i*-PrO)$_2$TiCl$_2$ catalyzed reactions.[13]



68 69 70

Entry	R	*T*(°C)	Time(h)	%Yield	%ee config
1	C_7H_{15}-	–20	24	83	97.4 (*R*)
2	C_5H_{11}-	–20	24	75	98.4 (*R*)
3	c-C_6H_{11}-	–20	90	36	89.1 (*S*)
4	c-C_6H_{11}-	rt	24	75	92.6 (*S*)
5	(*E*)–C_6H_5CH=CH-	–20	90	38	94.0 (*S*)
6	(*E*)–C_6H_5CH=CH-	rt	24	85	88.8 (*S*)
7	Ph-	rt	48	96	82.0 (*S*)
8	4-Py-	Rt	48	90	80.2 (*S*)

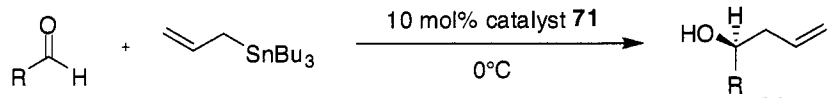
An extension of the Ti/BINOL system was developed by Maruoka and co-workers wherein a μ-oxo titanium dimer **71** was generated *in situ*. This method led to meaningful improvements in the enantioselectivity and reaction time (Table 9).[45]



71

As with most of the *in situ* generated catalysts the structure of the catalytically active species is not rigorously known but Maruoka and co-workers did observe a peak for the μ-oxo titanium dimer **71** in ESI–MS. They also demonstrate a positive nonlinear effect in the enantioselectivity when the catalyst was generated from enriched BINOL as opposed to enantiopure BINOL. This non linear effect reinforces the hypothesis that the active catalyst contains two molecules of BINOL.

Table 9: Selected examples of reactions catalyzed by (*S,S*) Bis-BINOL-Ti(IV) oxide 71.[45b]



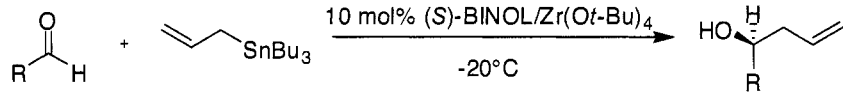
72 **73** **74**

Entry	R	Time(h)	%Yield	%ee(config)
1	$PhCH_2CH_2$-	4	84	99(*R*)
2	$CH_3(CH_2)_6$-	12	85	99(*R*)
3	$(CH_3)_2CH$-	28	71	99(*S*)
4	C_6H_5CH=CH-	15	70	95(*S*)
5	Ph-	7	90	96(*S*)
6	4-Br-C_6H_4-	15	85	98(*S*)
7	Fural	18	96	97(*S*)

Zirconium Binaphthol complexes

Umani–Ronchi followed up his work on BINOL/Ti with a slightly more active Zr(IV)-based Lewis acid.[17] The increase in activity of the catalyst enabled the reaction times to be shortened and the temperatures lowered. Kurosu and co-workers further modified these conditions by substituting $Zr(Ot\text{-}Bu)_4$ for $Zr(Oi\text{-}Pr)_4$, again decreasing the reaction times (Table 10) .[46]

Table 10: Selected examples of (*S*)-BINOL/Zr(O*t*-Bu)$_4$ catalyzed reactions.[46]

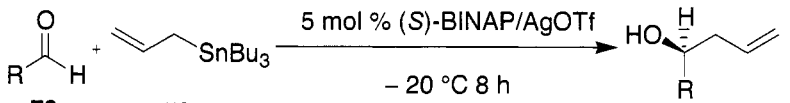


75 **76** **77**

Entry	R	Catalyst (mol%)	Time (h)	%Yield	%ee
1	Ph-	10	1.5	90	85–90
2	$PhCH_2CH_2$-	10	2.5	85	93
3	C_7H_{15}-	10	2.5	86	93
4	$TIPSOCH_2(CH_2)_3$-	10	2	80–90	90–93
5	$BnOCH_2(CH_2)_3$-	10	2	80–90	90–93
6	$TBSOCH_2CH_2$-	10	2.5	75	92
7	$BnOCH_2CH_2$-	20	2.5	88	93
8	$CH_3(CH_2)_4CC$-	10	1	89	90
9	(*E*)–C_6H_5CH=CH-	10	2.5	85	93
10	$MeO_2C(CH_2)_4$-	10	2	86	92

Silver complexes

Table 11: Selected examples of (*S*)-BINAP/AgOTf catalyzed reactions.[49]



78 **79** **80**

Entry	R	%Yield	%ee
1	Ph-	88	96(*S*)
2	(*E*)–C_6H_5CH=CH-	83	88(*S*)
3	1-naphthyl	89	97(*nd*)
4	furyl	94	93(*nd*)
5	(*E*)–*n*C_3H_7CH=CH-	72	93(*nd*)
6	2-MeC_6H_4-	85	97(*nd*)
7	4-$(MeO)C_6H_4$-	59	97(*nd*)
8	4-BrC_6H_4-	95	96(*nd*)
9	$PhCH_2CH_2$-	47	88(*nd*)

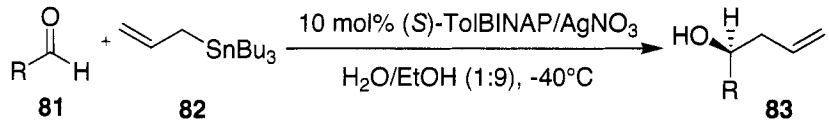
nd = not determined

Yamamoto reported that BINAP/AgOTf complexes are also competent asymmetric Lewis acids, generating the homoallylic alcohol in good yields and excellent enantioselectivities (Table 11).

An interesting BINAP/$AgNO_3$ complex developed by Loh and Zhou is able to work in a water-ethanol mixture (Table 12).[25] Silver-based systems

employing diphenylthiophosphoramides[47] or triazoles[48] as chiral ligands have proved less successful.

Table 12: Selected examples of (*S*)-Tol-BINAP/$AgNO_3$ catalyzed reactions.[25]



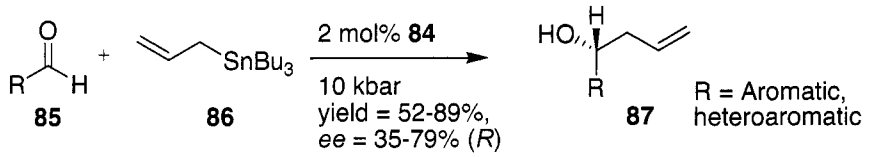
81 **82** **83**

Entry	R	Time (h)	%Yield	%*ee* (config)
1	Ph-	14	93	79(*S*)
2	1-naphthyl-	30	100	81(*S*)
3	2-naphthyl-	18	99	79(*S*)
4	3-OHC_6H_4-	60	92	71(*nd*)
5	3-ClC_6H_4-	14	95	73(*nd*)
6	3-$(CH_3O)C_6H_4$-	14	96	79(*nd*)
7	5-CH_3-furyl-	14	88	58(*nd*)
8	C_6H_5CH=CH-	20	98	58(*S*)
9	$C_6H_5CH_2CH_2$-	40	70	53(*S*)

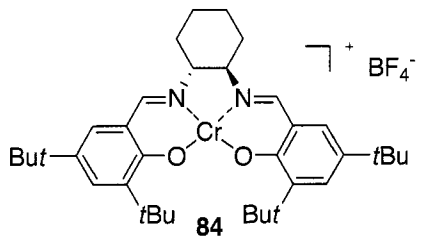
nd = not determined

Chromium-Salen Complexes

Kwiatkowski has reported a Cr-Salen complex (**84**) which at high pressures (10 kbar) produces the homoallylic alcohols in good yield and moderate enantioselectivities.[50,51]



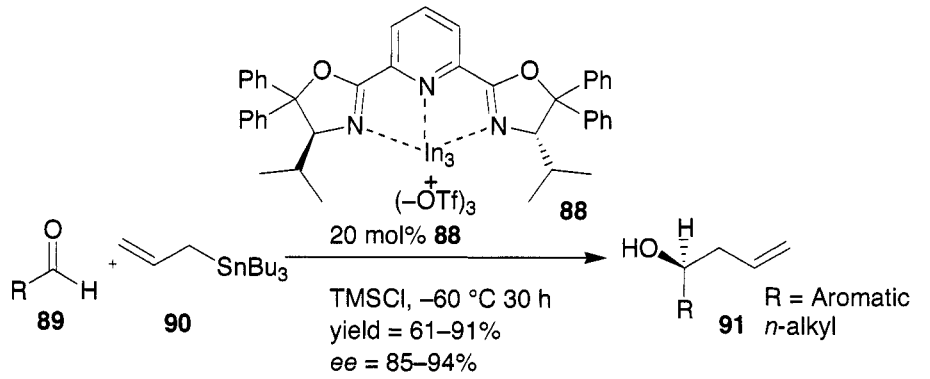
85 **86** **87**



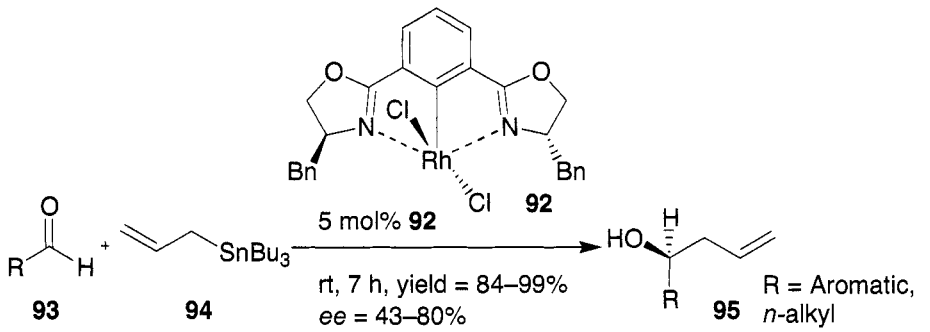
84

PyBox and PheBox systems

In an extension of the PyBox Lewis acids, Loh and co-workers have developed and In(III) based system (**88**) which is comparable to Keck's original Ti catalyst system in yields and enantioselectivities.[52] To ease in recycling the chiral pybox ligand, Loh has also investigated running the reaction in the presence of ionic liquids to aid in the recovery of the ligand.[53]



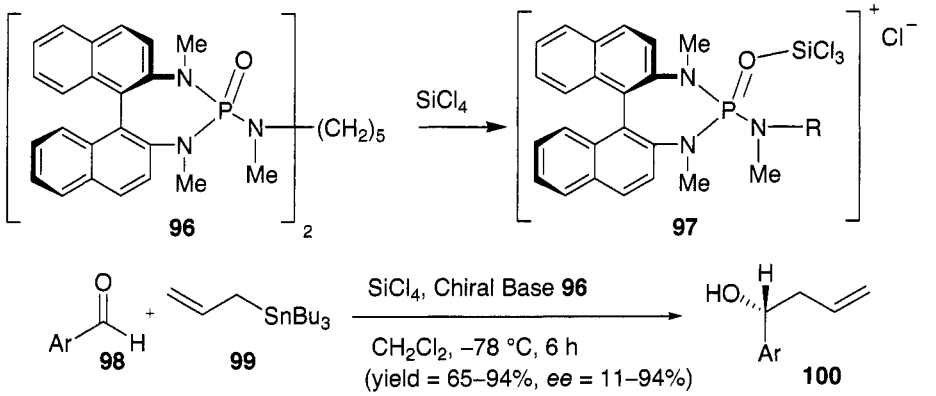
In a similar vein Nishiyama and co-workers demonstrated that a Rh(II) Phebox system (**92**) was able to affect the reaction at room temperature in good yield, albeit lower enantioselectivities.[54,55]



Chiral Phosphoramide activation of $SiCl_4$

Denmark has also applied his new method of Lewis base activation of Lewis acids to the Keck reaction.[56] This approach uses phosphoramide **96,** which can be viewed as a chiral version of HMPA. Phosphoramide **96** is used to activate the weak Lewis acid $SiCl_4$ and form the strong, cationic, chiral Lewis acid **97**. One benefit of this method is that there is very little background reaction due to the achiral Lewis acid $SiCl_4$, because the

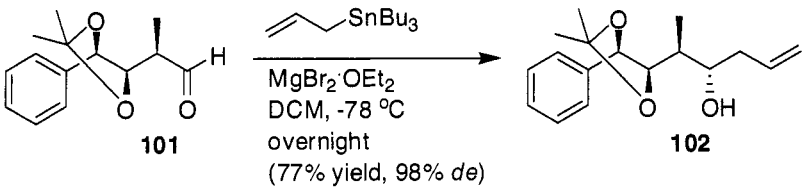
catalytically active species is only formed in the presence of the chiral Lewis base. The scope of the reaction is limited to aromatic aldehydes.



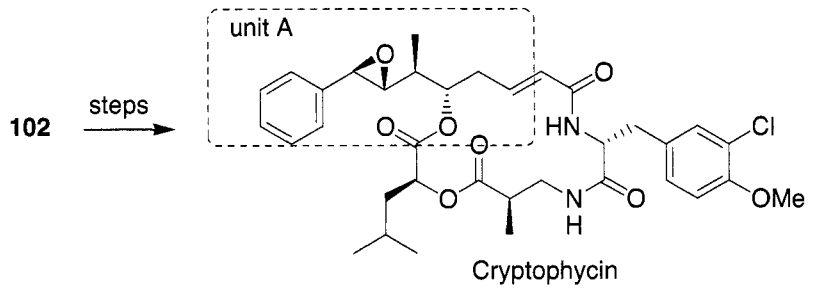
2.3.5 *Synthetic Utility*

The reports of new catalytic systems are generally tested on the same battery of aromatic, simple alkyl and, sometimes, simple heterocyclic aldehydes. Based on these methodology studies several systems have proven their worth in the more complex systems used in the total synthesis of natural products. This section discusses selected examples taken from the recent literature. We discuss first non-chiral Lewis acids, and then asymmetric catalytic systems.

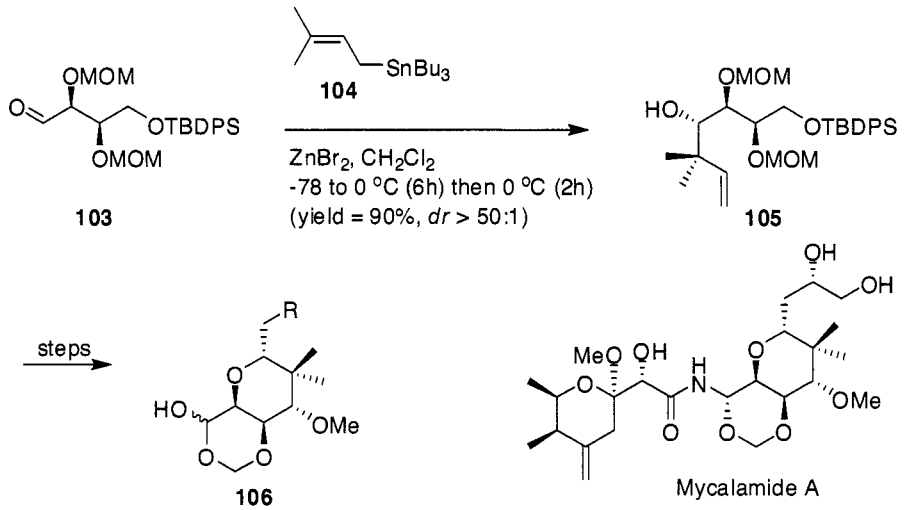
Examples using non-chiral Lewis acids



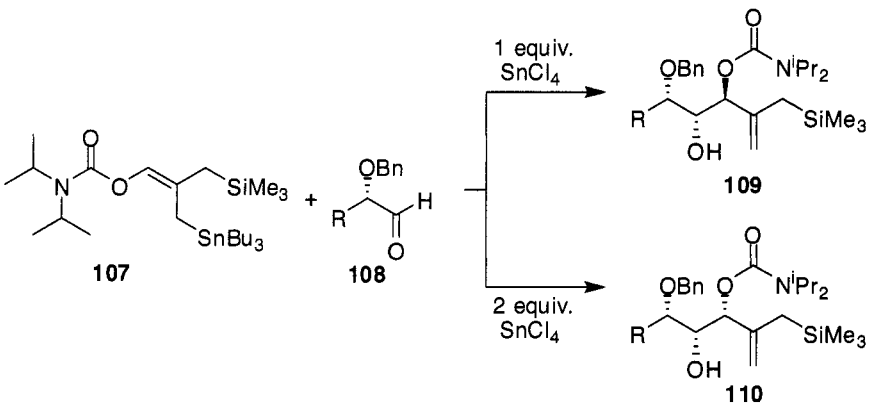
An example of chelation control is found in a study by Sewald directed at the synthesis of cryptophycin unit A.[57] The α-methyl-β-alkoxyaldehyde **101** reacted with allyltributylstannane in the presence of $MgBr_2 \cdot Et_2O$ to give a 98% *de* of the desired alcohol **102**. In this system, the induction from the β-alkoxy center superseded the mismatched induction from the α-methyl center.



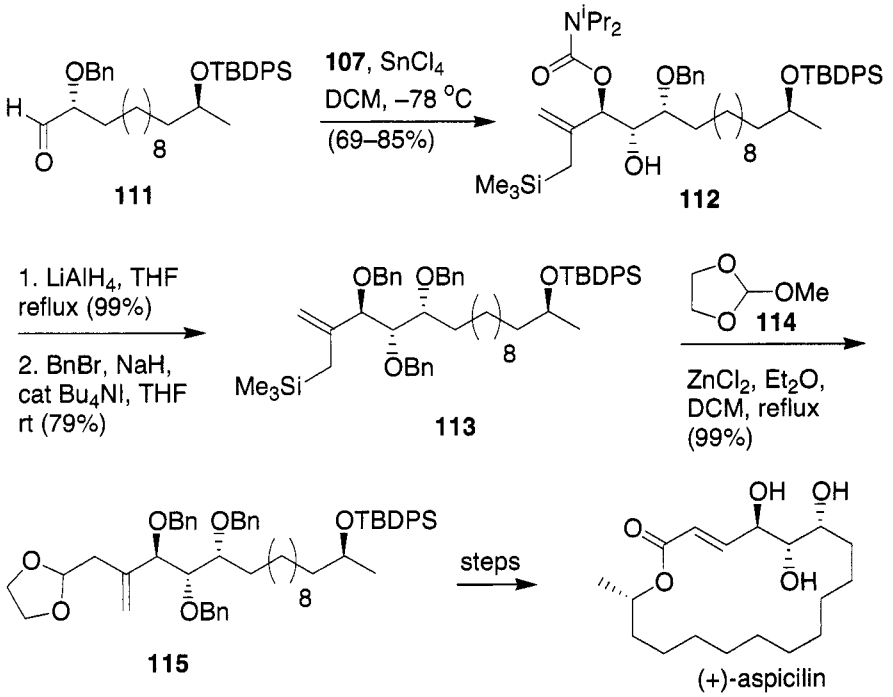
The fact that allylstannanes are highly reactive and react exclusively at the γ-carbon, regardless of steric hindrance, makes the Keck reaction a useful tool to introduce quaternary centers. Rawal used this feature to prepare the trioxadecalin core of Mycalamide A.[58] The tartrate-derived aldehyde **103** was reacted with homoprenyl stannane **104** in the presence of $ZnBr_2$ to generate a quaternary center under chelation-control conditions. The resulting alcohol **105** was further elaborated to the trioxadecalin **106**.



Examples of densely functionalized allylstannanes are rare. In this respect, Markó's stannane **107** stands out, by the presence of a silane and a protected alcohol. Stannane **107** reacts with α-alkoxyaldehyde **108** to give either a *syn–anti* or *syn–syn* configured triol (**109** and **110**, respectively). Remarkably, the relative stereochemistry is governed by the amount of $SnCl_4$ employed.

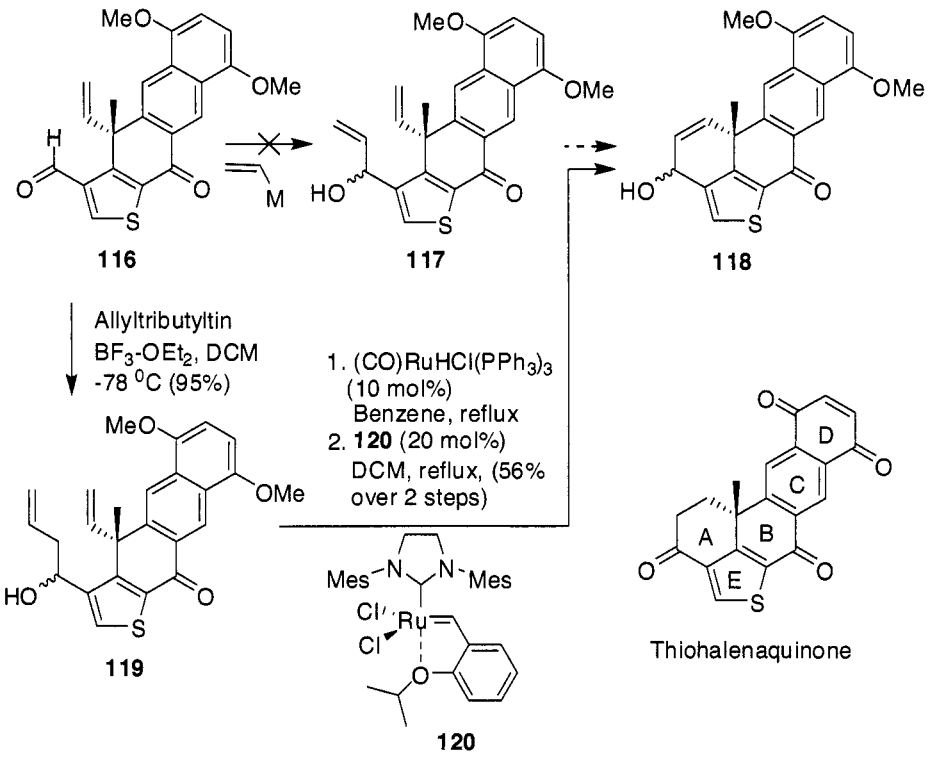


Markó demonstrated the utility of stannane **107** in the synthesis of the lichen macrolide (+)-aspicilin.[59] The Keck reaction of aldehyde **111** with stannane **107** provided allylsilane **112**. Protecting group manipulations gave **113**, and Sakurai reaction with orthoester **114** gave the ketal **115**, which was converted to the desired material.



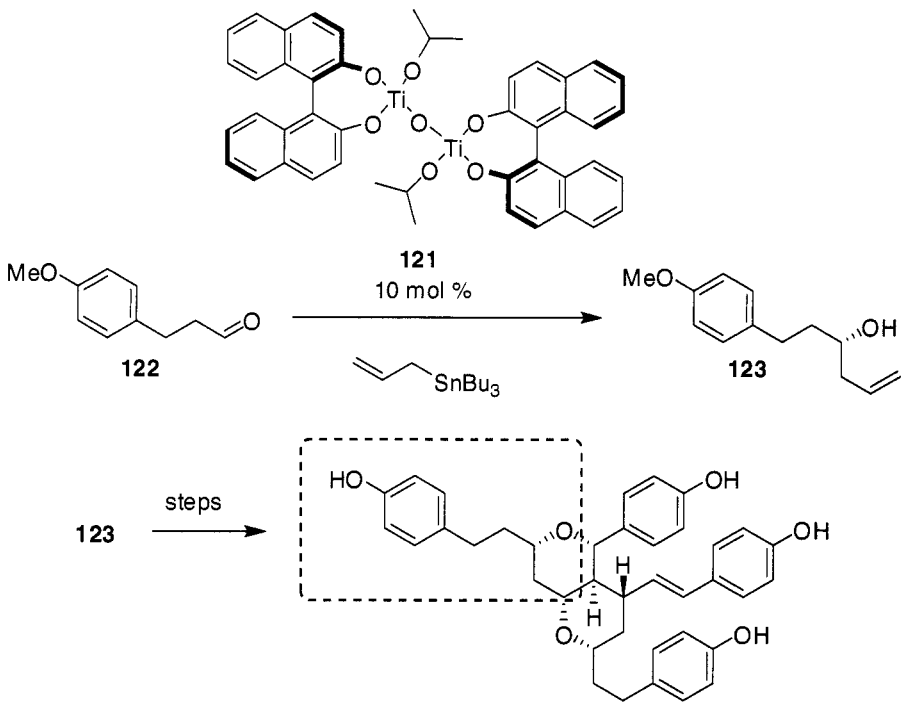
An interesting way to derivatize a homoallylic alcohol, which is the product of a Keck reaction, is to force the olefin to migrate. Wipf and co-workers met with an unexpected difficulty in the synthesis of (±)-

Thiohalenaquinone.[60] The initial plan entailed the addition of a vinyl metal species to aldehyde **116**, with the hope of obtaining allylic alcohol **117**, and following up with a ring-closing metathesis to construct the A ring as in **118**. However, treatment of **116** with a variety of vinyl organometallics provided complex reaction mixtures. Wipf's group circumvented the problem by introducing an allyl group with allyltributylstannane in the presence of BF_3•OEt_2 to obtain homoallylic alcohol **119** in excellent yield (95%). The homoallylic alcohol **119** was then isomerized to the allylic alcohol, using a Ru hydride catalyst to force the olefin migration. Ring-closing metathesis then provided the desired intermediate **118**.



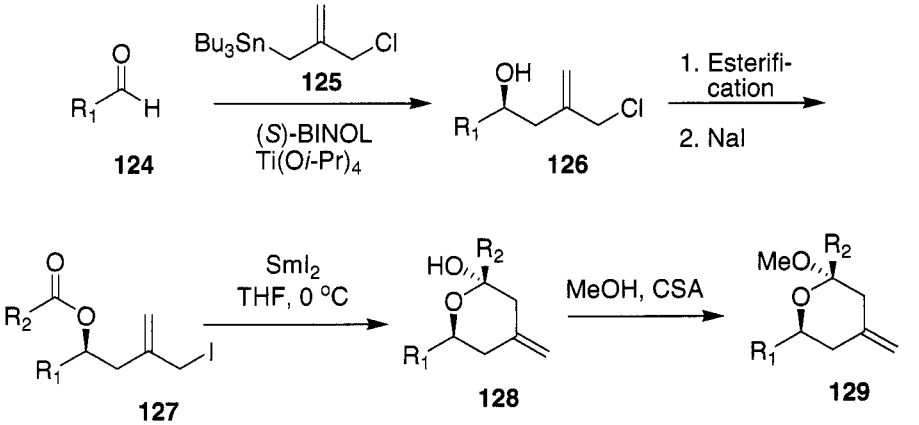
Examples using asymmetric catalysts

In a straightforward application of enantioselective Keck reaction, Lee used μ-oxo titanium catalyst **121** to convert aldehyde **122** into alcohol **123** to construct the "left-hand side" of the antitumor agent (–)-blepharocalyxin D.[61]

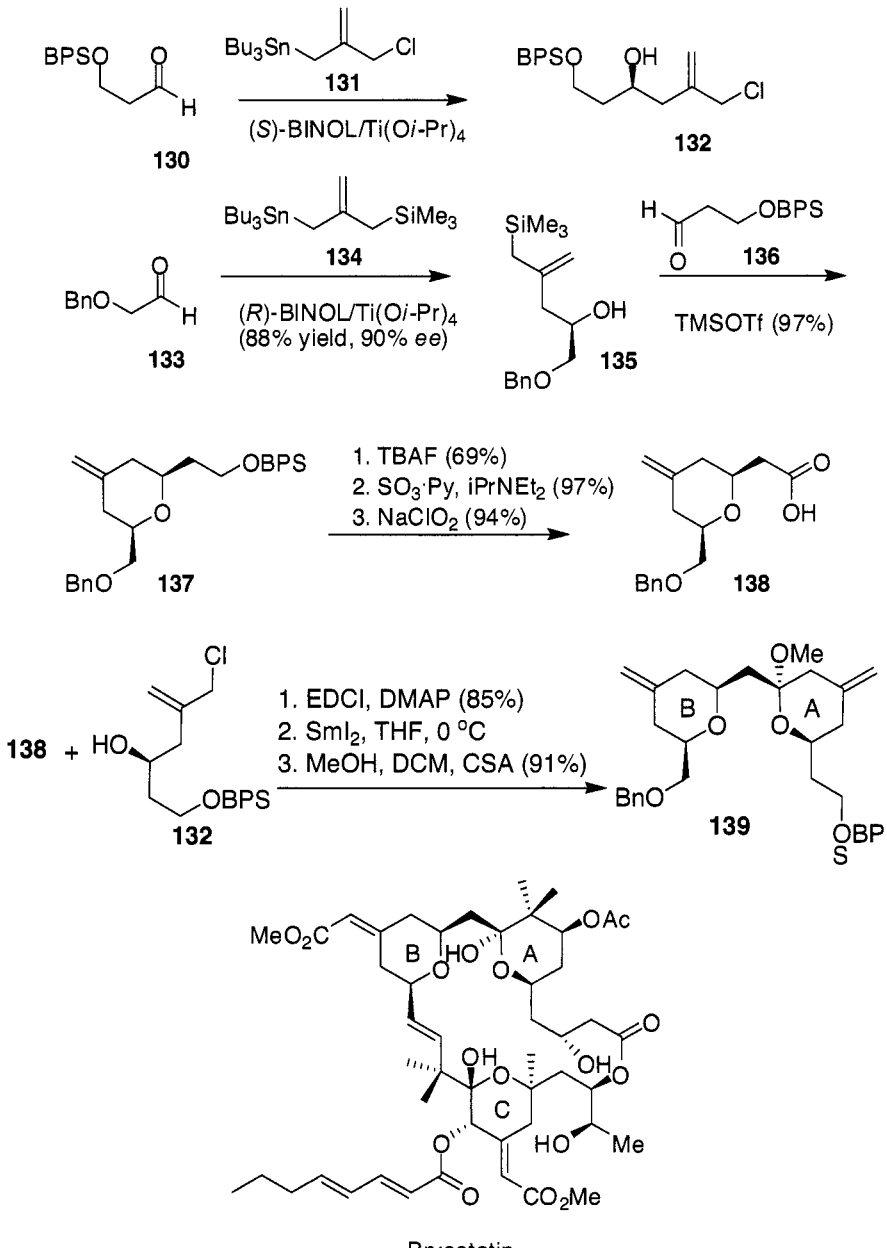


(-)-Blepharocalyxin D

The unusual chlorinated stannane **125** was used by Keck for the preparation of pyrans. The BINOL/Ti(O*i*-Pr)$_4$ catalyzed reaction of (2-chloromethyl)allylstannane **125** provided the homoallylic alcohol **126** in high yields and excellent enantioselectivities.[62] Esterification and treatment with NaI gave the iodinated ester **127**, poised for cyclization. SmI_2 promoted the cyclization to hemiketal **128**, which was derivatized to ketal **129** to simplify its chromatographic purification.

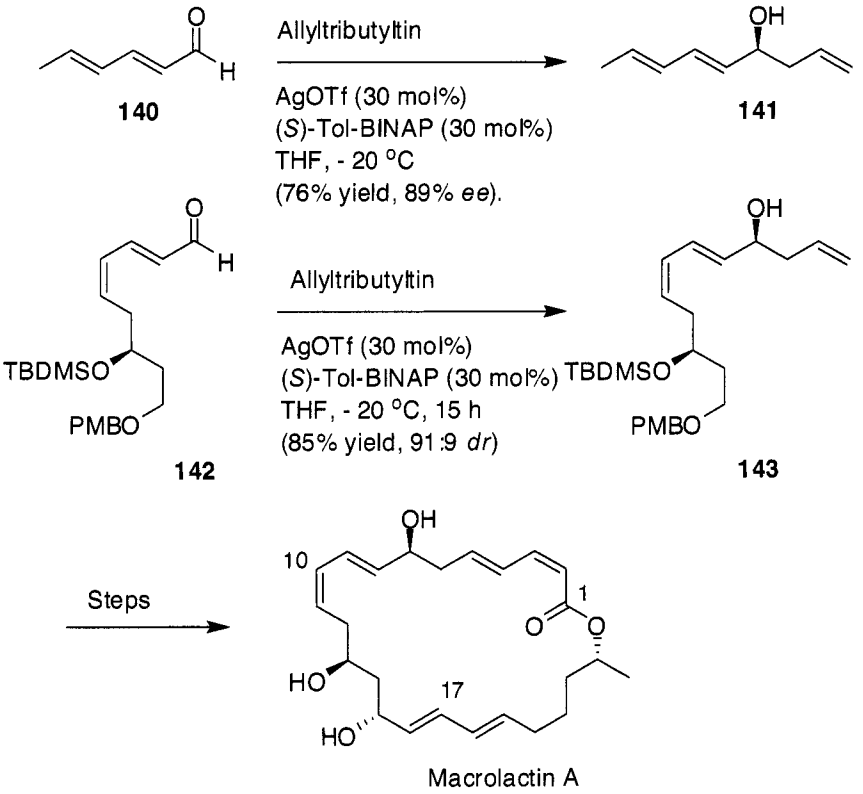


The methodology was adapted to the synthesis of a simplified fragment of bryostatin.[63] As in the previous example, an aldehyde (**130**) was reacted with (2-chloromethyl)allylstannane **131** using BINOL/Ti(O*i*-Pr)$_4$ catalysis to obtain **132**. In parallel, aldehyde **133** was subjected to a Keck reaction employing the silylated stannane **134**. The resulting allylsilane **135**



Bryostatin

was treated with aldehyde **136** and TMSOTf to trigger an intramolecular Sakurai reaction to give pyrane **137**. Functional group interconversions gave acid **138**, which was esterified with the previously obtained homoallylic alcohol **132**. Finally, a SmI_2-promoted cyclization provided **139**, a simplified version of the A/B ring system of bryostatin.



Silver-based catalysts have also been used in natural product synthesis. Campagne showed that sorbaldehyde (**140**) undergoes an asymmetric Keck reaction in the presence of AgOTf and (*S*)-Tol-BINAP to give **141**. Notably, the allyl group adds in a 1,2-fashion. Campagne then extended the methodology to construct the C4–C24 fragment of Macrolactin A.[64] The unsaturated aldehyde **142** was reacted under similar conditions to obtain **143**, which was elaborated to yield macrolactin A.

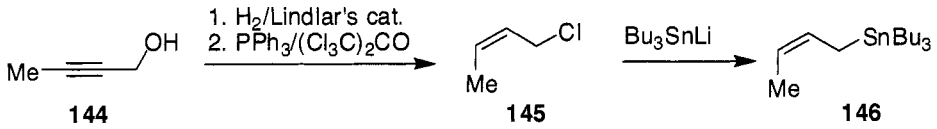
In conclusion, the Keck reaction has been successfully applied to numerous total syntheses demonstrating the generality of the reaction. One of the strengths of the Keck reaction is that it can be performed under relatively mild conditions (*e.g.*, $ZnCl_2$, $MgBr_2$), a useful feature if the substrate is sensitive to strong acids or strong bases. The asymmetric Keck reaction, based on BINOL ligands still usually requires high loadings of catalyst (20

mol%), but again the mildness of the conditions and the readily available chiral ligand make it an attractive reaction. The Keck reaction can also be used to synthesize quaternary centers. A limitation of the Keck reaction is that stannanes are not very stable species, and therefore highly functionalized stannanes are used only rarely. The toxicity of stannanes is another important limitation that precludes their use on industrial scale.

2.3.6 Experimental

Preparation of crotylstannanes and allylstannanes

Crotylstannanes enriched in either the *E* or *Z* isomer can be prepared by reaction of the corresponding crotyl chlorides with Bu_3SnLi, generated by deprotonation of tri-*n*-butylstannane with LDA.[65,66] The *E/Z* stannanes are never obtained completely free of their geometric isomer, and the isomeric composition of each lot of stannanes is typically measured by NMR.



144 **145** **146**

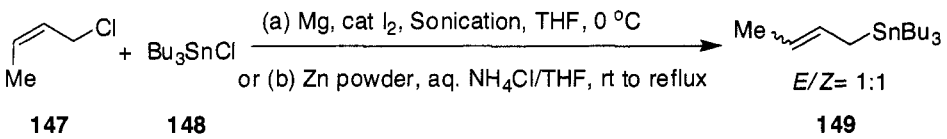
( )-2-Butenyltri-*n*-butylstannane (146).[67]

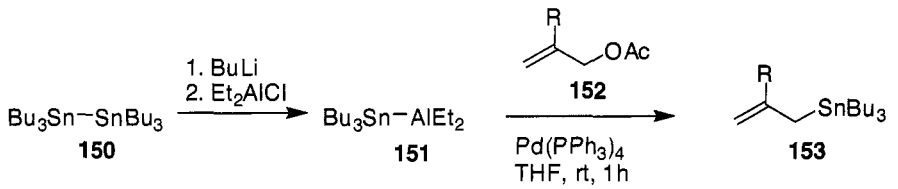
This compound was prepared in three steps starting from 2-butyn-1-ol. A mixture of 2-butyn-1-ol (**144**) (10.0 g, 142.6 mmol) and Lindlar's catalyst (1.0 g) in CH_3OH (150 mL) was stirred at 25 °C under 1.0 atm. of H_2 for approximately 2 h, at which time the alkyne was judged, using TLC, to have been completely consumed. The mixture was then filtered through a pad of Celite and concentrated. Purification by distillation yielded 9.77 g (135.5 mmol, 95%) of (*Z*)-2-buten-1-ol (lit. bp 123.6 °C). (*Z*)-2-Buten-1-ol was converted to the chloride by treating a solution of the alcohol in hexachloroacetone with PPh_3.[68] Purification by distillation yielded (*Z*)-1-chloro-2-butene (**145**) (lit. bp 84.1 °C (758 mmHg)). The procedure described by Matarasso–Tchiroukhine was followed for the preparation of the (*Z*)-crotyltin reagent.[65] To a stirred suspension of finely cut lithium wire (1.26 g, 182.6 mmol) in dry THF (60 mL) under N_2 at 25 °C was added Bu_3SnCl (19.84 g, 60.96 mmol). When the reaction had begun, as evidenced by the evolution of heat and the formation of a tan color, an additional 90 mL of THF was added and stirring at 25 °C was continued for 8 h. After allowing the mixture to stand for 1 h, it was filtered through a plug of glass wool under N_2 into a dry flask, which was then cooled to –40 °C. To this flask was added a solution of (*Z*)-1-chloro-2-butene (5.52 g, 60.96 mmol) in THF (6 mL). The mixture was stirred at –40 °C for 30 min, then quenched by adding a

saturated aqueous solution of NH_4Cl, which had been cooled to 0 °C. The solution was brought to room temperature, and the aqueous phase was extracted twice with ether. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by distillation to yield 16.42 g (43.28 mmol, 71%) of (*Z*)-2-butenyltributylstannane (**146**), as a colorless oil (bp 100–110 °C (1.0 mmHg)).

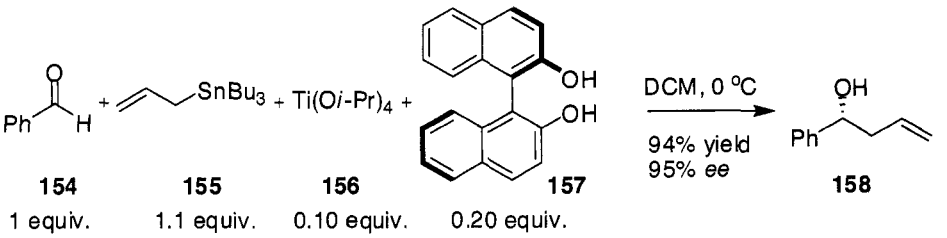
(*E*)-2-Butenyltributylstannane.
This compound was prepared from (*E*)-crotyl chloride and Bu_3SnCl, using the procedure described above.

Other methods of preparing allylstannanes include (1) reacting allyl chlorides, Bu_3SnCl, and Mg in one pot with sonication,[69,70] (2) reacting allyl bromides, Bu_3SnCl, and Zn powder in saturated aqueous NH_4Cl/THF,[69,71] (3) reacting allylmagnesium halides or allyllithium reagents with Bu_3SnCl; note that a Wurz coupling can complicate the preparation of the Grignard reagent (4) reacting allyl acetates with Bu_3SnCl in the presence of catalytic Pd and stoichiometric SmI_2,[72] (5) reacting allylacetates with $Bu_3SnAlEt_2$ (prepared from Bu_3SnLi and Et_2AlCl) under $Pd(PPh_3)_4$ catalysis.[73]





The original Keck procedure[15]



A mixture of (*R*)-1,1′-binaphthalene-2,2′-diol (22.5 mg, 0.078 mmol) and 1M titanium isopropoxide (39 μL, 0.039 mmol in dichloromethane) in dichloromethane was stirred at room temperature for 1 h. Benzaldehyde (41.2 mg, 0.394 mmol) was added to the red-brown solution, the contents were cooled to 0 °C and allyltri-*n*-butylstannane (144 mg, 0.435 mmol) was added. After 3 h at 0 °C, saturated $NaHCO_3$ (0.5 mL) was added and the contents stirred for 1h, dried (Na_2SO_4) and filtered. The crude material was purified by chromatography over silica gel eluting with 19 : 1 (v/v) hexanes/acetone followed by 17:3 (v/v) hexanes/acetone to give (*R*)-(+)-phenyl-3-buten-1-ol as a clear oil (54.9 mg, 94% yield, 95% *ee*).

Doucet–Santelli modification, using toluene as solvent[21]

The modification by-passes the use of molecular sieves, often recommended by other authors, and is claimed to improve the reproducibility of the reaction. In a Schlenk tube, 2 mL of degassed toluene was added to 60 mg (0.2 mmol) of (*R*)-1,1′-binaphthalene-2,2′-diol, then 59 μL (0.20 mmol) of titanium isopropoxide was added. After stirring for 1 hour, the solvent was removed. These complexes are *not air stable* and were stored in Schlenk tubes under Argon. For the catalytic allylation reactions the complexes were prepared just before use.

To 0.2 mmol of a solution of (*R*)-(+)-1,1′-bi(2-naphthol)titanium isopropoxide in toluene in a Schlenk tube were added 0.4 mmol of the aldehyde and 0.45 mmol of allyltributyltin. The solution was stirred at 20 °C over 20 hours, quenched with 1 mL of water, 10 mL of ether was added to the mixture, then the organic layer was washed with water and was dried over $MgSO_4$. After evaporation of the solvent, the product was purified by chromatography on silica gel (pentane/ether).

2.3.7 References

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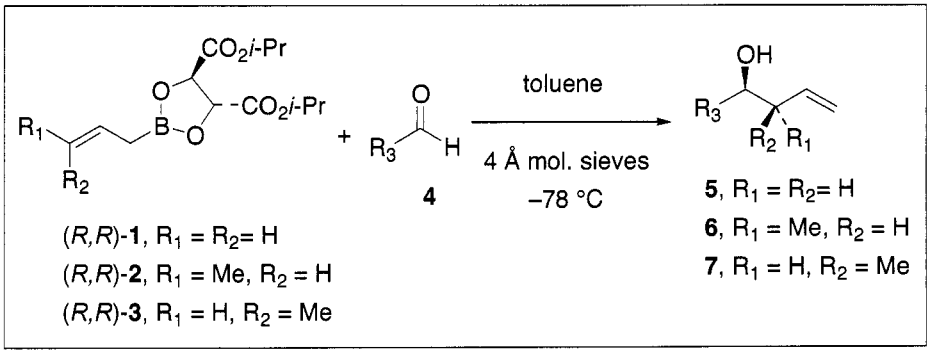
2.4 Roush Allylboronation

Sherry R. Chemler

2.4.1 Description

The Roush allylboronation refers to the enantioselective addition of tartrate-modified allyl- and crotylboronate reagents to aldehydes for the synthesis of homoallylic alcohols.[1–3] Allylboronate **1** and the (*E*)- and (*Z*)-crotylboronates **2** and **3** are available in both enantiomeric forms via synthesis from the corresponding (*R,R*)- and (*S,S*)-diisopropyl tartrate (DIPT) enantiomers. Reagents **1–3** react with achiral aliphatic aldehydes in excellent yields (> 70%) and good to excellent enantioselectivity (72–91% *ee*). Aromatic and α,β-unsaturated aldehydes react with somewhat lower selectivity (55–77% *ee*). Reactions of reagents **1–3** with achiral aldehydes have been applied broadly in organic synthesis. Their double asymmetric reactions with chiral aldehydes offer instances of superior selectivity, especially in instances where the facial preference is matched, thus, these reagents have been used most frequently in this context. The homoallylic alcohol products (*e.g.*, **5–7**) are routinely elaborated to more complex intermediates by using the terminal alkene for further functionalization.



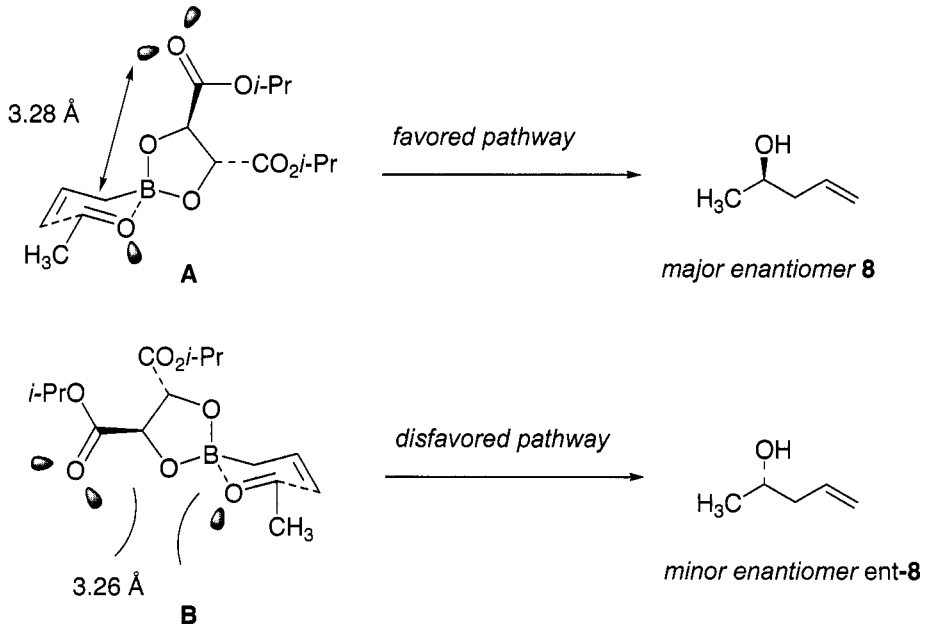
2.4.2 Historical Perspective

The synthesis and use of tartrate-modified allylboronate **1** was first reported by Roush and co-workers in 1985.[4,5] The synthesis and use of the corresponding (*E*)- and (*Z*)-crotylboronate reagents **2** and **3** was published by Roush and co-workers shortly thereafter.[6,7] The ease of synthesis, stability and efficient reactivity of these reagents offers advantages over many other allyl- and crotylmetal reagents.[2] Roush and co-workers have extensively explored the enantioselective allylations with achiral aldehydes as well as the

double asymmetric reactions with chiral aldehydes. A report outlining the factors that influence the stereoselectivity in these reactions was reported in 1990.[8] Since their introduction, these reagents have been used by the Roush group and several other research groups in the enantioselective synthesis of natural products and analogs thereof (section 2.4.6, *vide infra*).

2.4.3 Mechanism

Roush and co-workers have shown that the nature of the substituents on the dioxaborolane auxiliary profoundly affects the rate and enantioselectivity of the allylboration reaction; reagents with ester substituents are far more reactive and more selective than reagents with alkyl substituents.[9] The enantioselectivity of reagents **1–3** is thought to arise more from electronic attraction and repusion than from steric hindrance.

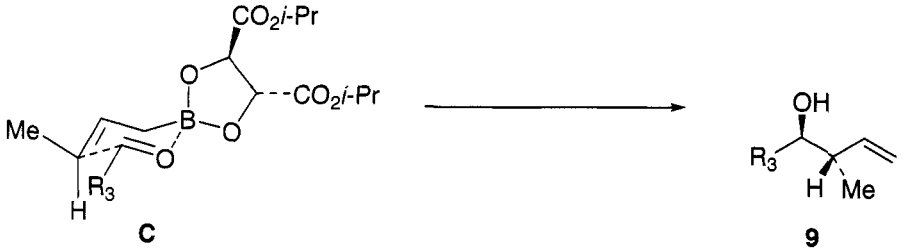


The stereochemical outcome of the enantioselective allylation is rationalized via formation of the major product via transition state **A**, where the (*R,R*)-DIPT crotylboronate **1** adds to the *Si* face of the aldehyde's carbonyl carbon.[4] Conversely, transition state **B** leads to the minor enantiomer via *Re* face addition. A number of theories have been put forth to rationalize the preference for **A** over **B**.[4,10–12] Roush and co-workers originally proposed that transition state **B** is disfavored due to electron repulsion between the uncomplexed aldehydic lone electron pair and a lone

pair on a carbonyl oxygen of the tartrate auxilliary. They subsequently proposed that an attractive electrostatic interaction between the δ^+ aldehyde carbonyl carbon and the δ^- tartrate carbonyl oxygen in **A** could contribute to the preference for **A** over **B**.[10] Gung and Roush subsequently reported *ab initio* calculations of these transition states with acetaldehyde.[12] Transition state **A** was calculated to be 1.61 kcal/mol lower than **B** (B3LYP/6-31G*). An attractive interaction between the ester carbonyl oxygen and the boron-activated aldehydic carbonyl carbon was indicated by the short interatomic distance (3.28 Å) between these two atoms in **A**. An n/n repulsive interaction was also noted in **B**, where the inter-atomic distance between the ester carbonyl oxygen and the aldehyde carbonyl oxygen is 3.26 Å.

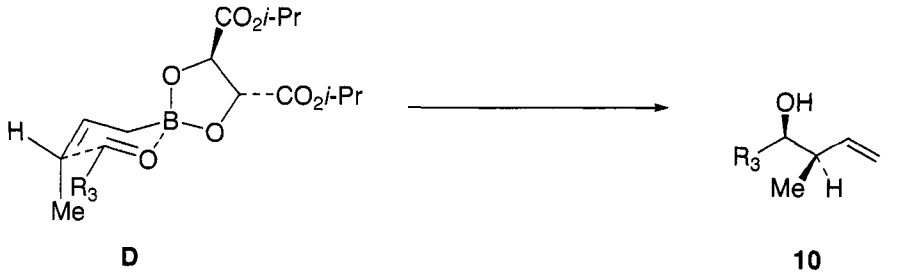
The relative stereochemistry observed in the reactions of these crotylboronates with aldehydes is consistent with cyclic Zimmerman–Traxler transition states[13] where the aldehyde positions its R group in the pseudo-equatorial position about the six-membered ring transition state. Thus, the (*E*)-reagent **2** leads to the *anti* diastereomer via **C** while the (*Z*)-reagent **3** leads to the *syn* diastereomer via **D**.

The (*E*)-crotylboronate **2** gives anti-homoallylic alcohol **9**.



C **9**

The (*Z*)-crotylboronate **3** gives syn-homoallylic alcohol **10**.

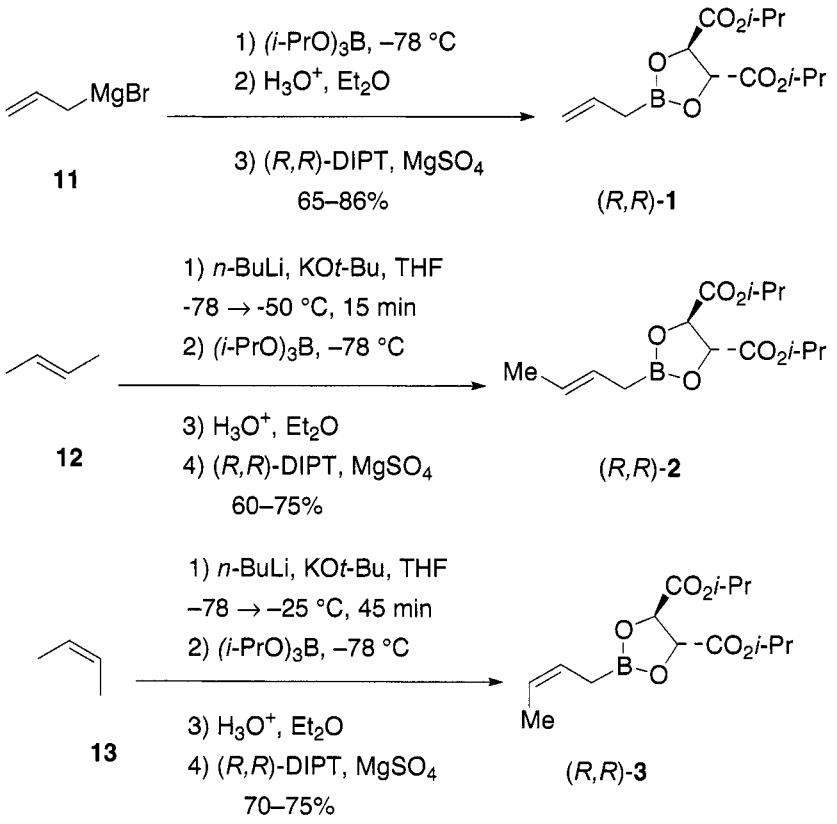


D **10**

2.4.4 Synthetic Utility

(*R,R*)-Allylboronate **1** is prepared from the reaction of allyl magnesium bromide with triisopropyl borate followed by esterification with (*R,R*)-

diisopropyl tartrate (DIPT) in the presence of $MgSO_4$.[8] The (*E*)- and (*Z*)-crotylboronates **2** and **3** are prepared[7] in high isomeric purity (> 98%) from (*E*)- and (*Z*)-2-butene by way of the (*E*)- and (*Z*)-crotylpotassiums,[14] which are known to be configurationally stable at low temperature. Reagents **1-3** are often used without purification and can be stored without decomposition at low temperature (*e.g.*, –20 °C) for several months. Stock solutions of these reagents in toluene are often prepared, and a titration protocol using cyclohexanecarboxaldehyde as a standard is used to determine reagent concentration.[7]

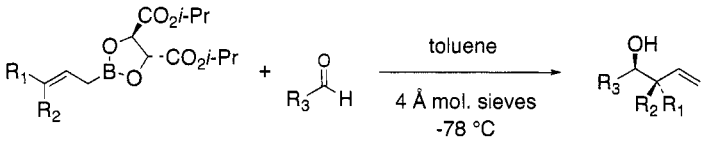


Reactions of 1-3 with Achiral Aldehydes

The reactions of reagents **1-3** with a variety of achiral aldehydes have been reported by Roush and co-workers.[4,7,8,15,16] A few of these reactions are summarized in Table 1. The diastereoselectivity is uniformally high (> 95:5) while the enantioselectivity varies from moderate to excellent (55-91% *ee*), depending upon the aldehyde and reagent structure. The (*E*)-crotylboronate **2** is generally the most enantioselective while the (*Z*)-crotylboronate **3** is

generally the least. Aliphatic aldehydes undergo allylboration with higher enantioselectivity than α- or β-alkoxy-substituted aldehydes. The reactions of aliphatic aldehydes are also more enantioselective than the reactions of aromatic or α,β-unsaturated aldehydes. Toluene (0.2 M with respect to allylboronate) is the solvent that provides the highest level of asymmetric induction except in the case of aromatic aldehydes, where THF provides higher enantioselectivity.[8] The use of 4 Å molecular sieves (15–20 mg/mL) to ensure dry reaction conditions is important for obtaining high levels of asymmetric induction (hydrolysis of the reagents by water forms achiral allylboronic acid, which may lead to racemic products), and temperature is also an important variable, with lower temperatures (typically –78 °C) giving the highest enantioselectivity.[8]

Table 1. Enantioselective Reaction of Allylboronates **1-3** with Achiral Aldehydes



(*R,R*)-**1**, $R_1 = R_2 = H$ **4** **5**, $R_1 = R_2 = H$
(*R,R*)-**2**, $R_1 = Me$, $R_2 = H$ **6**, $R_1 = Me$, $R_2 = H$
(*R,R*)-**3**, $R_1 = H$, $R_2 = Me$ **7**, $R_1 = H$, $R_2 = Me$

R_3CHO	reagent	major product[a]	yield (%)	ee (%)
n-$C_9H_{19}CHO$	(*R,R*)-**1**	**5a**, $R_3 = n$-C_9H_{19}	86	79
n-$C_9H_{19}CHO$	(*R,R*)-**2**	**6a**, $R_3 = n$-C_9H_{19}	87	88
n-$C_9H_{19}CHO$	(*R,R*)-**3**	**7a**, $R_3 = n$-C_9H_{19}	80	82
$TBSO(CH_2)_2CHO$	(*R,R*)-**1**	**5b**, $R_3 = (CH_2)_2OTBS$	ND[b]	66
$TBSO(CH_2)_2CHO$	(*R,R*)-**2**	**6b**, $R_3 = (CH_2)_2OTBS$	71	85
$TBSO(CH_2)_2CHO$	(*R,R*)-**3**	**7b**, $R_3 = (CH_2)_2OTBS$	68	72
$C_6H_{11}CHO$	(*R,R*)-**1**	**5c**, $R_3 = C_6H_{11}$	97	87
$C_6H_{11}CHO$	(*R,R*)-**2**	**6c**, $R_3 = C_6H_{11}$	85	87
$C_6H_{11}CHO$	(*R,R*)-**2** (-95 °C)	**7c**, $R_3 = C_6H_{11}$	100 (GC)	91
$C_6H_{11}CHO$	(*R,R*)-**3**	**7c**, $R_3 = C_6H_{11}$	90	83
C_6H_5CHO	(*R,R*)-**1**	**5d**, $R_3 = C_6H_5$	78	72
C_6H_5CHO[c]	(*R,R*)-**2**	**6d**, $R_3 = C_6H_5$	91	66
C_6H_5CHO[c]	(*R,R*)-**3**	**7d**, $R_3 = C_6H_5$	94	55
n-$C_7H_{15}CH{=}CHCHO$	(*S,S*)-**1**	*ent*-**5e**, $R_3 = (E)$-$CH{=}CHC_7H_{15}$	ND	-60
n-$C_7H_{15}CH{=}CHCHO$	(*R,R*)-**2**	**6e**, $R_3 = (E)$-$CH{=}CHC_7H_{15}$	91	74
n-$C_7H_{15}CH{=}CHCHO$	(*R,R*)-**3**	**7e**, $R_3 = (E)$-$CH{=}CHC_7H_{15}$	83	62

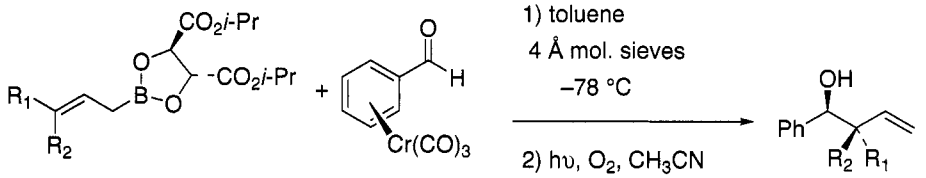
[a]Diastereoselectivity >95 : 5. [b]Yield not determined. [c]Reaction run in THF.

The Roush group has also reported the synthesis and use of tartrate-derived lactam allylboronate auxiliaries.[17,18] Although these reagents

demonstrated higher asymmetric induction in reactions with achiral aldehydes, their cumbersome synthesis makes their use less attractive than other reagents.

Allylborations of Metal-Complexed Unsaturated Aldehydes

Reactions of reagents **1** and **2** with metal-complexed aromatic, propargylic and dienylic aldehydes provides homoallylic alcohol products with improved selectivity compared to their uncomplexed counterparts.[19–22] The reaction of benzaldehyde chromium tricarbonyl complex **14** with (*R,R*)-**1** followed by oxidative decomplexation provided (*S*)-**15** in 90% yield and 83% *ee*.[19] The (*E*)-crotylboration of **14** with (*R,R*)-**2** provided **16** in 90% yield and 92% *ee*. Reaction of aldehyde **14** with (*Z*)-crotylboronate **3**, however, provided adduct **17** in only 41% *ee*.

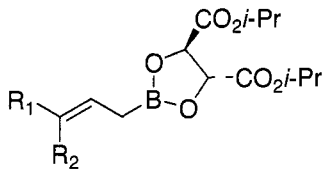


(*R,R*)-**1**, $R_1 = R_2 = H$
(*R,R*)-**2**, $R_1 = Me$, $R_2 = H$
(*R,R*)-**3**, $R_1 = H$, $R_2 = Me$

14

product	yield (%)	*ee* (%)
15, $R_1 = R_2 = H$	90	83
16, $R_1 = Me$, $R_2 = H$	90	92
17, $R_1 = H$, $R_2 = Me$	ND	41

The asymmetric allylboration of 2-decynal (**18**) provides addition products **19–21** in 72%, 72% and 58% *ee* with reagents **1–3**, respectively. In contrast, the allylborations of 2-decynal-dicobalt hexacarbonyl complex **22** with **1–3** followed by decomplexation with $Fe(NO_3)_3$ in EtOH at room temperature provides adducts **19–21** with improved%*ee*'s of 92%, 96% and 86%, respectively, in 85–95% yield.[19]



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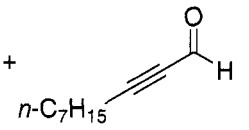
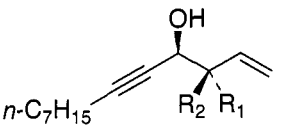


(*R,R*)-**1**, $R_1 = R_2 = H$
(*R,R*)-**2**, $R_1 = Me$, $R_2 = H$
(*R,R*)-**3**, $R_1 = H$, $R_2 = Me$

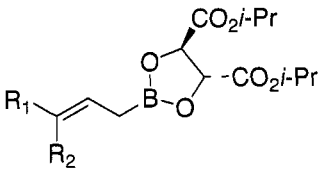
18

toluene

4 Å mol. sieves
-78 °C



19, $R_1 = R_2 = H$, 72% ee
20, $R_1 = Me$, $R_2 = H$, 72% ee
21, $R_1 = H$, $R_2 = Me$, 58% ee



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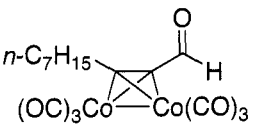


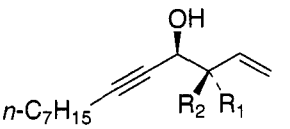
(*R,R*)-**1**, $R_1 = R_2 = H$
(*R,R*)-**2**, $R_1 = Me$, $R_2 = H$
(*R,R*)-**3**, $R_1 = H$, $R_2 = Me$

22

1) toluene
4 Å mol. sieves
-78 °C

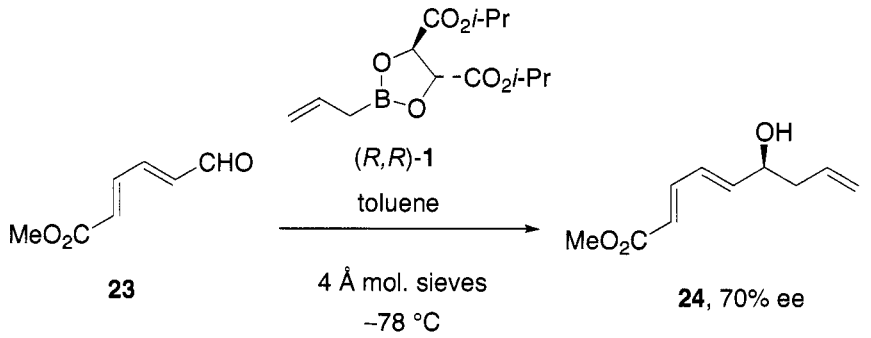
2) $Fe(NO_3)_3$, EtOH

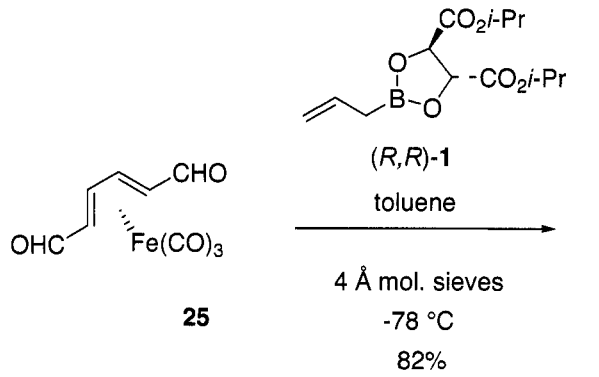
85-95%

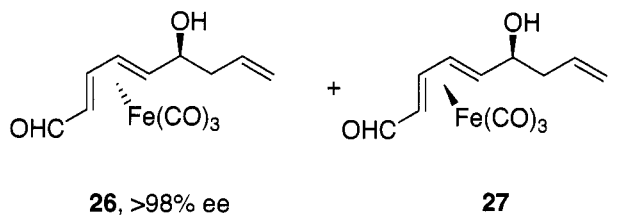


19, $R_1 = R_2 = H$, 92% ee
20, $R_1 = Me$, $R_2 = H$, 96% ee
21, $R_1 = H$, $R_2 = Me$, 86% ee

Finally, the reaction of dienylic aldehyde **23** with (*R,R*)-**1** provides the allylic alcohol **24** in 70% *ee* while reaction of the *meso* iron tricarbonyl-complexed dienylic dialdehyde **25** with (*R,R*)-**1** provides the *anti* diastereomer **26** with 45 : 1 selectivity and > 98% *ee*.[22]



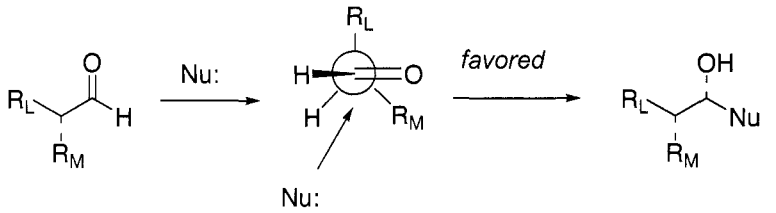




Allylborations of Chiral Aldehydes

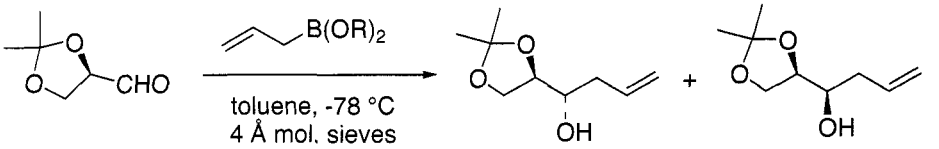
Chiral aldehydes **28** with α-stereocenters undergo addition reactions with nucleophiles with predictable stereoselectivity patterns. The Felkin–Anh model[23,24] proposes that the nucleophile approaches *anti* to the α-substituent that is either the largest or a heteroatom, and approaches the aldehyde via the

Burgi–Dunitz angle[25] of 107°, passing the least sterically hindering α-substituent in its approach (transition state **E**). In the double asymmetric reactions of α-chiral aldehydes with chiral allylboronates **1**–**3**, the α-stereocenter and the chiral boronate auxiliary both influence the stereochemical outcome of the reaction.



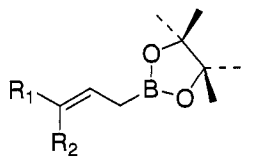
28 **E** **29**

α-Alkoxy aldehydes



30 79-91% **31** **32**

Reagent	**31** : **32**
(*R,R*)-**1** (matched)	98 : 2
33	80 : 20
(*S,S*)-**1** (mismatched)	7 : 93



pinacol allylboronates

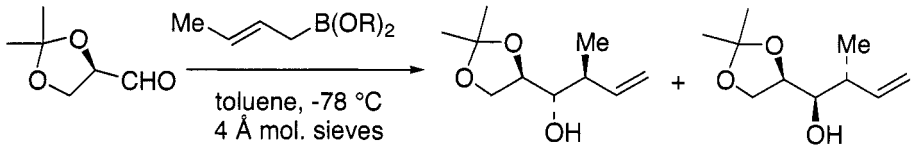
33, $R_1 = R_2 = H$

34, $R_1 = Me$, $R_2 = H$

35, $R_1 = H$, $R_2 = Me$

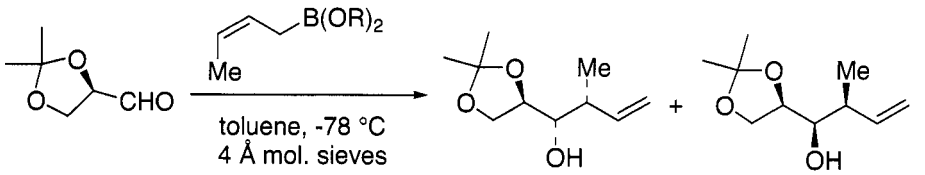
The allylation and crotylation of α-alkoxy aldehydes provide chiral 1,2-diol synthons which can be used in the synthesis of polyoxygenated small molecules, for example, natural and unnatural sugars.[26,27] The tartrate-derived allylboronates **1** and **2** provide reagent-controlled selectivity in reaction with chiral glyceraldehyde acetonide **30**.[4,6,8,16,28] The intrinsic selectivity of the aldehyde is estimated by its reactions with pinacol allylboronates **33** and **34**. The reagents **1** and **2** overcome the aldehyde's

intrinsic selectivity in mismatched reactions. Aldehyde **30** has very high intrinsic selectivity for adduct **38** in the reaction with (*Z*)-crotylboronates as illustrated in its reaction with the (*Z*)-pinacol crotylboronate **35**; in this case, the tartrate-derived (*Z*)-reagent **3** is unable to overcome the aldehyde's preference.



30 80-87% **36** **37**

Reagent	**36** : **37**
(*R*,*R*)-**2** (matched)	91 : 9
34	55 : 45
(*S*,*S*)-**2** (mismatched)	2 : 98



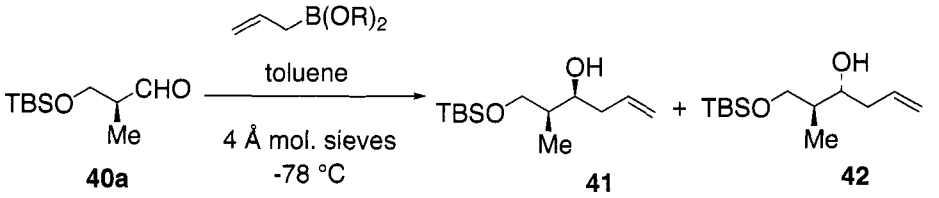
30 80-87% **38** **39**

Reagent	**38** : **39**
(*R*,*R*)-**3** (matched)	>99.8 : <0.2
35	97 : 3
(*S*,*S*)-**3** (mismatched)	84 : 16

α-Methyl-β-alkoxy aldehydes

The reactions of allylboronates with α-methyl-β-alkoxy aldehydes provides propionate adducts which are useful for the synthesis of polypropionate natural products.[29,30] The reaction of (*R*,*R*)-**1** with aldehyde (*S*)-**40a** provides

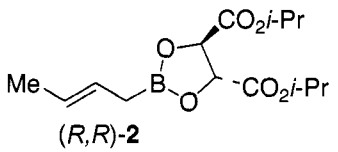
the Felkin adduct **41**; this matched reaction occurs with 89 : 11 selectivity.[29] The corresponding reaction of (*S,S*)-**1** with (*S*)-**40a** provides *anti*-Felkin adduct **42** with 81 : 19 selectivity. For point of reference, the achiral pinacol allylboronate **33** reacts with aldehyde **40a** to provide a 52 : 48 ratio of the Felkin and anti-Felkin products **41** and **42**, respectively, indicating the aldehyde has a low intrinsic facial preference in reactions with allylboronates.



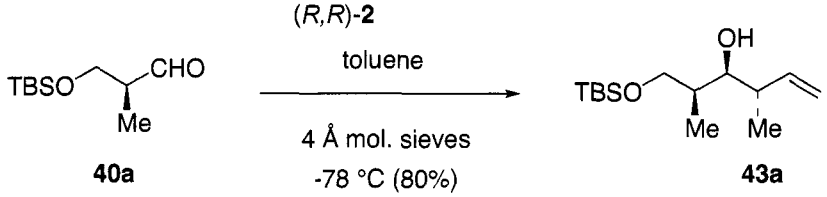
40a **41** **42**

71-72%

reagent	**41** : **42**
(*R,R*)-**1**	89 : 11
33	52 : 48
(*S,S*)-**1**	19 : 81

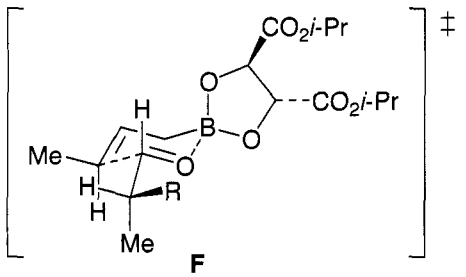


(*R,R*)-**2**

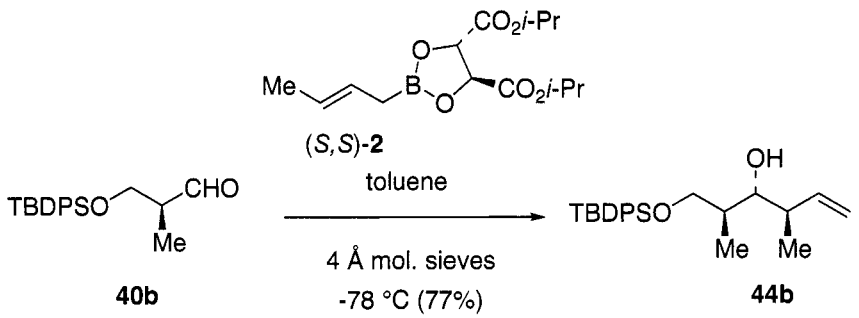


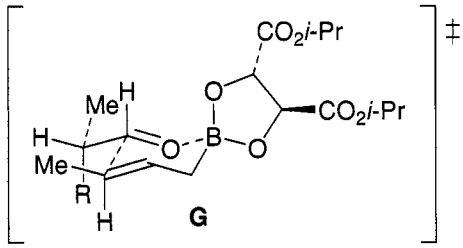
40a **43a**

selectivity = 97 : 3



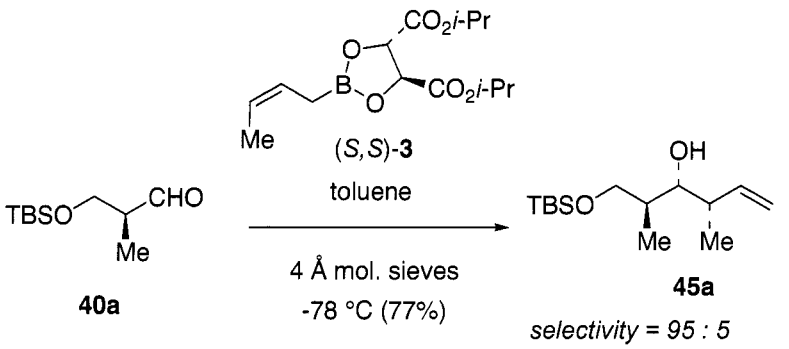
F

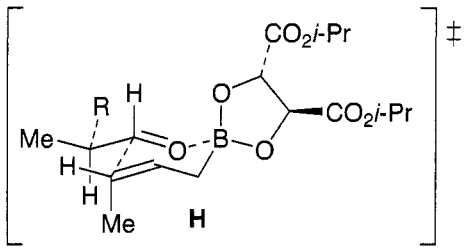


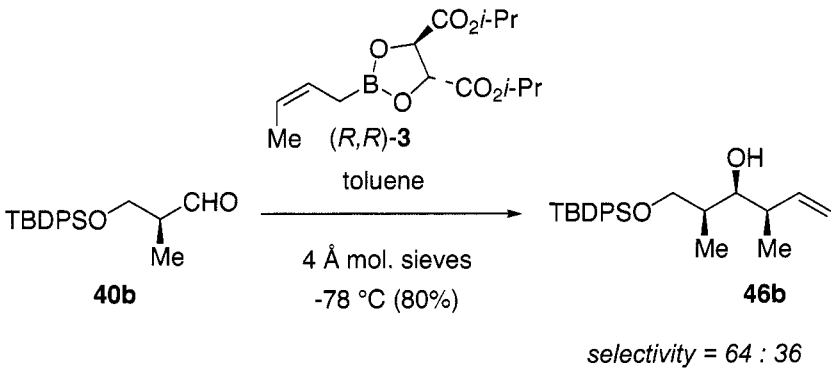


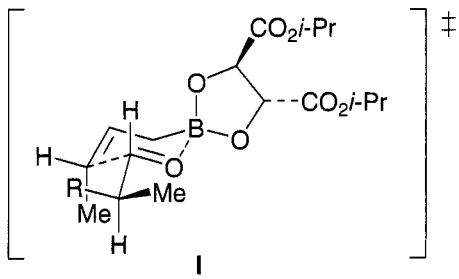
Dipropionates are available through the reaction of the (*E*)-and (*Z*)-crotylboronates **2** and **3** with α-methyl-β-hydroxy aldehydes. The *syn,anti*-dipropionate **43a** emerges as the major product with 97 : 3 selectivity from the matched crotylation reaction of aldehyde **40a** with (*R,R*)-**2**. This is the intrinsically favored adduct, and its formation can be rationalized via the Felkin transition state **F**. The *anti,anti*-dipropionate **44b** is the major adduct (selectivity = 90 : 10) of the mismatched reaction of aldehyde **40b** and (*S,S*)-**2**. Its formation can be rationalized via anti-Felkin transition state **G** and is an example of a reagent-controlled reaction.

In reactions of α-methyl chiral aldehydes with (*Z*)-enolates and Type I[31] (*Z*)-crotylmetal reagents like **3**, the anti-Felkin addition product is favored due to unfavorable *syn*-pentane interactions in the Felkin transition state.[32] Thus, in the matched reaction, the (*S,S*)-**3** reagent reacts with aldehyde **40a** to provide the *anti,syn*-dipropionate **45** with 95 : 5 selectivity. The stereochemical outcome of the reaction can be rationalized by anti-Felkin transition state **H**, where the nucleophile must approach near the methyl substituent. The mismatched reaction between aldehyde **40b** and (*R,R*)-**3** provides a mixture of dipropionates where the *syn,syn*-dipropionate **46** is only modestly favored (64 : 36 = sum of all other diastereomers). Transition state **I**, that rationalizes the formation of the major product, is less favorable as the nucleophile must approach the carbonyl carbon past the larger R substituent.


CO2i-Pr
O
B
O
CO2i-Pr
Me
(S,S)-3
toluene
TBSO
CHO
Me
40a
4 Å mol. sieves
-78 °C (77%)
OH
TBSO
Me Me
45a
selectivity = 95 : 5


CO2i-Pr
R
H
O
Me
B
O
CO2i-Pr
H
H
Me
H
‡

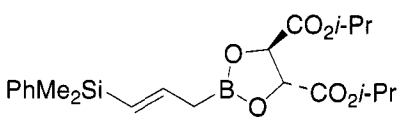

CO2i-Pr
O
B
O
CO2i-Pr
Me
(R,R)-3
toluene
TBDPSO
CHO
Me
40b
4 Å mol. sieves
-78 °C (80%)
OH
TBDPSO
Me Me
46b
selectivity = 64 : 36


CO2i-Pr
O
B
O
CO2i-Pr
H
H
O
R
Me
Me
H
I
‡

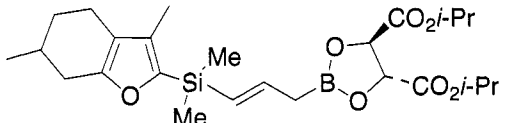
As a general rule, the success of reagents **1-3** in overcoming the intrinsic selectivity of an aldehyde in mismatched reactions becomes increasingly more difficult as the size of the aldehyde's large α-substitutent increases, thus, mismatched reactions should be planned early in a synthetic sequence, when the aldehyde is still relatively small.[30]

2.4.5 Variations

The (*E*)-γ-(silyl) allyl boronates **47** and **48** were subsequently introduced in order to access more highly oxygenated aldehyde addition products.[33,34] For example, the allylic silane addition products can undergo subsequent oxidation to provide 1,2- and 1,4-diol products. The allylsilane products are also allylmetal reagents; Roush and co-workers have demonstrated their ability to undergo addition reactions with Lewis acid activated aldehydes to form tetrahydrofuran products.[35]

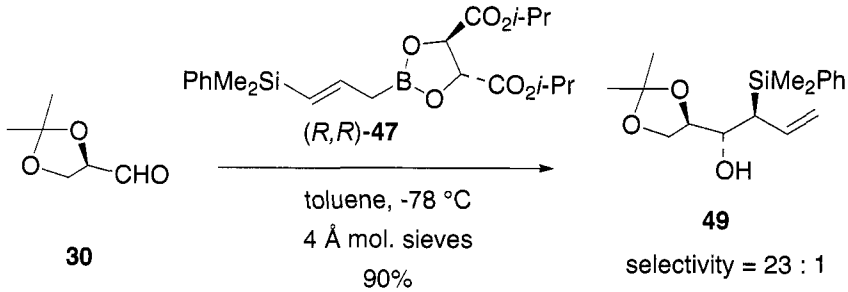


(*R,R*)-**47**



(*R,R*)-**48**

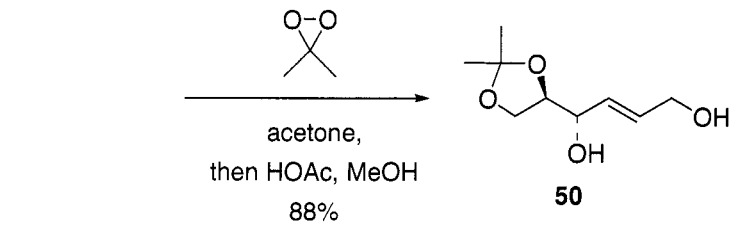
The (*E*)-γ-(dimethylphenylsilyl) tartrate allylboronate **47** undergoes addition to achiral aliphatic aldehydes in 88–95% yield and 81–87% *ee*. Higher levels of enantioselectivity can be achieved using (*E*)-γ-(dimethylphenylsilyl)diisopinocampheyl allylborane.[35] The matched double asymmetric reactions between reagent **47** and chiral aldehydes can be highly diastereoselective. The resulting allylsilane products, *e.g.*, **49** and **51**, can undergo oxidation to the epoxides with dimethyldioxerane and acid-catalyzed Petersen elimination to generate the 1,4-diols **50** and **52**. Fleming–Tamao oxidation[36,37] of adduct **49**, to provide the 1,2-*anti* diol **53** (*vide infra*) is not possible as a competitive Petersen elimination process predominates.[33]



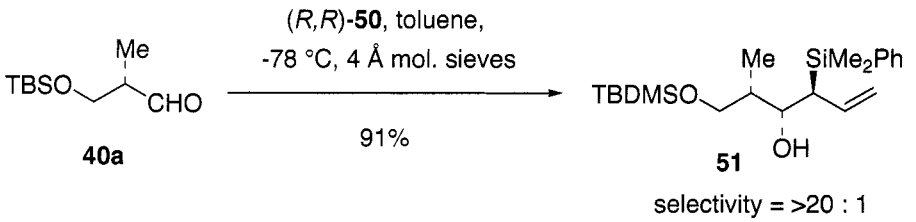
30

49

selectivity = 23 : 1

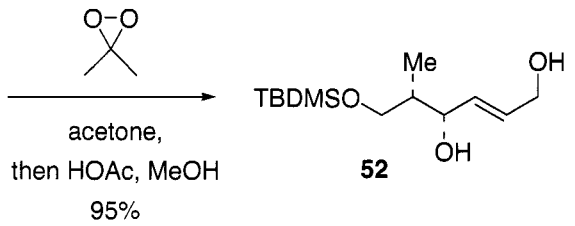


50



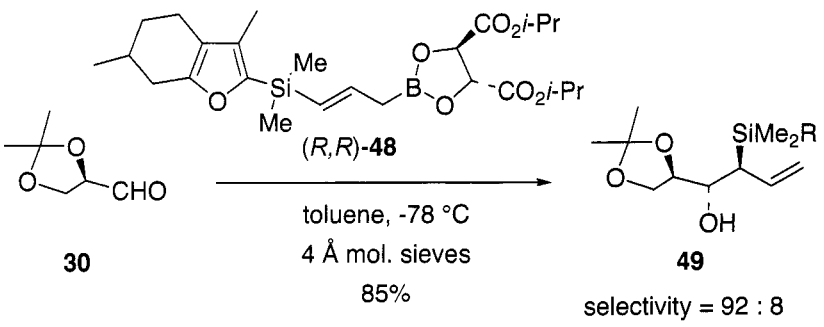
40a **51**

selectivity = >20 : 1



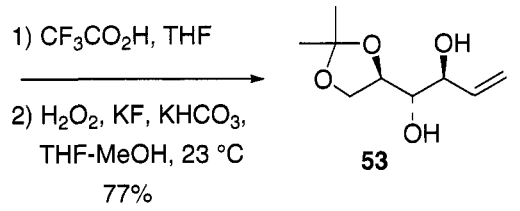
52

In order to access the 1,2-*anti* diol oxidation product, (*E*)-γ-[(menthofuryl)dimethylsilyl]allyl boronate **48** was designed.[34] This reagent reacts selectively with chiral aldehydes to form addition products with useful levels of selectivity. Fleming–Tamao oxidation[36,37] of the allylsilane addition products provides 1,2-*anti* diols without substantial Peterson elimination.



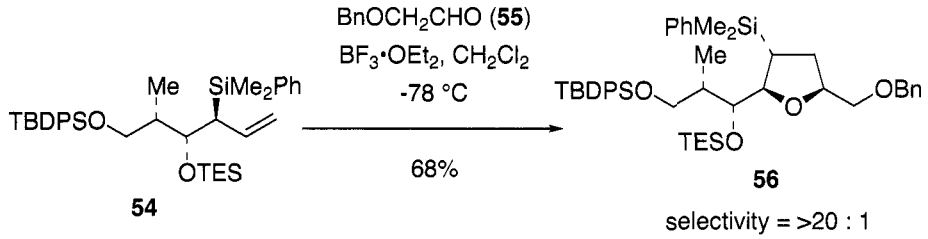
30 **49**

selectivity = 92 : 8



53

Allylation adducts of (*E*)-γ-(dimethylphenylsilyl)allylboronate **47** selectively undergo addition reactions with aldehydes. Lewis acid catalyzed [3 + 2] cycloaddition reaction of these allylsilanes with various aldehydes, *e.g.,* **55**, provides tetrahydrofuran adducts with high diastereoselectivity.[35]



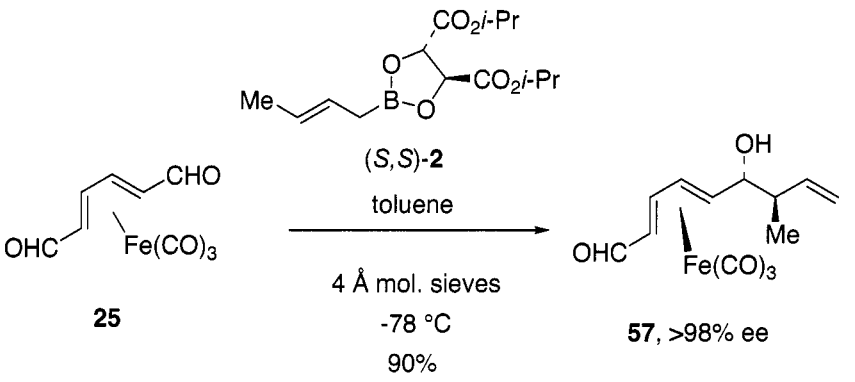
54

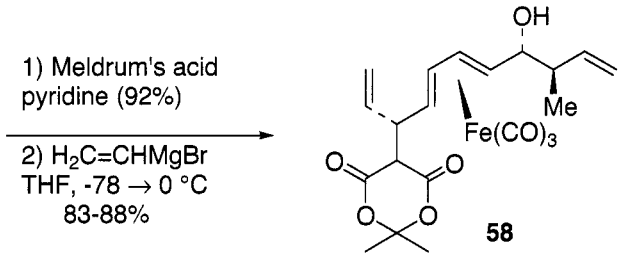
56

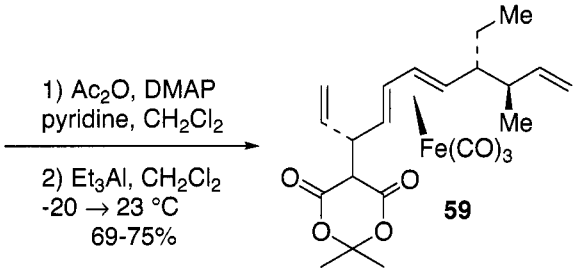
2.4.6 *Applications in Natural Product Synthesis and Structure-Activity-Relationship Studies*

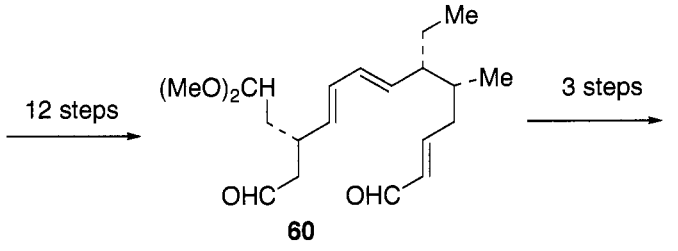
The chiral allylboronates **1-3** and γ-(silyl)allylboronates **47** and **48** have been used in the synthesis of numerous natural products and their analogs.[30,38–60]

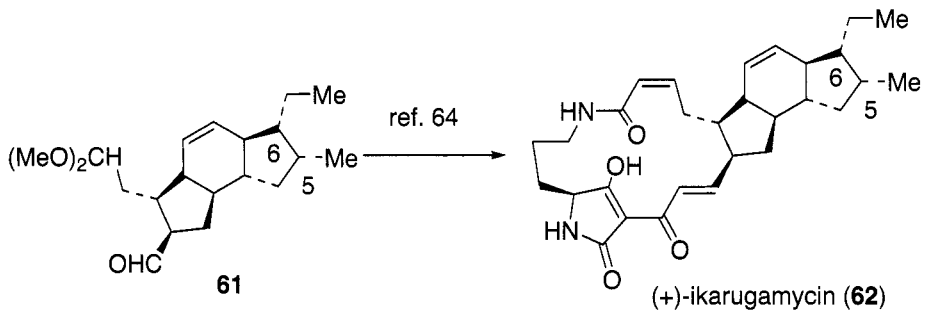
Roush and Wada completed a formal total synthesis of (+)-ikarugamycin,[41] a macrocyclic lactam that demonstrated antiprotozoal and antiamoebic activity as well as inhibition of gram-positive bacteria.[61] Roush's synthesis utilized the crotylboronation reaction of iron tricarbonyl-complexed dienyl dialdehyde **25** with (*S,S*)-**2** as a key step, which occured in 90% yield and > 98% *ee.* The allylic alcohol adduct was elaborated to dienylic alcohol **57**, which underwent acetylation and displacement of the acetate with retention of configuration through reaction with triethylaluminum, thereby installing the vicinal C(5) and C(6) stereocenters. The iron tricarbonyl complexation of the diene was key to enabling this substitution reaction.[62,63] The resulting adduct **59** was subsequently elaborated to indacene **61**, an intermediate in Boeckman's synthesis of ikarugamycin,[64] through a 15-step synthetic sequence, including the intramolecular Diels–Alder reaction of **60**.


CO2i-Pr
CO2i-Pr
Me
(S,S)-2
toluene
4 Å mol. sieves
-78 °C
90%
CHO
OHC
Fe(CO)3
25
OH
Me
OHC
Fe(CO)3
57, >98% ee

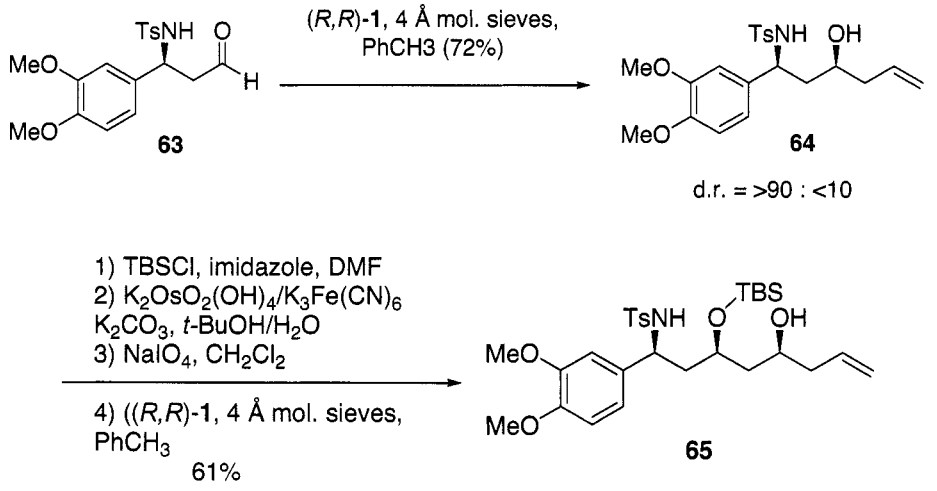

1) Meldrum's acid
pyridine (92%)
2) H2C=CHMgBr
THF, -78 → 0 °C
83-88%
OH
Me
Fe(CO)3
58

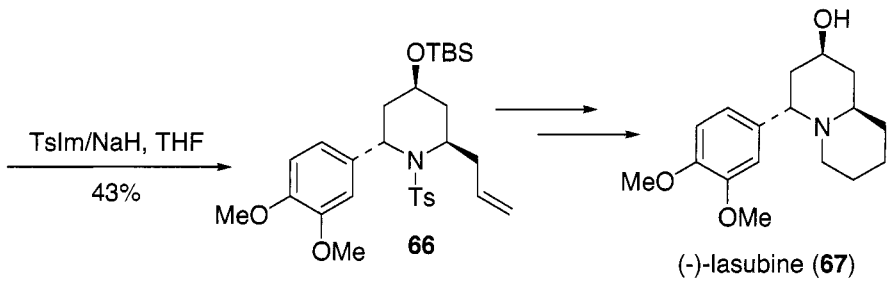

1) Ac2O, DMAP
pyridine, CH2Cl2
2) Et3Al, CH2Cl2
-20 → 23 °C
69-75%
Me
Me
Fe(CO)3
59


12 steps
(MeO)2CH
Me
Me
OHC
OHC
3 steps
60

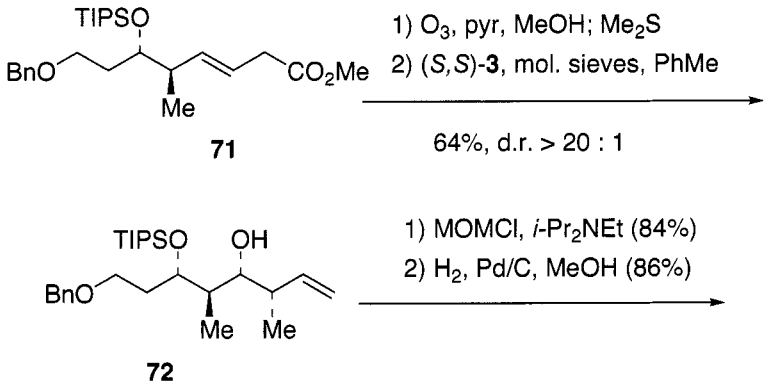


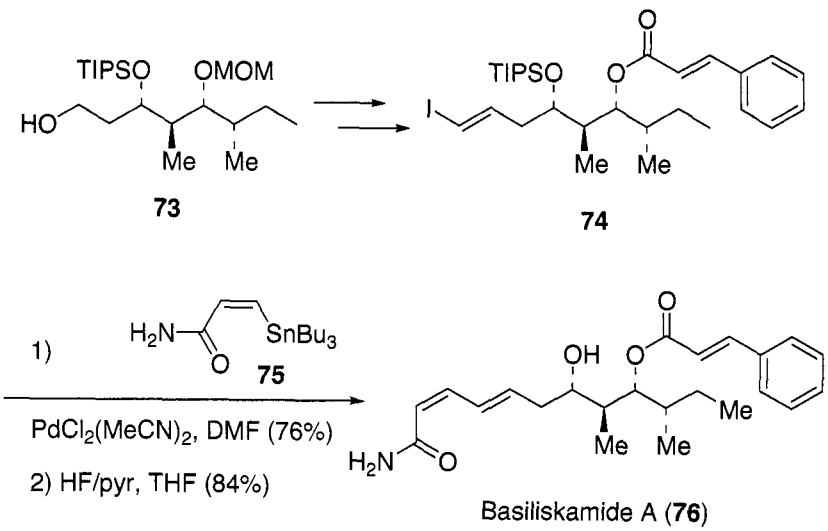
The allylboronate reagent **1** was used twice in the synthesis of (–)-lasubine I by Wang and Liao.[58] (–)-Lasubine I (**67**) is a bioactive alkaloid isolated from the *Lythraceae* plant.[65] (–)-Lasubine I contains three stereocenters in a quinolizidine core. Roush allylation of aldehyde **63** with (*R,R*)-**1** provided the 1,3-aminoalcohol **67** in > 90 : < 10 diastereoselectivity. Alcohol protection and alkene oxidation provided an intermediate aldehyde which underwent Roush allylation with (*R,R*)-**1** to provide homoallylic alcohol **65** in 61% overall yield. Tosylation of the alcohol with TsIm/NaH and intramolecular displacement with the amine provided piperidine **66**. Piperidine **66** was elaborated to (–)-lasubine in 4 steps.



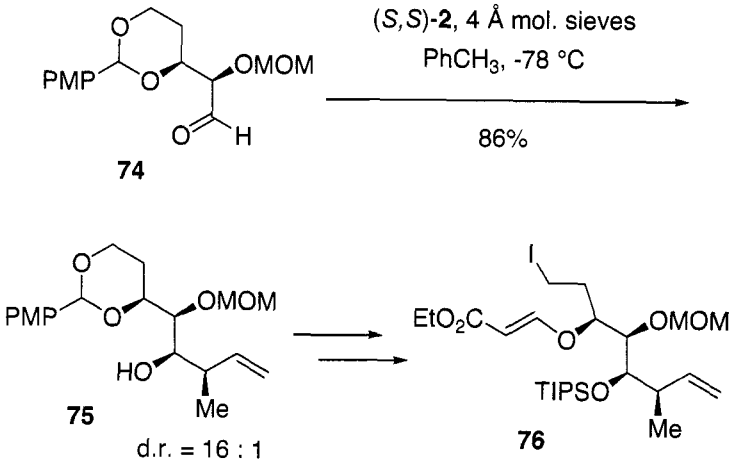


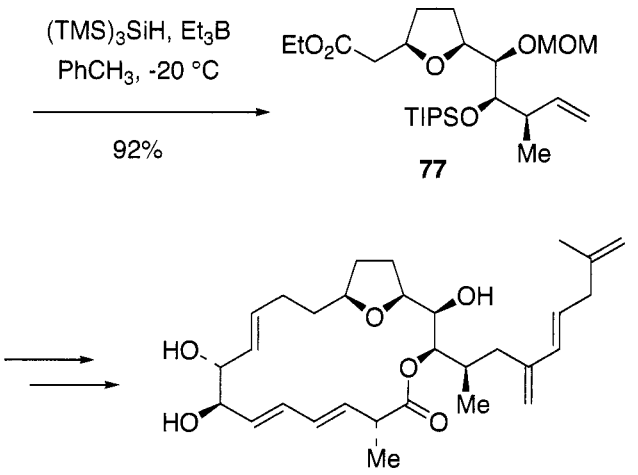
The use of aldol and allylation reagents is especially applicable for the synthesis of the stereochemically rich polyketide natural products. For example, the (*Z*)-crotylboronate reagent **3** was used by Panek and co-workers in their total synthesis of the polyketide antibiotics basiliskamides A and B.[50] Intermediate **68**, obtained by Panek's selective crotylsilane allylation methodology, was oxidized to the aldehyde by cleavage of the alkene with ozone (Me_2S work-up). The aldehyde underwent selective crotylation with (*S,S*)-**3** to give adduct **69** in 64% combined yield and in > 20:1 diastereoselectivity. The alcohol was protected as the methyloxymethyl ether and the alkene was hydrogenated to provide **70**. Alcohol **70** was elaborated to vinyl iodide **71**, which underwent Stille coupling[66] with vinylstannane **72**. Deprotection of the silyl ether of the coupling product provided basiliskamide A (**73**). The use of the (*S,S*)-**3** reagent was particularly atom-economical as the resulting terminal alkene in the addition product was simply hydrogenated to provide the ethyl side chain in the natural product.





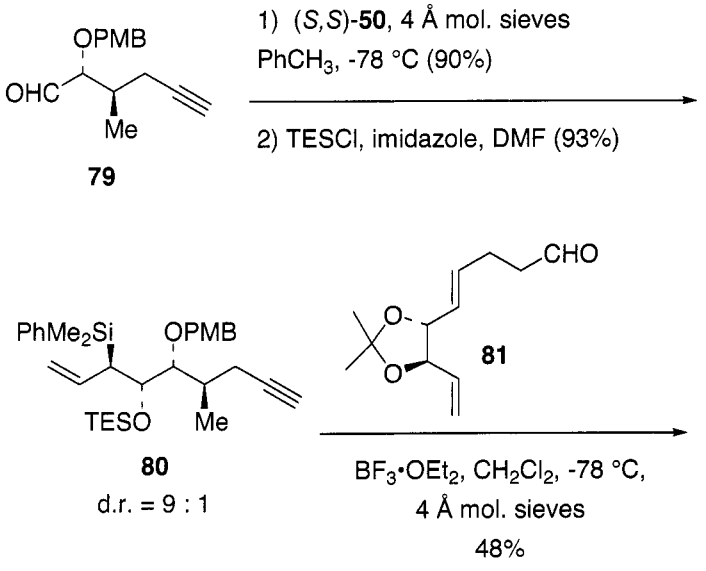
The (*E*)-crotylboronate **2** was used by Lee and co-workers in their total synthesis of the cytotoxic 18-membered macrolide, amphidinolide E.[55] Crotylation of the advanced aldehyde **74** provided stereotetrad **75** with 16 : 1 diastereoselectivity. This intermediate was elaborated to enoate **76**, which underwent a diastereoselective radical cyclization to efficiently provide the *cis*-tetrahydrofuran **77**, which was converted to the natural product via several additional transformations.

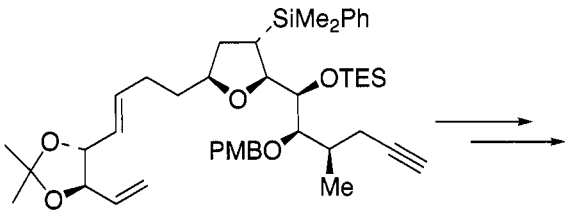




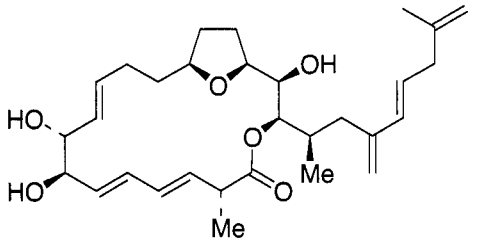
(-)-Amphidinolide E (**78**)

Roush and co-workers synthesized amphidinolide E in a unique sequence wherein γ-silylallylboronate **47** was used to synthesize a synthetically advanced allylic silane intermediate that served to form the tetrahydrofuran ring in reaction with advanced aldehyde **81**.[56]



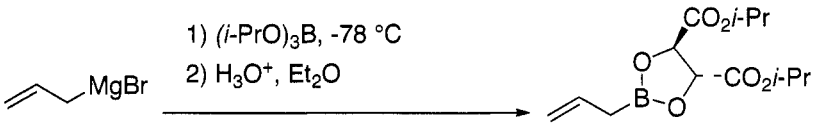


82



(-)-Amphidinolide E (**83**)

2.4.7 Experimental



11

(*R,R*)-**1**

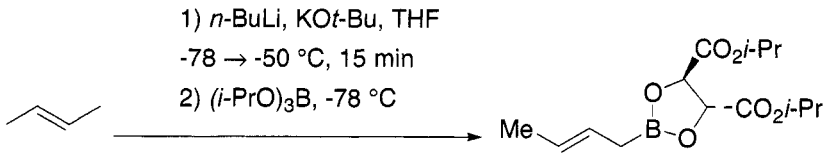
65-86%

Synthesis of (4*R*,5*R*)-Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate [(*R,R*)-Tartrate Allylboronate 1][4,8]

Solutions of triisopropyl borate (40 mmol) in dry Et_2O (10 mL) and allylmagnesium bromide (**11**) in Et_2O (40.0 mmol, 0.87 M) were added dropwise simultaneously, but separately, to 10 mL of dry Et_2O at –78 °C. The mixture was stirred for 0.5 h at –78 °C, allowed to warm to rt, and stirred for 3 h. The slurry was recooled to 0 °C, and then 40 mmol of aqueous HCl (1 N solution saturated with NaCl) was added drop-wise over 15 min. The mixture was warmed to room temperature and stirring was continued for 10 min. The organic layer was separated and directly treated with (*R,R*)-diisopropyl tartrate (40 mmol). The aqueous phase was extracted with 5:1 Et_2O/CH_2Cl_2 (3 × 50 mL). The combined organic layers were stirred over anhydrous $MgSO_4$ for 2.5 h and then filtered under Ar. The filtrate was

concentrated *in vacuo* to give a clear, colorless, semi-viscous liquid. Dry toluene was added to give 50.0 mL of a clear solution.

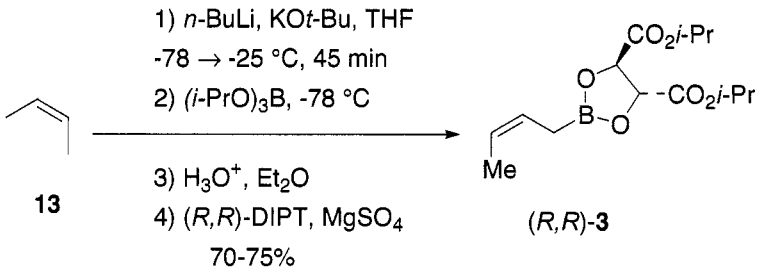
Titration: A 1 mL aliquot of the solution of crude reagent was treated with 4 Å molecular sieves (activated). After being stirred for 15 min at rt, a known excess of cyclohexanecarboxyaldehyde was added. The reaction was quenched 15 min later with excess $NaBH_4$ in EtOH, stirred for 30 min, and then diluted with 1:1 Et_2O/1 M NaOH. The organic layer was separated, dried over anhydrous Na_2SO_4, and then analyzed by capillary GC (50 m × 0.25 mm Bonded FSOT Carbowax 20M; 100 °C/4 min → 10 °C/min → 190 °C) for cyclohexylmethanol (t_R 7.6 min) and 1-cyclohexylbut-3-en-1-ol (t_R 9.6 min). The yield of allylboronate reagent **1** was found to be 86% (yields in the range of 65-75% are typical), and the concentration of the standardized solution was calculated to be 0.7 M. Reagent **1** can be purified by distillation of the crude product (88-90 °C, 0.03 mm /Hg) through a short path column. Data for (*R,R*)-**1** (distilled): $[\alpha]_D^{20} = +47.9$ (c 1.96, CH_2Cl_2).



Preparation of (*R,R*)-Diisopropyl Tartrate (*E*)-Crotylboronate (2)[7]

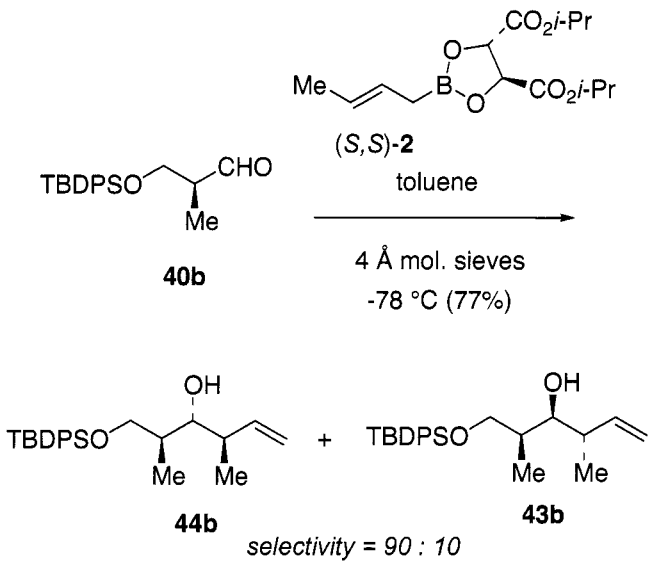
An oven-dried 1 L three-neck round-bottom flask equipped with a magnetic stir bar and a –100 °C thermometer is charged with 350 mL of anhydrous THF and KO*t*-Bu (48.0 g, 425 mmol). This mixture is flushed with Ar and cooled to –78 °C, and then trans-2-butene (**12**) (42.0 mL, 450 mmol), condensed from a gas lecture bottle into a rubber-stoppered 25 mL graduated cylinder immersed in a –78 °C dry ice-acetone bath, is added via cannula. *n*-BuLi (2.5 M in hexane, 170 mL, 425 mmol) is then added drop-wise via cannula at a rate such that the internal temperature does not rise above –65 °C. After completion of the addition (roughly 2 h on this scale), the cooling bath is removed and the reaction mixture is allowed to warm until the internal temperature reaches –50 °C for exactly 15 min and then is immediately recooled to –78 °C. Triisopropylborate (80.0 g, 98.2 mL, 425 mmol) is then added dropwise via cannula to the (*E*)-crotylpotassium solution at a rate such that the internal temperature does not rise above –65 °C. On this scale the addition time was approximately 2 h. After the addition is complete, the reaction mixture is maintained at –78 °C for 10 min and then rapidly poured into a 2-L separatory funnel containing 800 mL of 1

N HCl saturated with NaCl. The aqueous layer is adjusted to pH 1 by using 1 N HCl, and then a solution of (*R,R*)-diisopropyl tartrate (100 g, 425 mmol) in 150 mL of Et_2O is added. The phases are separated, and the aqueous layer is extracted with additional Et_2O (4 × 200 mL). The combined extracts are dried with $MgSO_4$ for at least 2 h at rt and then vacuum filtered through a fritted glass funnel under N_2 blanket into an oven-dried round-bottom flask. The filtrate is then concentrated on the rotary evaporator to a colorless thick liquid, and then is pumped to constant weight (125 g) at 0.5–1.0 mm Hg. It is necessary for the neat reagent to be stirred for residual volatile materials, especially residual THF, to be removed efficiently. The yield of this batch of reagent, determined by the titration procedure described, was 60%. [The yield of the reagent is further improved to 82–89% by performing the butene metalation at a higher concentration (0.9 M).] Reagent **2** can be purified by Kugelrohr distillation (80 °C, 0.1 mm Hg). Reagent (*S,S*)-**2** prepared from (*S,S*)-DIPT had $[\alpha]_D^{20}$ +36.5 ° (neat).



Preparation of (*R,R*)-Diisopropyl ( )-Crotylboronate (3)[7]

The preparation of (*Z*)-crotylboronate **3** from (*Z*)-2-butene is analogous to that described for the *E* reagent with the following modification: upon completion of the *n*-BuLi addition, the reaction mixture is warmed to –20 to –25 °C for 30–45 min before being recooled to –78 °C. This ensures near quantitative formation of the (*Z*)-crotylpotassium. Temperature control is less critical here since the (*Z*)-crotylpotassium is highly favored at equilibrium (99 : 1). The remainder of this preparation is the same as that described above for the synthesis of **2**. On a 100 mmol scale, the yield of (*Z*)-crotylboronate is 70–75% and the isomeric purity is > 98%. Tartrate crotylboronate **3** can be purified by Kugelrohr distillation (92 °C, 0.6 mm Hg). Distilled (*R,R*)-**3** had $[\alpha]_D^{25}$ – 80.2° (c 2.42, $CHCl_3$).



Preparation of (2*S*,3*S*,4*R*)-2,4-Dimethyl-1-[(*tert*-butyldiphenylsilyl)oxy]-hex-5-en-3-ol (44b)[30]

To a slurry of 2 g of 4 Å powdered molecular sieves (activated by flame-drying or equivalent dehydration method) in 100 mL of anhydrous toluene under Ar at room temperature was added (*S,S*)-**2** (170 mL, 170 mmol, 1.0 M solution in toluene, 99% isomeric purity). After being stirred for 10 min at room temperature, the mixture was cooled to –78 °C. A solution of aldehyde **40b** (crude from a Swern oxidation,[67] theoretically 113 mmol) in 100 mL of dry toluene was then introduced drop-wise via cannula over a 2 h period. After the addition was complete, the solution was maintained at –78 °C for 10 h. Excess ethanolic $NaBH_4$ (ca. 0.75 g in 10 mL of absolute EtOH) was then added drop-wise via pipette, the cooling bath was removed and the solution warmed to 0 °C. The mixture was then diluted with 300 mL of 1 N NaOH and stirred vigorously for 2 h. The layers were then separated and the aqueous layer was extracted with Et_2O (5 × 300 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated to a thick yellow liquid. HPLC analysis revealed a 90 : 10 diastereomeric ratio. The crude product was flash chromatographed on SiO_2 (9:1 hexane:Et_2O) provided 18.8 g of pure **44b**, 6.58 g of a 95 : 5 mixture of **44b** and its *syn,anti*-diastereomer (**43b**) and 7.10 g of a 50 : 50 mixture of **44b** and its *syn,anti*-diastereomer (**43b**). The combined yield was 32.5 g (77% overall from the alcohol precursor). Data for **44b**: $[\alpha]_D^{20}$ +26.2° (c 2.5, $CHCl_3$).

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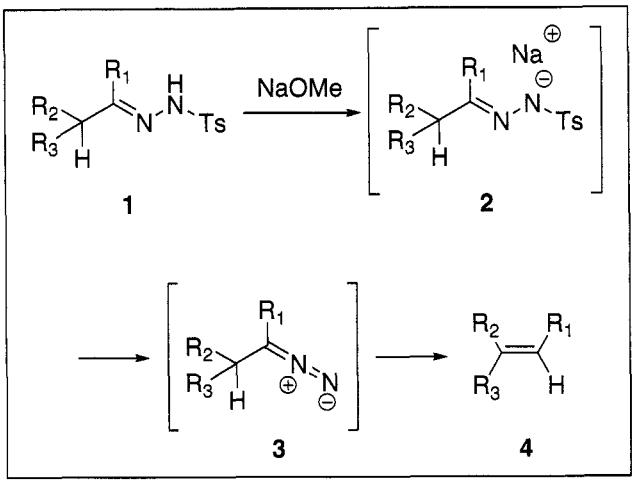
Chapter 3. Miscellaneous Homologation Reactions

3.1 Bamford–Stevens reaction

Paul Humphries

3.1.1 Description



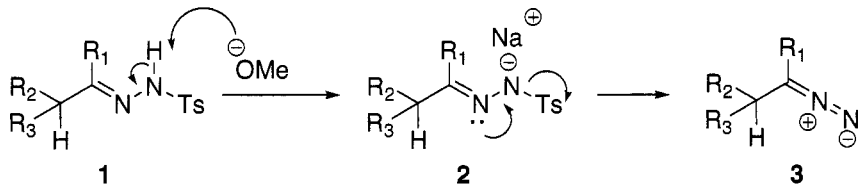
The Bamford–Stevens reaction is the formation of an alkene **4** by the treatment of the tosylhydrazone **1**, of an aldehyde or a ketone, with a base.[1] A few diazo compounds **3** can be isolated if mild temperatures are employed; however in the majority of cases, the diazo compounds thermally decompose to form alkenes.

2.1.2 Historical Perspective

The titled reaction was first reported by William Randall Bamford and Thomas Stevens Stevens in 1952 at The University of Sheffield.[2] It is closely related to the Shapiro reaction, in which tosylhydrazones are treated with alkyl lithium reagents to form alkenes.[3] This valuable transformation has received extensive attention, as testified by the references cited herein.

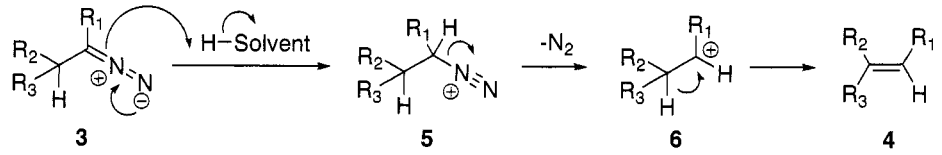
2.1.3 Mechanism

The mechanism was originally proposed by Powell and Whiting,[4] with further corroboration by others soon thereafter.[5] The first step of the Bamford–Stevens reaction is the formation of the diazo compound **3**, via the tosylate salt **2**.[6]



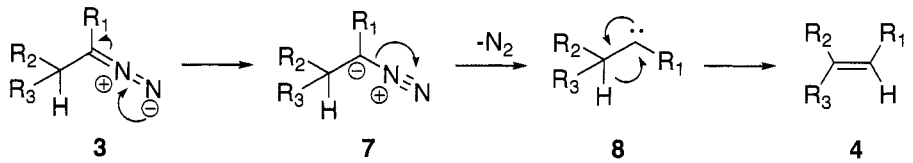
1 2 3

The mechanism for alkene formation was found to be dependent upon the reaction conditions.[7] For instance, in protic media, the diazo compound **3** can be protonated to form a diazonium ion **5**, resulting in the formation of a carbocation **6** upon loss of dinitrogen.



3 5 6 4

This pathway does not occur in the absence of protons, and in aprotic media, dinitrogen loss results in the formation of carbene intermediates **8**.



3 7 8 4

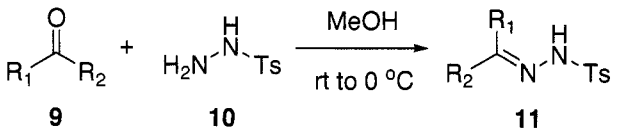
The migration of hydrogen may immediately follow, or be simultaneous with, the loss of dinitrogen.

3.1.4 Variations and Improvements

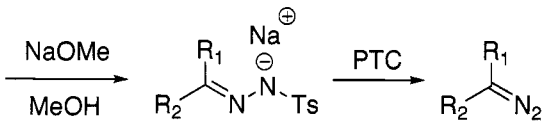
Initially, the decomposition of tosylhydrazones with base (and variations thereof) was used as a preparative procedure to synthesize a series of aryldiazomethanes and is still a standard method for their generation.[6,8] This procedure initially involves deprotonation of the tosylhydrazone **1** to form the corresponding anion. When the reaction is performed cold, the tosylhydrazone salt **2** can sometimes be isolated. Upon heating (generally 60 °C or higher), the tosylate anion will dissociate, generating the diazo compound **3**. It has been found that this reaction must be performed in either a polar media such as pyridine or methanol, or in a basic aqueous two-phase system.

The Aggarwal group has recently found that the diazo compounds can be generated under mild conditions and in non-polar media by gently

warming (30–40 °C) a suspension of the isolated tosylhydrazone salt **12** in the presence of a phase-transfer catalyst (PTC).[9] As the salt is not very soluble in highly non-polar solvents, the PTC is necessary to aid the passage of the anion from the solid to the liquid phase where decomposition (diazo formation) occurs. As every component in the reaction mixture, except for the diazo compound **13**, is fairly inert, they then proceeded to add substrates directly to the in situ generated diazo compounds without the worry of these substrates reacting with the reagents promoting the decomposition of the tosylhydrazone salts **12**. Thus, as the diazo compound is formed, it can immediately be "trapped out" in a subsequent reaction. This in situ generation of diazo compounds not only keeps the diazo concentration low and minimizes hazards associated with the more concentrated diazo solutions, but it also prevents dimerization of the diazo compounds to form azines or alkenes through common decomposition pathways for these molecules.



9 **10** **11**

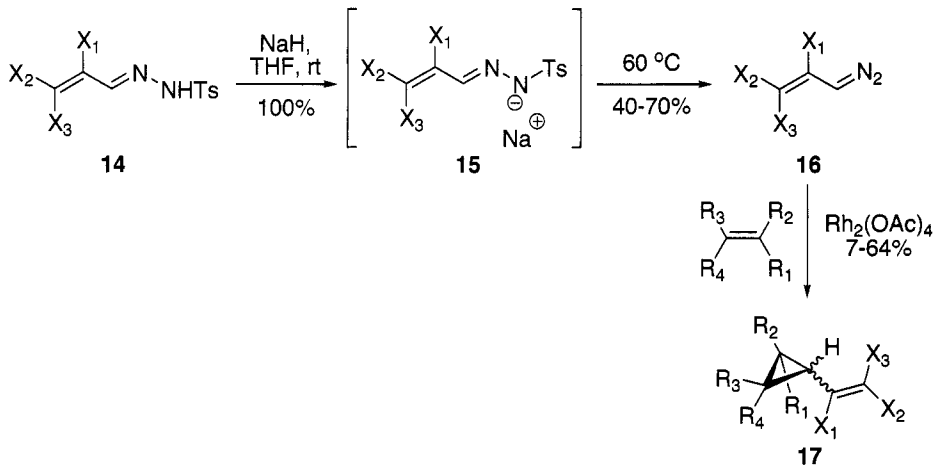


12 **13**

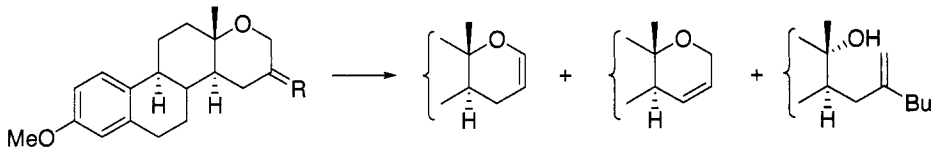
3.1.5 Synthetic Utility

General Utility

The groups of de Meijere and Kostikov utilized the Bamford–Stevens reaction whilst demonstrating the dirhodium(II) tetraacetate catalyzed (chlorovinyl)cyclopropanation of enol ethers and dienol ethers.[10] The resulting vinylcyclopropanes **17** play an important role as precursors to cyclopentenes en route to cyclopentanoid natural products.[11]

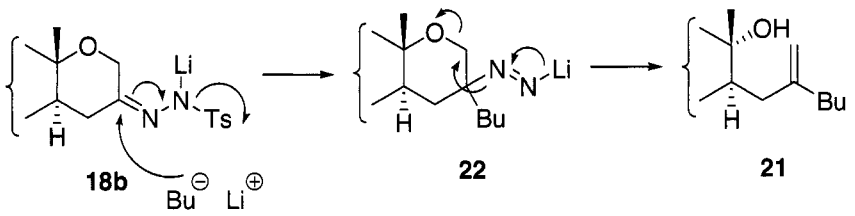


Nickon investigated the 1,2-hydrogen shifts in thermal and photic Bamford–Stevens reactions of cyclohexanones.[12] Under conditions known to favor the Shapiro reaction, tosylhydrazone **18a** afforded the two expected alkenes **19** and **20** as well as an unexpected product (identified as **21**) in a ratio of 15:60:25. Under conditions known to favor the Bamford–Stevens reaction, lithium salt **18b** was subjected to thermolysis (neat, 170 °C) and also to photolysis (pentane suspension, –70 °C). Under both sets of conditions the three products **19**, **20** and **21** were formed in approximately the same ratio (84:4:12 and 83:6:11), thus demonstrating the switching of major alkene product from **19** to **20** on moving from the Shapiro reaction to the Bamford–Stevens reaction.

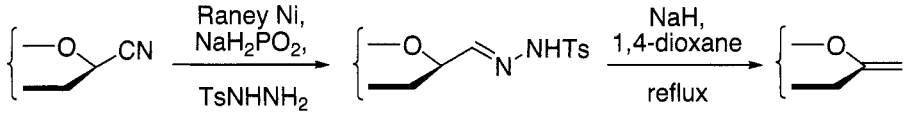


i) Shapiro: xs BuLi / hexane / rt	15	:	60	:	25
ii) B-S: Δ / neat / 170 °C	84	:	4	:	12
iii) B-S: hυ / pentane / -70 °C	83	:	6	:	11

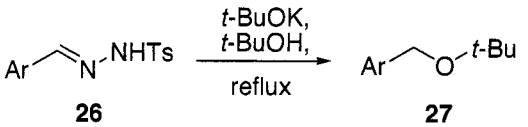
One reasonable pathway to unexpected ring-opened product **21** is shown below, although several variations can be written. Related types of alkylations of tosylhydrazones have been reported for other alkyllithium reagents.[13]



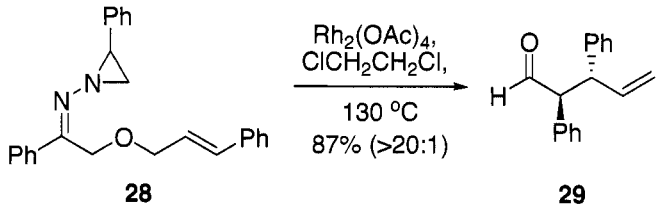
Somsák described a new route to *exo*-glycals **25** from readily available glycosyl cyanides **23** via the Bamford–Stevens reaction of 2,5- and 2,6-anhydroaldose tosylhydrazones **24**.[14] *exo*-Glycals are useful carbohydrate derivatives exemplified by their applications in syntheses.[15]



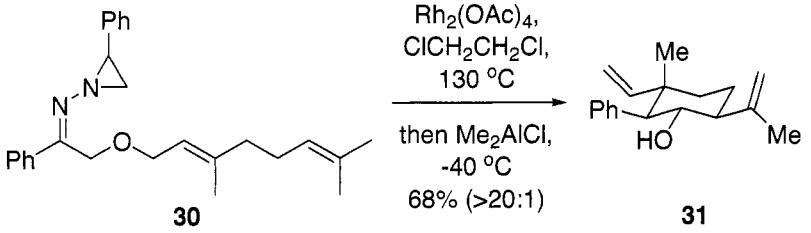
Direct conversion of tosylhydrazones to *tert*-butyl ethers under Bamford-Stevens reaction conditions was recently demonstrated by Chandrasekhar.[16] This general methodology involves simply refluxing a solution of the tosylhydrazone **26** and potassium *tert*-butoxide in *tert*-butanol, thus affording the required *tert*-butyl ether **27** in high yield.



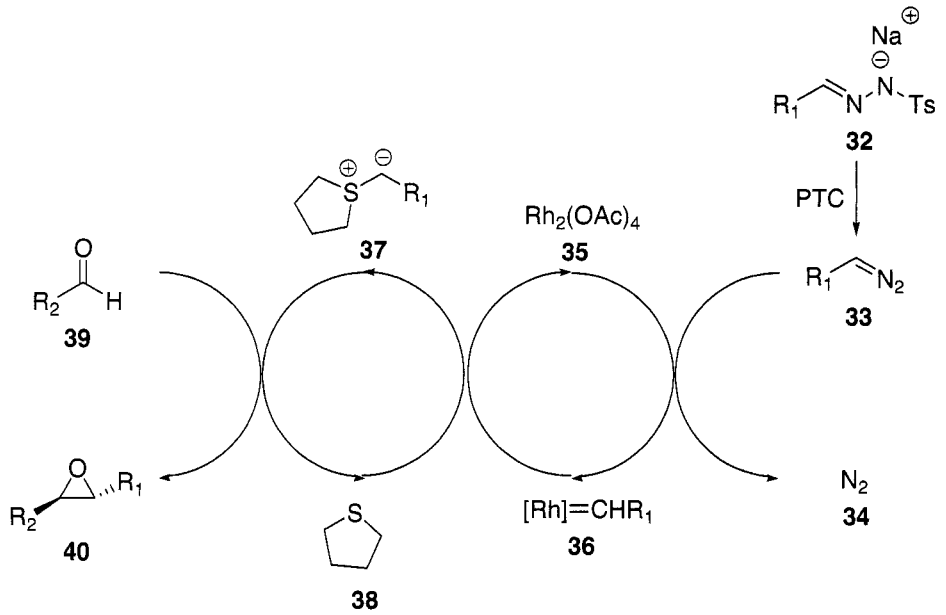
The development of a tandem rhodium-catalyzed Bamford–Stevens/thermal aliphatic Claisen rearrangement sequence was elegantly demonstrated by Stoltz.[17] As a general method to prepare non-carbonyl-stabilized diazo compounds in situ, this group chose to investigate the decomposition of *N*-aziridinyl imines (also known as Eschenmoser hydrazones) **28**.[18]



In addition to the Bamford–Stevens/Claisen sequence, the same group investigated a number of cascade reactions, wherein a third chemical step occurs after the initial tandem process. For instance, Lewis acid promotion of neryl ether **30** induces a cascade terminating in a carbonyl-ene reaction to produce cyclohexanol **31** with excellent diastereoselectivity.

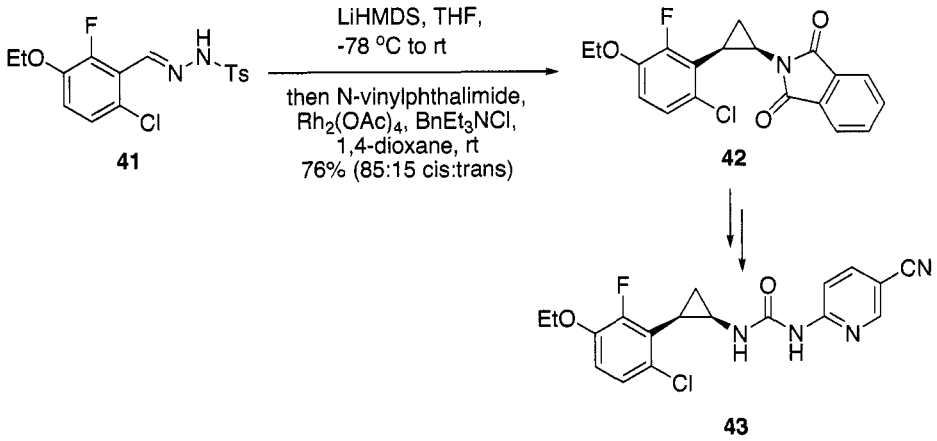


As mentioned previously, the Aggarwal group has utilized the Bamford-Stevens reaction as a method to in situ generate diazo compounds **33** and further "trap out" these in a subsequent reaction. This in situ concept was initially tested on the sulfur-ylide **37** mediated epoxidation of aldehydes **39**.[9]



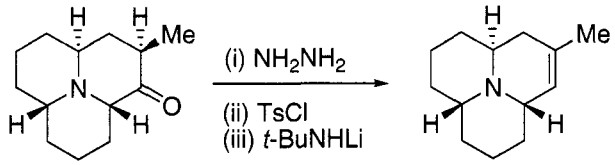
The *in situ* technology was applied to other reactions, such as aziridination of imines,[19] aldehyde homologation,[20] cyclopropanation of alkenes,[19] 1,3-dipolar additions to alkynes,[21] and Wittig olefination.[22] Further

demonstration of this in situ technology was achieved by applying it towards the synthesis of HIV-1 reverse transcriptase inhibitor **43**.[23]

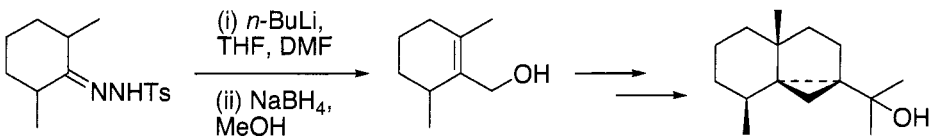


Applications in the total synthesis of natural products

Mueller and Thompson utilized the Bamford–Stevens reaction in their total synthesis of hippocasine **45**.[24] Thus, conversion of ketone **44** into the derived tosylhydrazone and treatment with lithium *tert*-butylamide afforded hippocasine **45**. The reaction occurred exclusively in the desired direction presumably due to selective removal of the axial proton, although hindered, alpha to the methyl group rather than the less hindered, but equatorial, proton alpha to the nitrogen atom.

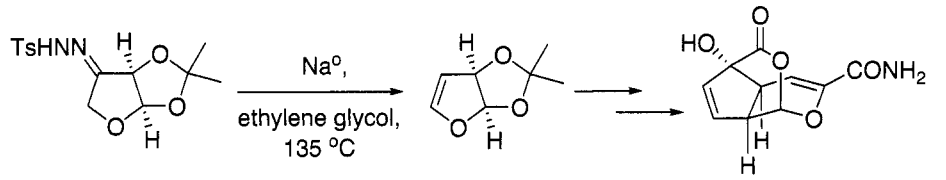


Chen's stereospecific total synthesis of cycloeudesmol **48** started with the hydrazone **46**, which was converted to the allylic alcohol **47** by the Bamford–Stevens reaction followed by DMF trapping of the vinyl anion and sodium borohydride reduction.[25] This allylic alcohol **47** was then taken on through a further ten steps to yield the natural product cycloeudesmol **48**.



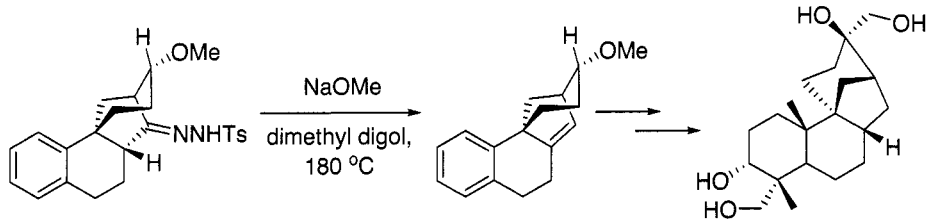
46 47 48

Smith and co-workers utilized the Bamford-Stevens reaction en route to a total synthesis of echinosporin **51**.[26] Tosylhydrazone **49** was heated with sodium in ethylene glycol to afford key intermediate **50** on large scale. Dihydrofuran **50** was then taken through a further ten steps to afford echinosporin **51**.



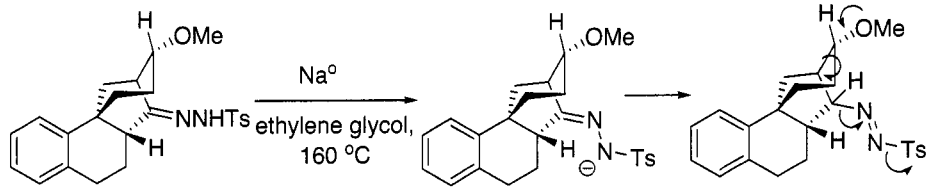
49 50 51

The Mann group demonstrated a new approach to the skeleton of the aphidicolin diterpenoid **54**.[27] Treatment of tosylhydrazone **52** with aprotic Bamford-Stevens conditions afforded the required alkene **53**.

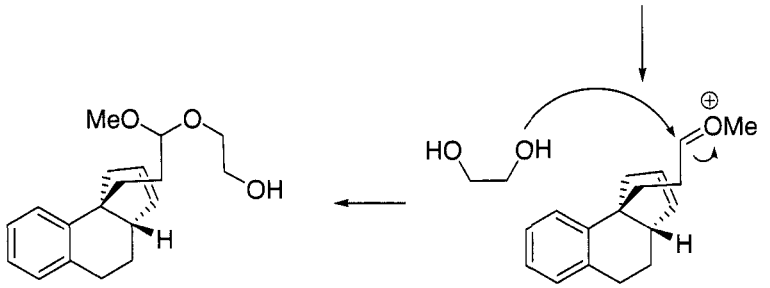


52 53 54

However, protic Bamford–Stevens conditions gave the unusual mixed acetal **58**, presumably via the mechanism shown.



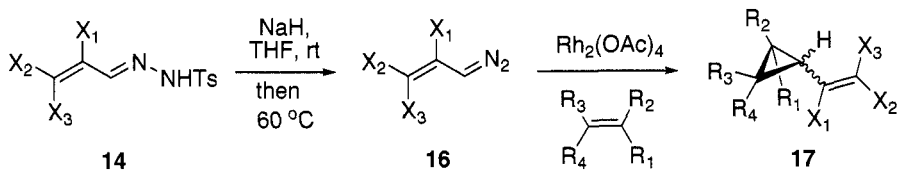
52 55 56



58 57

3.1.5 Experimental

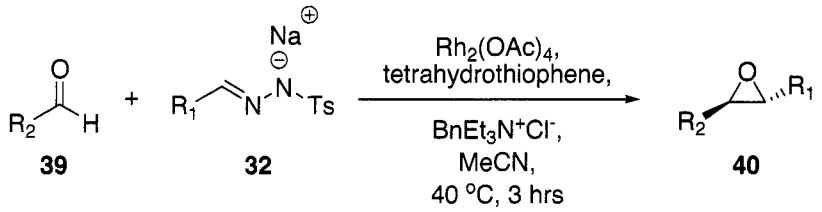
Original Bamford-Stevens Reaction: (Chlorovinyl)cyclopropanation of Enol Ethers to Form Vinylcyclopropanes (17)[10]



14 16 17

To solution of the respective tosylhydrazone **14** (7 mmol) in dry tetrahydrofuran (30 mL) was added, in several portions, sodium hydride (0.168 g, 7 mmol). The mixture was stirred at ambient temperature until the evolution of hydrogen had ceased, then warmed to 60 °C and the colored solution bulb-to-bulb distilled under reduced pressure (0.1 Torr). Because of the sensitivity of chlorodiazopropenes **16** to light, this operation is performed in vessels wrapped with aluminum foil. The tetrahydrofuran solution of **16** is transferred into a precision dropping funnel (or a syringe on a syringe pump, kept cold with a wrapping containing dry ice) and slowly (over a period of > 5 h) added to a vigorously stirred solution of the alkene (50 mmol) and dirhodium(II) tetraacetate (0.01g, 0.1 mol%) within 5 hrs at ambient temperature. After the nitrogen gas evolution has ceased, the title product **17** (7-64%) is purified by bulb-to-bulb distillation under reduced pressure (0.1 Torr).

In Situ Bamford-Stevens Reaction: Catalytic Synthesis of Epoxides (40) From Aldehydes Using Sulfur Ylides[9]



39 **32** **40**

To a round bottom flask fitted with a nitrogen balloon was added sequentially: tetrahydrothiophene (20 mol%), anhydrous acetonitrile (1 mL), rhodium(II) acetate dimer (0.0015 g, 1 mol%), benzyl triethylammonium chloride (0.015g, 20 mol%), aldehyde **39** (0.33 mmol) and tosylhydrazone sodium salt **32** (0.5 mmol). The reaction mixture was stirred vigorously at ambient temperature for 10 mins, then at 40 °C for 3 hrs. The reaction was quenched by the addition of water (0.5 mL) and ethyl acetate (0.5 mL). The layers were separated and the aqueous layer washed with ethyl acetate (2 × 0.5 mL). The combined organic phases were dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo*. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash column chromatography to afford the corresponding epoxide **40** (59–97%).

3.1.6 References

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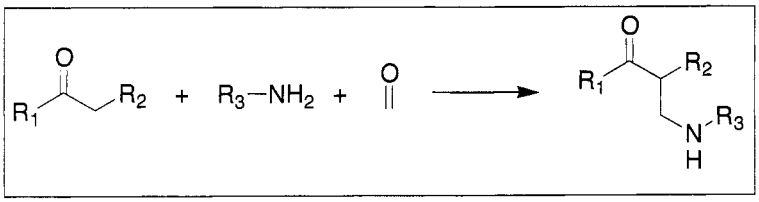
3.2 Mannich reaction

Paul Galatsis

3.2.1 Description

The Mannich reaction,[1] historically, has involved the condensation of formaldehyde, a primary or secondary amine, and an enolizable carbonyl compound. The resultant β-amino-carbonyl compound, or Mannich base, requires protic solvents and high reaction temperatures for its formation.



Over the years with the advent of milder and more controlled reaction conditions, the aldehyde component has increased in its diversity with a concomitant increase in functional group inter-compatibility. These changes also have enabled the extension of the nature of the active hydrogen (nucleophilic) species beyond enols. More recently, the utility of the Mannich reaction has been enhanced with enantioselective and catalytic variations.

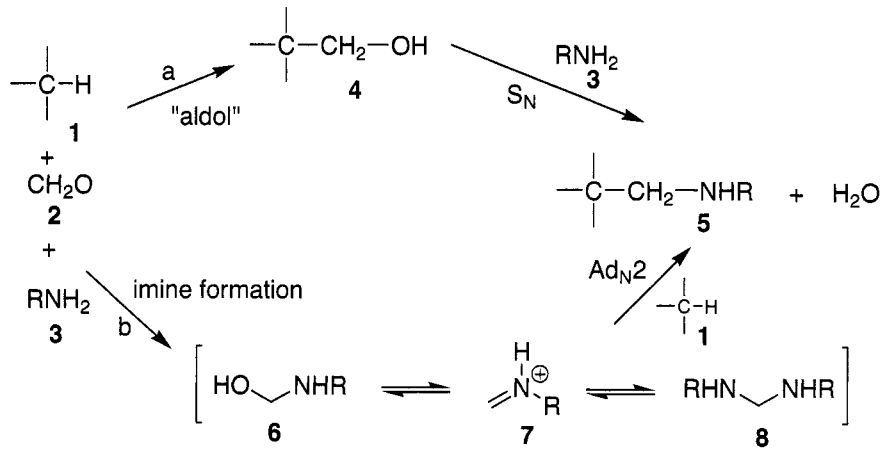
3.2.2 Historical Perspective

During the time frame from 1903 to 1909, a series of papers appeared from two groups. The first group, Tollens and coworkers,[2] disclosed the reaction of acetophenone and formaldehyde with salts of ammonia. The second group, Petrenko-Kritschenko and coworkers,[3] published similar chemistry using aldehydes with acetone diethyl dicarboxylate and ammonium salts. While the chemistry was similar, these groups failed to notice the generality of the methodology. It was in 1912, when Carl Mannich,[4] studying the reaction of antipyrine salicylate and formaldehyde with ammonium chloride, recorded the more general scope of this chemistry and the reaction became associated with his name.

3.2.3 Mechanism

The mechanistic details of the Mannich reaction have been the focus of considerable attention.[1,5] In principle, one could conceive of two possible

pathways this reaction might follow. The first option would involve aldehyde **2** undergoing a nucleophilic, carbonyl 1,2-addition (aldol reaction) with the active hydrogen species **1** to afford the corresponding hydroxymethyl derivative (aldol product) **4**. This intermediate could then react with amine species **3**, in a nucleophilic displacement fashion, to produce Mannich base **5**. An alternative option would involve amine species **3** adding to aldehyde moiety **2** to produce hemi-aminal **6**, the related iminium ion species **7**, or the methylene bis-amine species **8**, that subsequently reacts with active hydrogen compound **1** to afford Mannich base **5**.

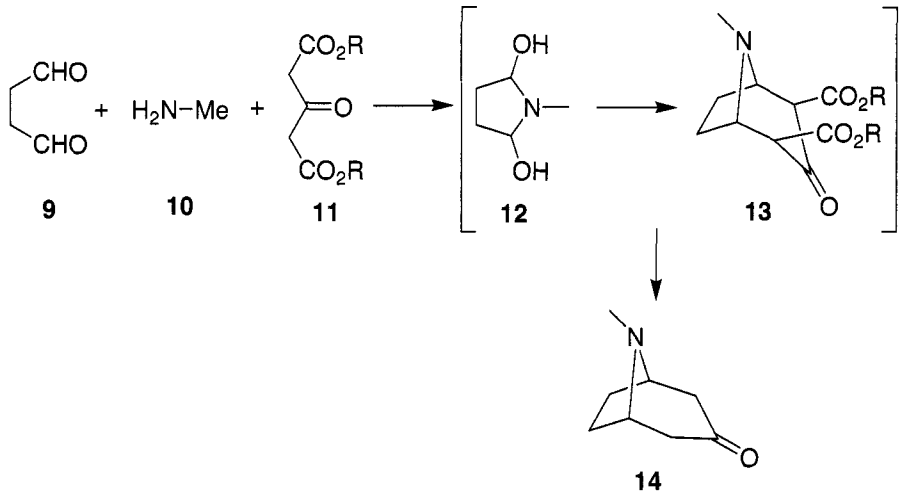


Experimental evidence has lead to the conclusion that option "a" does not occur. Kinetic effects, pH dependencies, stoichiometry, and solvent polarity all led to the second option, b, as being the actual mechanistic pathway. Under basic conditions, the key reactive intermediate is the hydroxymethyl amine species **6**. The Mannich base **5** is produced through a nucleophilic displacement by the corresponding anion (enolate) of the active hydrogen species **1**. As the pH shifts to more acidic conditions, the relative proportions of the reactive intermediates also shift. The hydroxymethyl amine **6** becomes protonated and, with loss of an equivalent of water, generates iminium ion **7**. Subsequently, this species can react directly with the active hydrogen species **1** or via the methylene bis-amine **8**, formed by the addition of a second equivalent of amine **3** to iminium ion **7** (under conditions of excess amine).

3.2.4 Variations, Improvements or Modifications

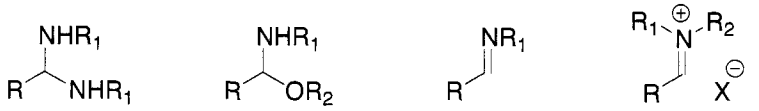
The shortcomings of the classical version of the Mannich reaction stems from the high reaction temperatures and extended reaction times which leads to side reactions and diminished yields.[1] However, there are examples of

how powerful the original version of the reaction can be. Consider Robinson's biomimetic synthesis of tropinone **14**.[6] Combination of dialdehyde **9** with methyl amine **10** generated bis-hemi-aminal **12**, *in situ*, which was then able to react with acetone dicarboxylate **11** to generate **13**. After decarboxylation, **14** could be isolated.



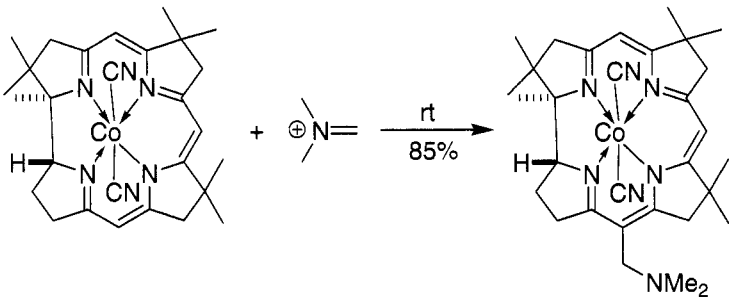
9 **10** **11** **12** **13** **14**

Pre-forming the electrophilic species in this reaction has greatly increased its utility and the diversity of substrates that have been exploited.[1] Species that have been used include aminal **15**, hemi-aminal **16**, imine **17**, and iminium ion **18**.



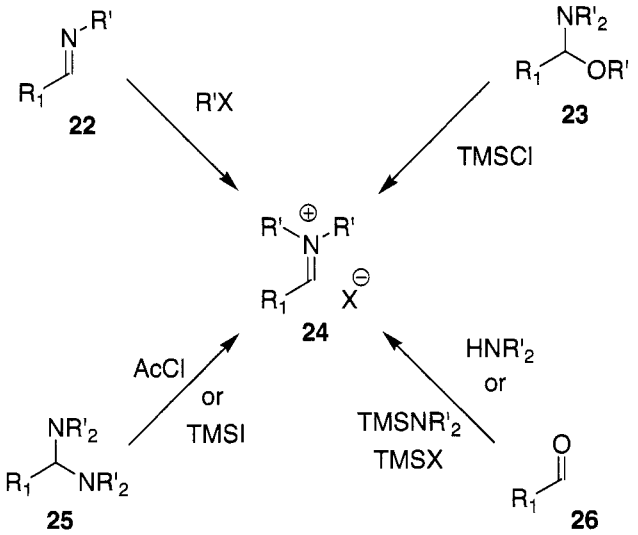
15 **16** **17** **18**

Imines[1] are generally less electrophilic than the corresponding aldehyde but this diminished level of activity can be countered by suitable activation with Lewis acids. Formaldehyde imines are generally stable only at low temperatures and are best formed *in situ*. However, there are exceptions like Eschenmoser's salt **20**.[7] This methylene iminium salt is a relatively stable solid that is now commercially available. The utility of this reagent was illustrated in the Mannich reaction of corrin **19** with **20** to generated **21**.



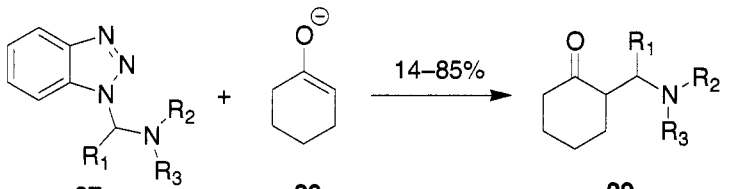
19 **20** **21**

Functionalized iminium salts **24** can be readily prepared by a number of methods and allows the reaction to be conducted at lower temperatures and in non-protic solvents thus allowing other, more sensitive active hydrogen species to participate in this reaction.[1] These methods can include alkylation of existing imine **22**, cleavage of aminals **25** or hemi-aminals **23** with acetyl chloride or trimethylsilyl iodide/chloride, or in a direct fashion from carbonyl derivative **26** with amine salts or with trimethylsilyl amines.



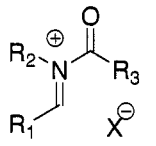
22 **23** **24** **25** **26**

A special case of aminals is the one derived from benzotriazole.[1e,8] These *N*-(α-aminoalkyl)triazoles **27** are readily prepared by condensation of an amine, aldehyde, and, in this case, benzotriazole. The derivatives **27** can be regarded as masked imines/iminium ions and can react with the appropriate nucleophiles in a Mannich sense. Thus treating the enolate of cyclohexanone (**28**) with a diverse array of triazoles (**27**) was able to give rise to the corresponding Mannich bases **29**.



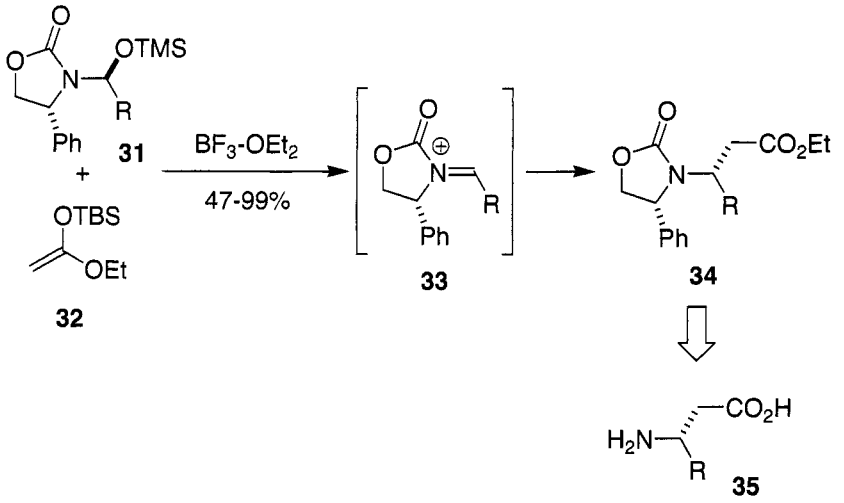
27 28 29

Finally, *N*-acyliminium ions **30** have also found great utility in the Mannich reaction.[9] Their increased reactivity, compared to iminium ions, has extended the versatility of the Mannich reaction in organic chemistry.



30

For example, consider a recent communication on the synthesis of β-amino acids.[10] Hemi-aminal **31**, under the influence of boron trifluoride, could be converted to acyl iminium ion **33**. Capture of the electrophilic species **33** with the ketene acetal **32** provided ready access to **34**. These advanced intermediates could be transformed into the desired β-amino acids **35**.

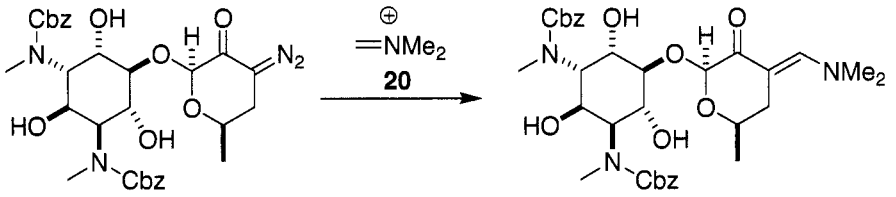


31 **32** **33** **34** **35**

With the advent of these pre-formed Mannich reagents, the diversity of the active hydrogen species **1** has greatly increased. In addition to the standard carbonyl compounds, additional functional groups (boron enol

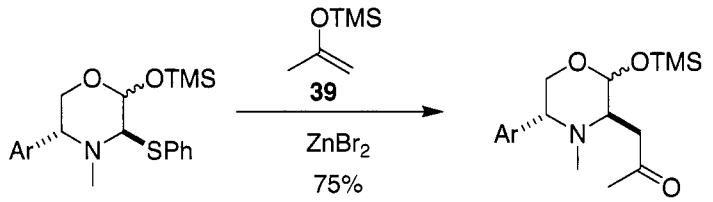
ethers, silyl enol ethers, alkyl enol ethers, enamines, acids/esters, phenols, and heterocycles) have seen utility in the Mannich reaction.

Highly elaborate enolates with sensitive functional groups survive the Mannich transformation. Spectinomycin analogs **37** could be prepared from diazoketone **36** with **20**.[11]



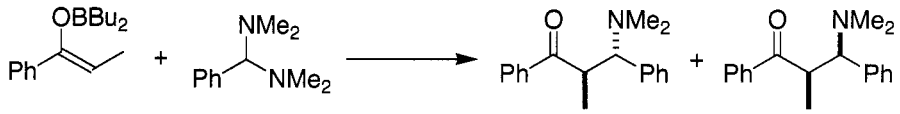
36 **37**

Simple silyl enol ethers have been shown to be of synthetic utility. Thus, the iminium ion generated by activation of **38** with zinc bromide could react with **39** to afford ketone **40** in good yield.[12]



38 **40**

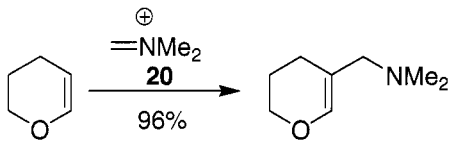
Additionally, more advanced derivatives of enolates have reactivity compatible with the Mannich reaction. Boron enolate **41** could be paired with aminal **42** to generate the corresponding Mannich bases **43** and **44**.[13]



anti- *syn-*

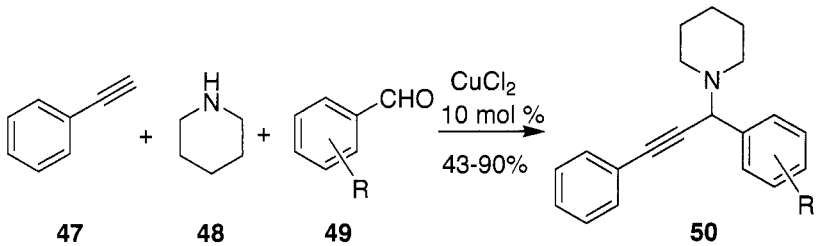
41 **42** **43** **44**

Heterocycles were also shown to be good partners for these reactions. While ring frameworks such as indoles and quinolines can readily form Mannich bases, a simple example is illustrated in the formation of **46** from **45** upon exposure to **20**.[14]



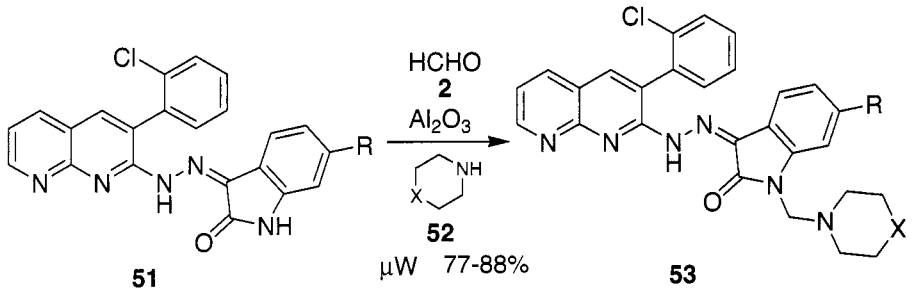
45 **46**

Solvent-free reaction conditions have been reported along with the use of catalytic cuprous chloride.[15] Mixing, neat acetylide **47**, piperidine **48** and aldehyde **49** with 10 mol % $CuCl_2$ at 80° C under vacuum afforded the condensed product **50**.



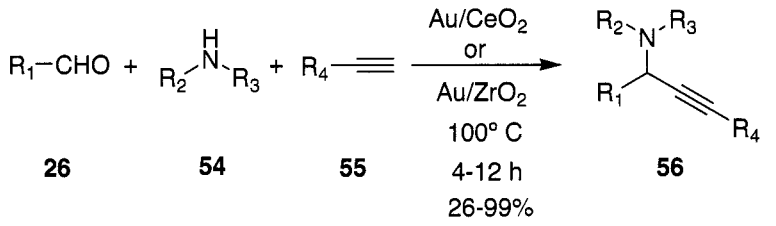
47 **48** **49** **50**

Microwave irradiation has been shown to be synergistic with a solvent-free reaction medium.[16] Lactam **51**, upon microwave irradiation in the presence of alumina, was found to undergo the Mannich reaction to afford **53** using formaldehyde **2** and amine **52**.



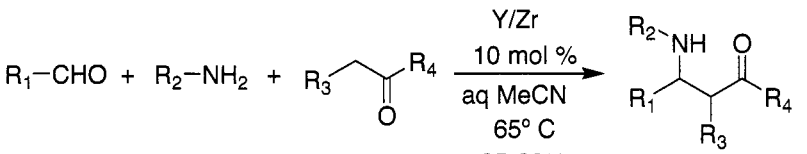
51 **53**

Gold derivatives have also been found to facilitate the Mannich reaction.[17] Thus, the heterogeneous catalyst, gold supported on nanocrystalline CeO_2 or ZrO_2, was found to accelerate the reaction of aldehyde **26**, amine **54**, and acetylide **55** to produce **56**, with a turn-over number (TON) 50-fold greater than the homogeneous variation.



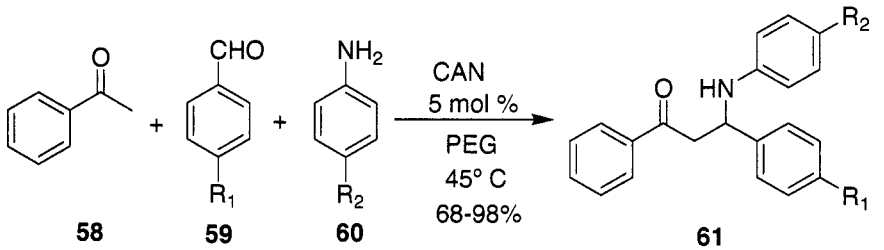
26 **54** **55** **56**

The easily prepared and regenerated catalyst, yttria-zirconia, efficiently condenses aldehyde **26**, amine **56**, and ketone **57** to generate the desired product **58**.[18]



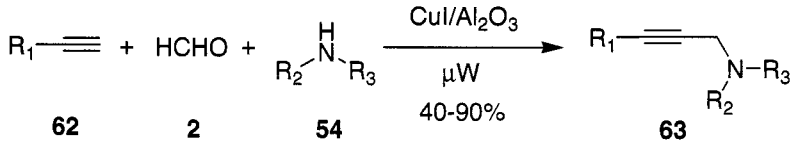
26 **56** **57** **58**

Decreased reaction times have also been reported with the use of ceric ammonium nitrate (CAN).[19] In the reaction of acetophenone **58**, aldehyde **59**, and amine **60** to afford Mannich base **61**, the reaction time was reduced from 42 h to 7 h and the yield improved from 30 to 98% in going from no CAN to 5 mol %.



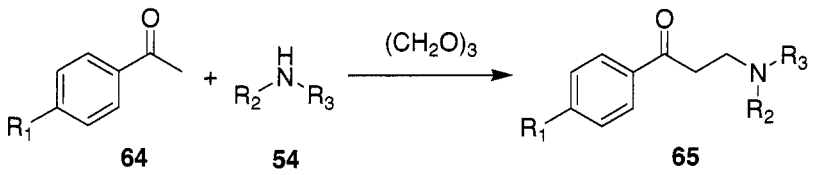
58 **59** **60** **61**

Environmentally friendly, Green Chemistry, conditions were developed in the doping of alumina with cuprous iodide.[20] The microwave transparent alumina resulted in keeping the bulk temperature low in the reaction of acetylide **62**, formaldehyde **2**, and amine **54** to produce **63**.



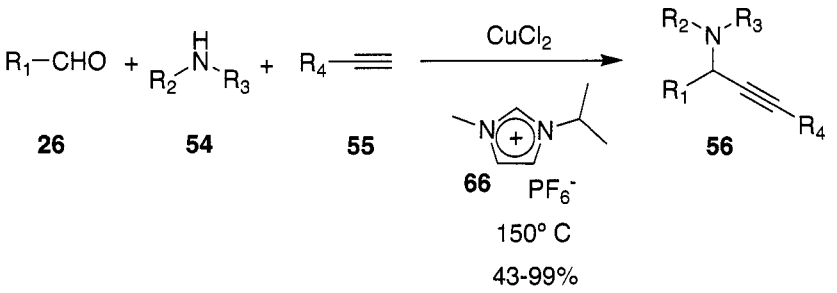
62 **2** **54** **63**

Microwave irradiation has been combined with ultrasound exposure and was found to decrease reaction time.[21] Thus, the reaction of ketone **64** amine **54** with paraformaldehyde to form **65** was found to proceed in 50 s as compared to 10 min with microwave irradiation and 20 min with ultrasound.



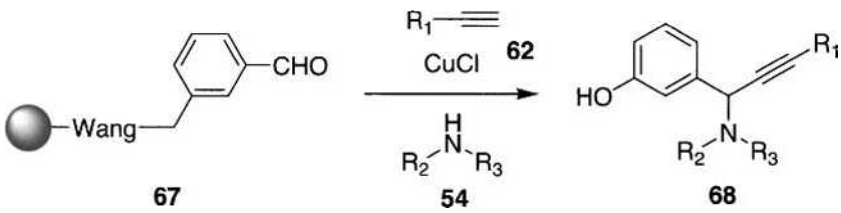
64 **54** **65**

Ionic liquids are known to be a heating aid as they interact efficiently with microwave irradiation producing a significant increase in temperature giving rise to a decrease in reaction time. This was the case in the reaction of aldehyde **26**, amine **54** and acetylide **55** to produce **56** using the ionic liquid **66**.[22]



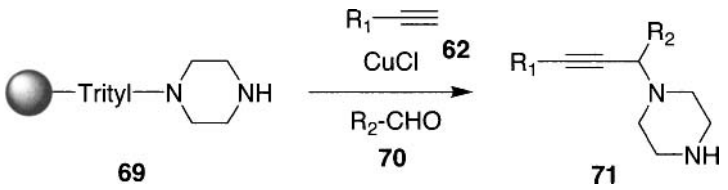
26 **54** **55** **66** **56**

Combinatorial chemistry techniques have found their way into the Mannich reaction. Resin-bound versions of the aldehyde and amine have been utilized in the preparation of library compounds.[23] Aldehyde-linked **67** was found to couple with acetylide **62** and amine **54** to produce **68** after cleavage from the resin.

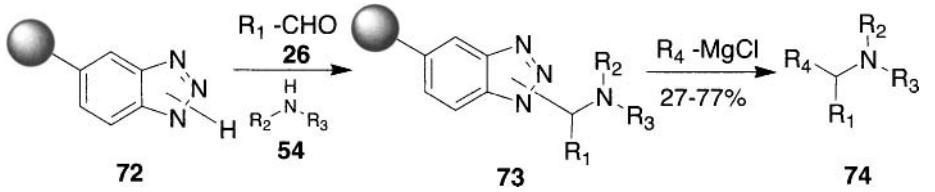


67 **54** **68**

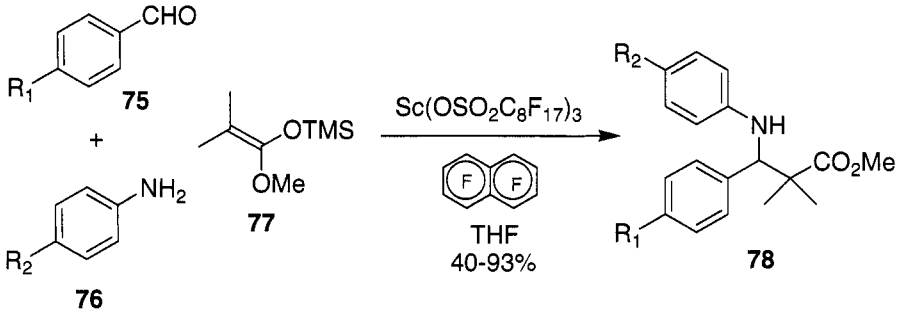
In a manner similar to the example above, amine-linked **69** could react with acetylide **62** and aldehyde **70** to afford, after cleavage, Mannich base **71**.



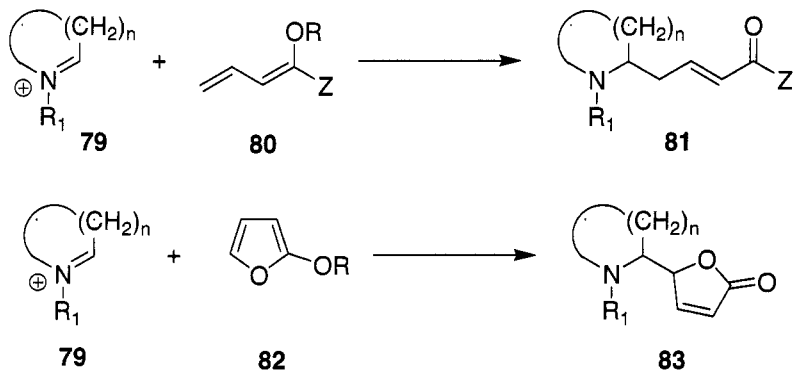
The benzotriazole iminium ion precursor formed the key strategy to a traceless linker approach.[24] Using solid-support triazole **72**, aldehyde **26**, and amine **54** were found to condense to Mannich base **73**. Treatment with Grignard reagents released the desired product **74** and allowed for the support to be recycled.



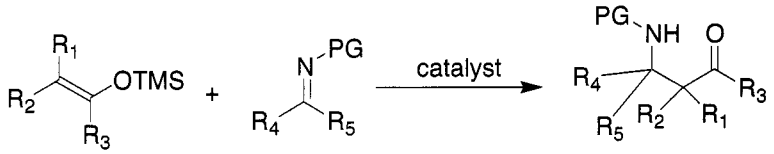
The practical aspects of the Mannich reaction can be made quite simple with the use of fluorous-based reagents.[25] Thus the reaction of aldehyde **75**, amine **76** and ketene acetal **77** to afford **78** could be repeated several times by taking advantage of the phase separation characteristics of the fluorous solvent and Lewis acid.

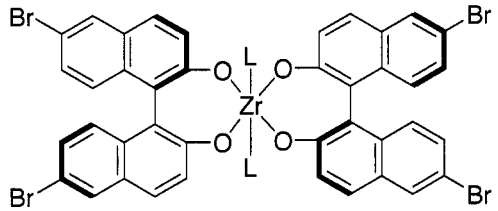


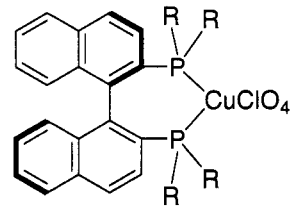
The vinylogous Mannich reaction has recently been elaborated.[26] There are two possible modes in which this variation of the Mannich reaction can be executed: a) acyclic dienol **80** can add to iminium ion **79** to generate **81** or b) alkoxyfuran **82** reacting with imine **79** to produce **83**.

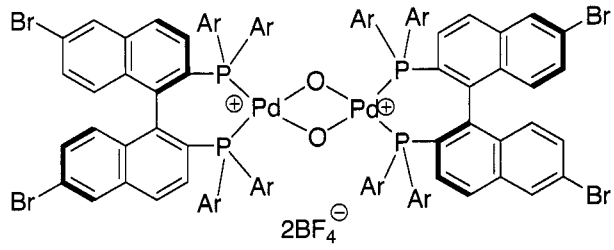


Transition metals have been found to catalyze Mannich reactions involving enol ether **84** and imine **85** to give **86**. Investigations into the scope of theses metals continues but representative examples including zirconium **87**, copper **88**, or palladium **89** have been disclosed.[27] The metal plays a key role in coordinating both the nucleophilic species and the imine species.

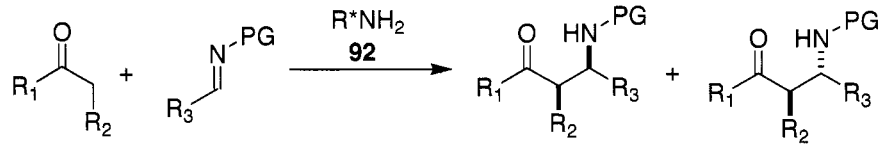






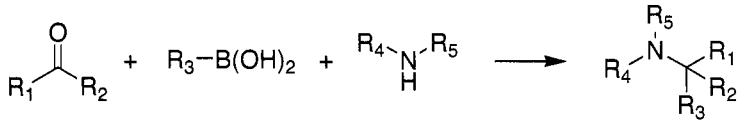


The rediscovery of organocatalysis that has occurred over the past decade was easily applied to the Mannich reaction. Use of chiral amines **92** like proline or cinchonine readily convert carbonyl compound **90** to a chiral enamine that is then able to couple with imine **91**. Chiral induction resulting from **92** gave rise to optically active Mannich bases **93** and **94**.[28]



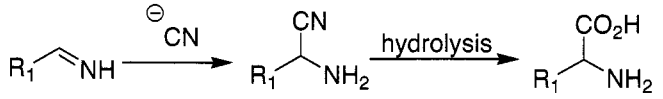
90 **91** **93** **94**

In its most general form, the boronic acid Mannich or Petasis reaction[29] involves the reaction of boronic acid **96**, carbonyl compound **95**, and amine **97** to produce secondary amine **98**.



95 **96** **97** **98**

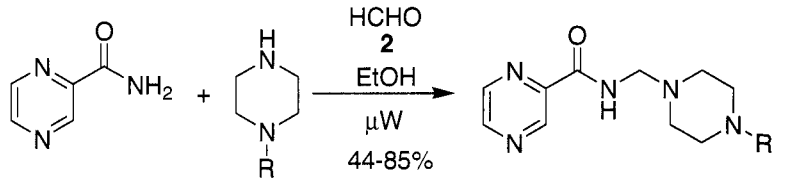
The Strecker reaction can be considered to be a special form of Mannich reaction where the nucleophile is a nitrile anion.[30] Thus, imine **99** is transformed to **100** which, upon hydrolysis, affords amino acid **101**.



99 **100** **101**

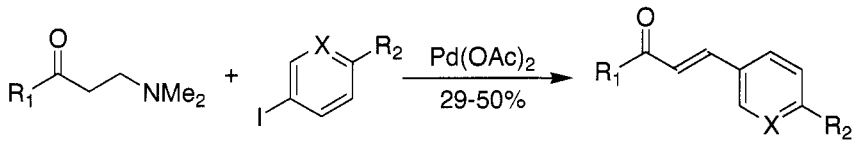
3.2.5 Synthetic Utility

Use of a relatively straightforward Mannich reaction provided ready access to compounds with antitubercular properties.[31] Microwave irradiation induced the coupling of amide **102** with piperazine **103** and formaldehyde **2** to prepare **104** in moderate to good yields.



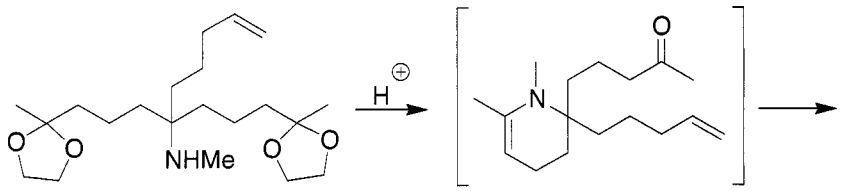
102 103 104

Historically, Mannich bases have provided ready access to enone systems by β-elimination of the amino group. A library of anti-leishmanial chalcones was prepared by a Heck reaction with Mannich bases serving as an enone precursor.[32] Palladium catalyzed cross-coupling of **106** with the enone derived from **105** was found to produce enone **107**.

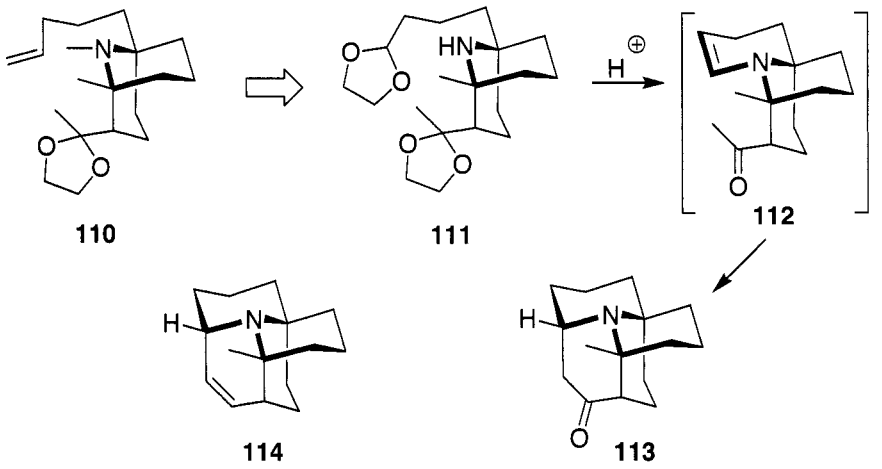


105 106 107

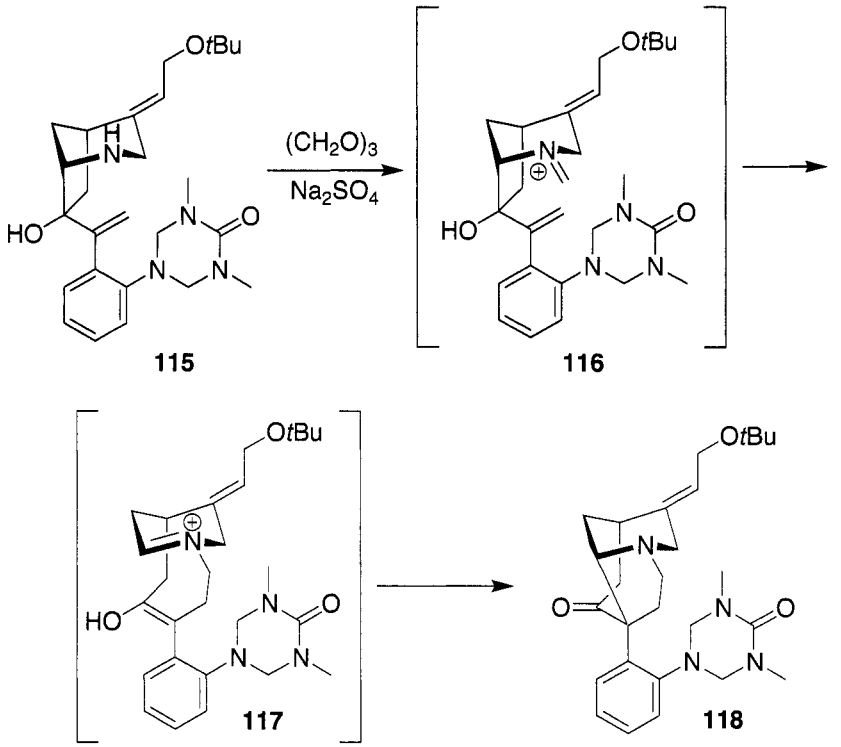
The total synthesis of the alkaloid porantherine **114** represented a tour-de-force in the Mannich reaction.[33] Exposure of **108** to acid unmasks the ketals which triggered the initial Mannich reaction to afford **109**. This intermediate was labile under these reaction conditions and underwent a second Mannich reaction to generate **110**. Elaboration of this compound provided access to **111**, the precursor to Mannich base **113** via the intermediacy of **112**. Reduction and dehydration then gave **114**.

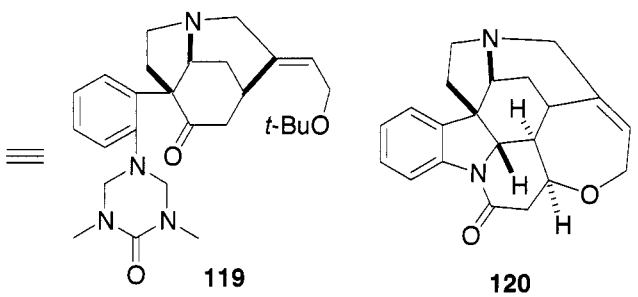


108 109

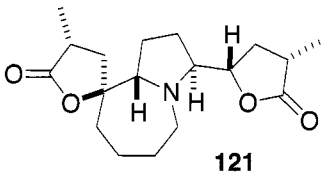


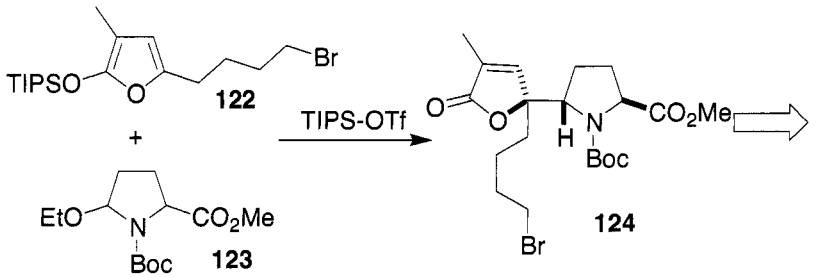
The total synthesis of (–)-strychnine **120** was accomplished using a tandem aza-Cope–Mannich reaction sequence.[34] Amine **115** was exposed to paraformaldehyde to generate **116**. This intermediate initiated the aza-Cope reaction to produce **117** and directly underwent the Mannich reaction to ultimately afford **118**. Redrawing **118** gives **119** and advanced compound on the way to **120**.

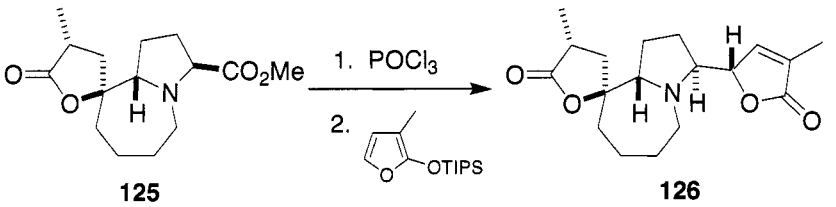




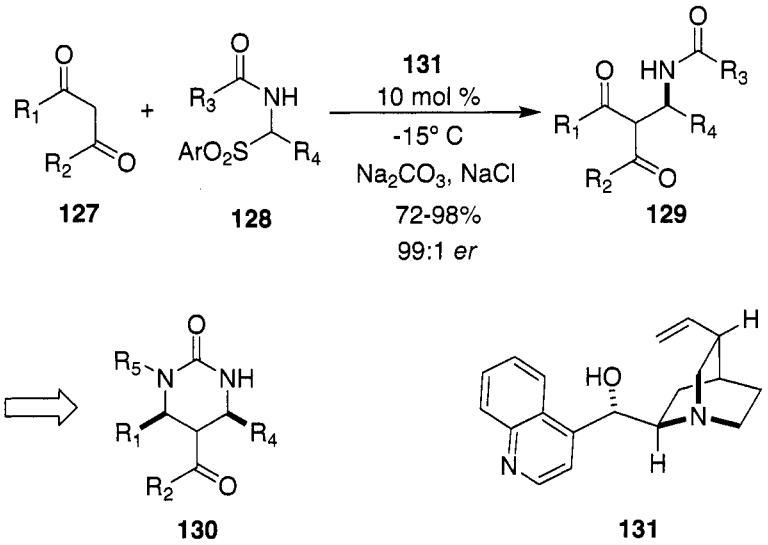
The synthesis of (+)-croomine **121** provided an example where both versions of the vinylogous Mannich reaction could be exploited in the same total synthesis.[35] To this end, the iminium ion derived from **123** afforded **124** upon reaction with **122**. Compound **109** was then elaborated to ester **125** which underwent a second vinylogous Mannich reaction to generate **126**. This advanced intermediate was ultimately converted into **121**.





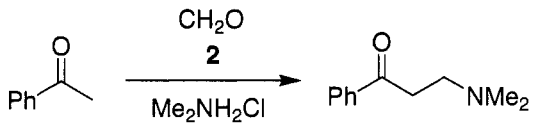


Highly functionalized heterocycles could be assembled using an organocatalytic, asymmetric variation of the Mannich reaction.[36] Cyclic urea **130** could be generated from Mannich base **129**. This compound was accessible by the reaction of **127** and **128** catalyzed by the chiral amine **129**.



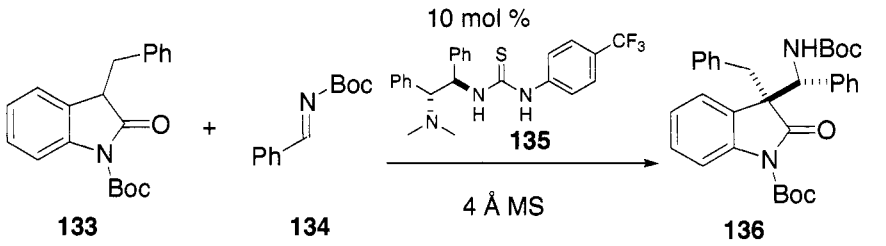
3.2.6 Experimental

Classic Mannich Reaction



3-(Dimethylamino)-1-phenylpropan-1-one (132)[37]

A mixture of acetophenone **58** (60.0 g, 0.5 mmol), dimethylamine hydrochloride (52.7 g, 0.65 mmol), and paraformaldehyde **2** (19.8 g, 0.22 mmol) with conc. HCl (1 mL) in 80 mL of 95% EtOH was heated at reflux for 2 h. The reaction mixture was diluted with 400 mL of acetone and allowed to cool to room temperature before storing in the refrigerator overnight. The resultant crystals were filtered, washed with acetone and dried to afford 72–77 g (68–72%).



(3*S*)-*tert*-butyl 3-benzyl-3-((*tert*-butoxycarbonyl)(phenyl)methyl)-2-oxoindoline-1-carboxylate (136)[38]

Catalyst **135** (4.5 mg, 0.01 mmol), indole **133** (0.1 mmol) and 4 Å molecular sieves (15 mg) were added to dry *m*-xylene (0.4 mL) at 5–10 °C. A solution of imine **134** (0.15 mmol) in dry *m*-xylene (0.1 mL) was added to the reaction mixture and when the reaction was judged complete by TLC, the product was isolated by flash chromatography on silica gel to afford **136** in 94% yield.

3.2.7 References

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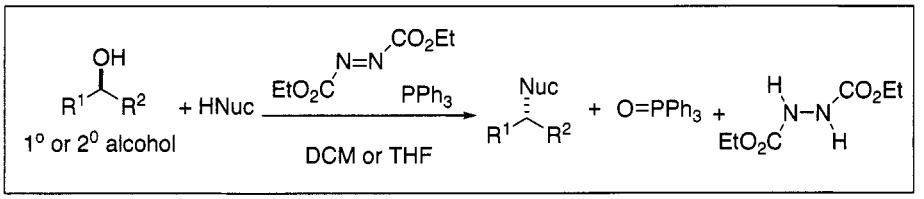
6.3 Mitsunobu Reaction

Daniel P. Christen

6.3.1 Description

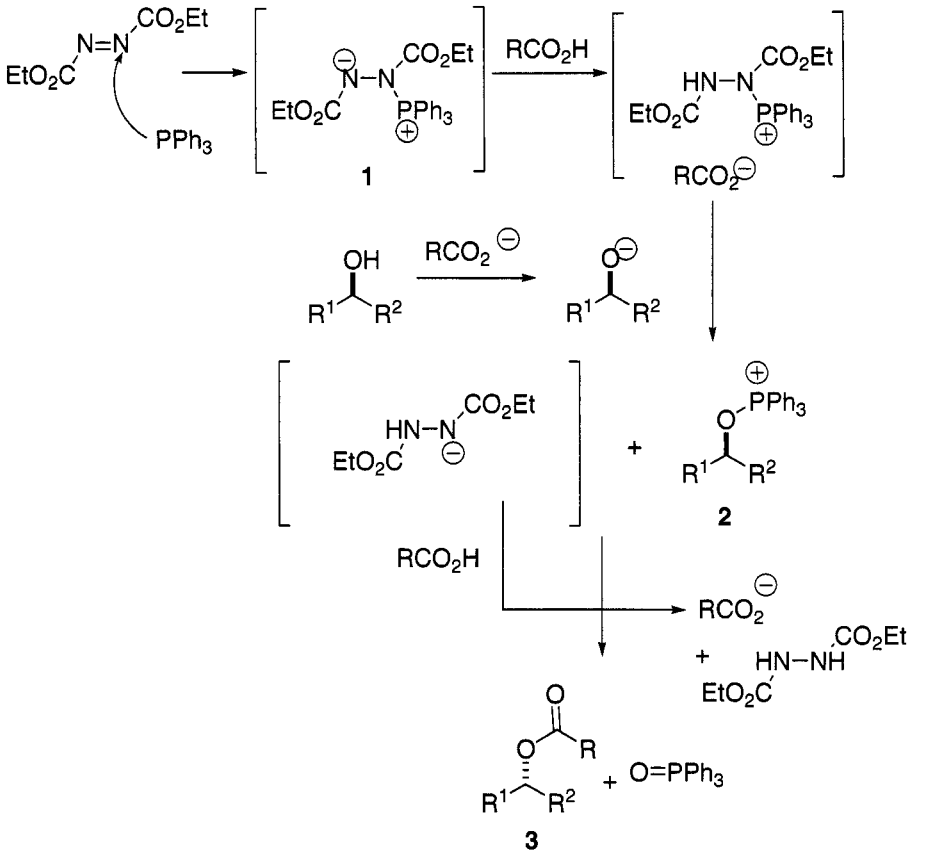
The Mitsunobu reaction, discovered by Mitsunobu in the late 1960s, has become one of the most widely used reactions in organic chemistry.[1–3] The reaction has become the standard method for the inversion of secondary alcohols, the conversion of alcohols into amines and sulfides, and many other applications. New uses for this versatile reaction continue to be developed. The Mitsunobu reaction, due to its mild reaction conditions, has found wide application in total synthesis, and heterocyclic and medicinal chemistry. Since the Mitsunobu reaction has been extensively reviewed during the last thirty years, this chapter will focus primarily on applications of the Mitsunobu reaction during the last fifteen years. This review will cover recent examples for the various uses of the Mitsunobu reaction and introduce several new applications of the reaction. Recently developed phosphine and azadicarboxylate reagents will be covered as well.



The Mitsunobu reaction was originally employed as a method to condense a carboxylic acid and an alcohol in the presence of triphenylphosphine and diethylazadicarboxylate (DEAD) to form an ester. Over time, the reaction has evolved to include a large set of acidic pronucleophiles that include carboxylic acids, amines, sulfides, etc. The general reaction is shown above for a chiral secondary alcohol. The nucleophile is incorporated into the product (with inversion), while the alcohol oxygen is found in the triphenylphosphine oxide. The reaction proceeds under neutral conditions at 0 °C or room temperature in almost all commonly used organic solvents (THF, Et_2O, CH_2Cl_2, toluene, EtOAc, CH_3CN, DMF, *etc.*)

6.3.2 *Mechanism*

The currently accepted mechanism, which is based primarily on experimental results, is outlined below.[9] The reaction begins with the nucleophilic attack of triphenylphosphine, on the N=N double bond of diethylazadicarboxylate (DEAD) to form betaine intermediate **1**. Crich and others have determined that this step is irreversible.[10] After protonation of the intermediate betaine, the alcohol in the reaction mixture is thought to attack the phosphorous center. Hughes *et al.* report that the alcohol is deprotonated by the carboxylate conjugate base prior to attack on the phosphorous.[11] The activated alcohol **2** then undergoes S_N2 reaction with the carboxylate in the reaction mixture to produce the inverted ester **3**.



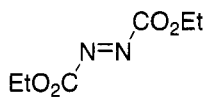
6.3.3 *Standard Methods, Variations and Improvements*

Extensive work has been carried out on the standard Mitsunobu reaction. Generally, the reaction is carried out according to two extreme approaches.

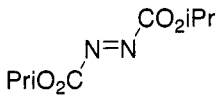
In the first, DEAD is usually added dropwise (either neat or in solution) to a cooled reaction mixture containing the starting alcohol, the acidic nucleophilic species and triphenylphosphine. Alternatively, the betaine intermediate is preformed by reacting DEAD and TPP together at lower temperature before adding the other reaction components. These conditions are usually sufficient to carry out the reaction. In some cases, modified TTP or DEAD analogs are used for less reactive reaction partners. Sometimes, removal of triphenylphosphine oxide or the reduced DEAD complicate the isolation of the desired product. This problem has led to the development of several alternative reagents and approaches to carry out the Mitsunobu reaction. Water soluble reagents, fluorinated reagents and solid-supported reagents have been developed to simplify the removal of byproducts arising during the Mitsunobu reaction.

Azadicarboxylates

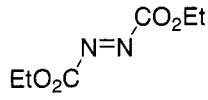
The commercially available diethyl azadicarboxylate like reagents are listed below. DEAD (**4**) and DIAD (**5**) are by far the most frequently used. The methyl (**6**), benzyl (**7**) and *tert*-butyl (**8**) analogs of the most commonly used reagents are also known, but used much less frequently. Bis-(2,2,2-trichloroethyl)azadicarboxylate, another commercially available compound, has also been reported, but applications thereof appear to be very limited. ADDP, 1,1′-(azodicarbonyl)-dipiperidine (**10**), was first reported by Tsunoda.[12] This reagent appears be useful for more difficult Mitsunobu reactions; related reagents in which the piperidine moiety has been replaced by morpholine or *N*-methyl piperazine are also known. These reagents and the reduced hydrazine products thereof can often be precipitated out by the addition of hexanes to the reaction mixture; additionally, treatment with mild acid can be useful in the removal of the *N*-methyl piperidine reagent.



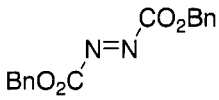
Diethyl azadicarboxylate (DEAD) (**4**)



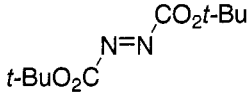
Diisopropyl azadicarboxylate (DIAD) (**5**)



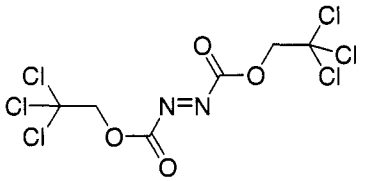
Dimethylazadicarboxylate (DMAD) (**6**)



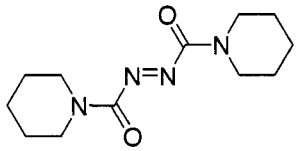
Dibenzyl azadicarboxylate (**7**)



Di-*t*-butyl azadicarboxylate (DBAD) (**8**)

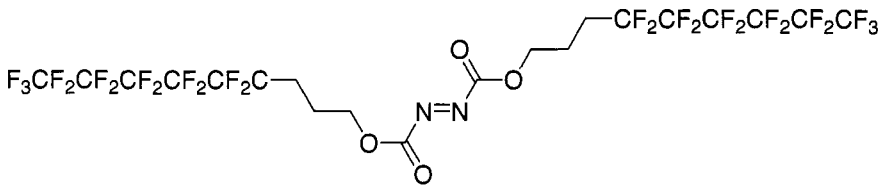


Bis(2,2,2-trichloroethyl)-azadicarboxylate(**9**)

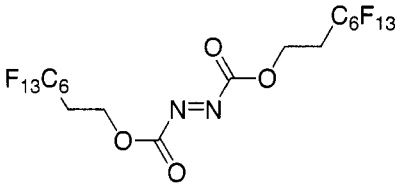


1,1'-(Azodicarbonyl)-dipiperidine (ADDP) (**10**)

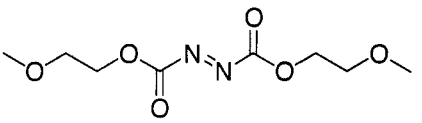
A more recent DIAD analog is the heavily fluorinated azadicarboxylate F-DIAD (**11**) shown below.[13] An analog of DEAD (fluorous-DEAD, **12**) has also been reported.[14] The fluorous approach to the Mitsunobu reaction will be discussed in greater detail below. More recently, Sugimura and Hagiya developed di-2-methoxyethylazodicarboxylate (DMEAD, **13**) as an alternative to DEAD/DIAD.[15] The hydrazinedicarboxylate byproduct arising from this analog has fair water solubility and may therefore be removed by an aqueous workup. Tsunoda's group has developed a number of other DIAD-like reagents to allow for the use of less acidic species as the nucleophile. *N,N,N',N'*-Tetramethylazadicarboxamide (TMAD, **14**) and 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD, **15**) are two such reagents.[16] The latter reagent, which is a cyclic analog of TMAD, was developed in order to minimise a side reaction in which activated TMAD or an equivalent reagent reacts with itself to form an oxadiazole. The more nucleophilic tributylphosphine (TBP) is usually used with these reagents. More recently, a novel and unorthodox strategy employing adamantyl substituted reagents was developed by Curran *et al.*[17] The reduced byproducts of the reaction were then removed with methylated β-cyclodextrin silica gel, which preferentially binds adamantyl substituted compounds.



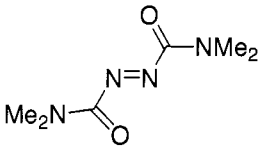
Bis (1H, 1H, 2H, 2H, 3H, 3H-perfluoronyl) azadicarboxylate (F-DIAD) (**11**)



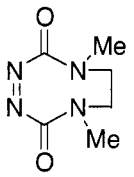
fluorous-DEAD (**12**)



Di-2-methoxyethylazodicarboxylate (DMEAD) (**13**)



N,N,N',N'-Tetramethyl-azadicarboxamide (TMAD) (**14**)

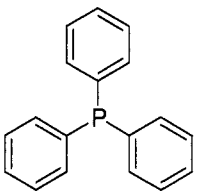


1,6-Dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD) (**15**)

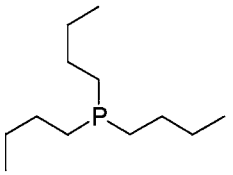
Phosphine reagents

The most commonly used phosphine reagents in the Mitsunobu reaction are the commercially available triphenylphosphine (TTP, **16**) and tributylphosphine (TBP, **17**). The oxides arising from the phosphines during the Mitsunobu reaction can frequently be precipitated out of the reaction mixture by titriation with diethyl ether. Usually, the residual phosphine oxide that remains can be removed via flash chromatography. For more polar reaction products this may not work. Thus, a considerable amount of work has been devoted to the discovery of alternative phosphine reagents as well. One of the reagents developed for this purpose is the commercially available diphenyl-2-pyridilphosphine (**18**). This phosphine and its oxide can be removed during an aqueous workup with an HCl wash. Phosphine **18** has been used in the phthalimide substitution reaction, benzylation, ester formation and a glycosidation reaction with 6-chloropurine. A particularly interesting pairing of reagents for the Mitsunobu reaction is di-*tert*-butylazadiacarboxylate (DBAD) and diphenyl-2-pyridilphosphine; this set provides water soluble byproducts after treatment with 4 N HCl in dioxane.[18] 1,2-Bis(diphenylphosphino)ethane (dppe, **19**) has been proposed as a TPP substitute for Mitsunobu reactions since the doubly oxidised reaction byproduct is more polar than the corresponding TTP oxide, and therefore easier to remove.[19] The use of (*m*-ClPh)$_3$P (**20**) has found applications in Mitsunobu reactions occasionally as well. One of the more intriguing applications of this phosphine was by Winssinger *et al.* in the preparation of HSP90 inhibitors based on radicinol.[20] In this context, the phosphine was necessary to suppress the competing esterification of a *para*-hydroxy group

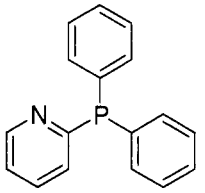
during the formation of an ester of an unprotected hydroxybenzoic acid intermediate. In addition to these phosphine reagents, a number of fluorous phosphine analogs of TPP (**21a–c**) have been developed. In these compounds, the aryl groups of TTP have been substituted by one or more fluorous aryl substituents. These reagents provide essentially the same yields as TPP in simple Mitsunobu reactions; the oxidized byproducts, however, are readily removed by extraction or a short plug of fluorinated silica gel.[21] The advantages of these particular phosphines are offset by their increased cost and poor atom economy.



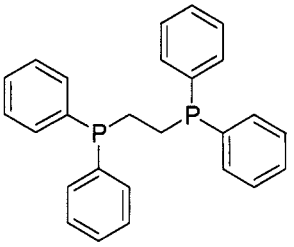
Triphenylphosphine (TPP) (**16**)



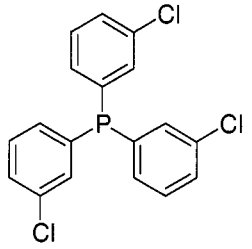
Tributylphosphine (TBP) (**17**)



Diphenyl-2-pyrydil-phosphine (**18**)



1,2-bis(diphenylphosphino)ethane (dppe) (**19**)



20

$p\text{-}C_9F_{17}(CH_2)_2C_6H_4P(Ph)_2$
$[p\text{-}C_6F_{13}(CH_2)_2C_6H_4]_2PPh$
$[p\text{-}C_6F_{13}(CH_2)_2C_6H_4]_3P$
(21a–c)

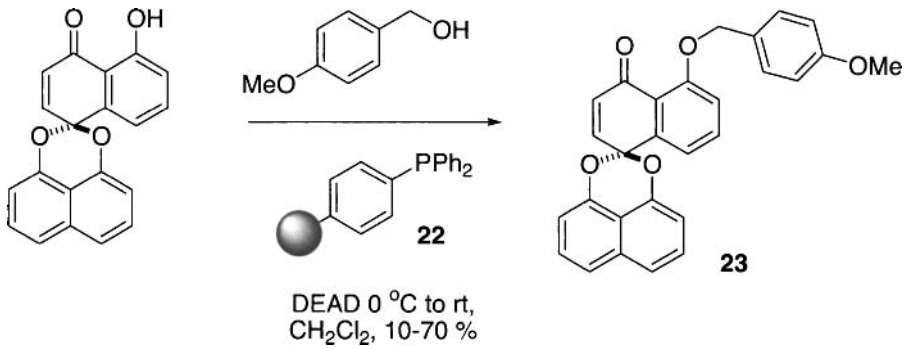
Supported TTP or DEAD

The renaissance of solid supported reagents and parallel synthesis during the last fifteen years found numerous applications in the Mitsunobu reaction. Solid-supported triphenylphosphine and azadicarboxylate reagents were developed to aid in the purification of Mitsunobu reactions or help with difficult reactions. These reagents have become commercially available. In addition, important yield-limiting reactants were tethered to solid supports

and then treated with TPP/DEAD to carry out desired Mitsunobu reactions; after washing off the soluble Mitsunobu reagents and byproducts, the desired product could be cleaved off the resin in more purified form. These strategies have proven to be viable alternative procedures for the Mitsunobu reaction.

Solid-supported triphenylphosphine, first reported by Havens *et al.* in 1983 for an esterification reaction, has found extensive applications in Mitsunobu chemistry.[22] For example, the preparation of aryl ethers from amino alcohols has been carried out; interestingly, addition of triethylamine led to better conversion in some cases.[23,24] More recently, Pelletier *et al.* prepared a series of primary amines by reaction of a primary alcohol in the presence of $(Boc)_2NH$, TBAD and solid-supported TPP. Typical reported yields were in excess of 75%.[25]

Wipf *et al.* have employed the Mitsunobu reaction for the preparation of an extensive series of naphthoquinone spiroketal analogs (**23**) based on diepoxin σ, palmarumycin CP1, and other natural products.[26] These sensitive intermediates were treated with an excess of alcohol, DEAD and diphenylphosphinopolystyrene (**22**) to give the desired products in good yield.



The use of supported alcohol derivatives in Mitsunobu reactions with TPP/DEAD or equivalent reagents is well known as well.[27] One of the first reports describing such an approach looked at the alkylation of resin-bound acyl tyrosines. For a more recent approach to prepare safinamide analogues see the cited paper by Carotti *et al.*[28]

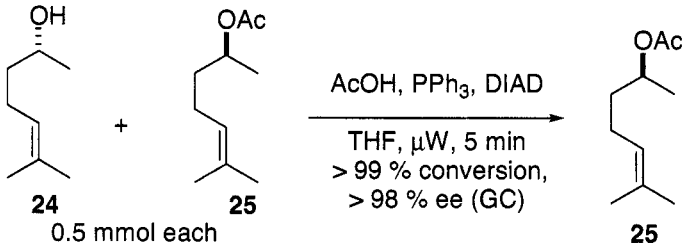
Fluorous DEAD/TPP

The application of fluorinated organic compounds and solvents has been a rapidly growing area of new chemistry since the seminal discovery of Hovarth *et al.*[29] More recently, fluorinated versions of tributyltin hydride, triphenylphosphine and ethyl azadicarboxylate have been developed to avoid

the purification problems sometimes associated with those reagents.[30] Addition of a fluorous tail to an organic reagent increases its solubility in fluorous solvents and frequently allows ready extraction of the reagent into fluorous solvents, whereas the desired organic compounds are left behind in a traditional organic solvent. Alternatively, fluorinated reagents or products can be selectively removed or purified using fluorinated silica gel (F-SPE).[31] Sample fluorinated azodicarboxylates (**11** and **12**) and phosphines (**21a-c**) were already listed above. These reagents generally give similar yields to those observed for the traditional Mitsunobu reaction, but their utility is offset by their increased cost and poor atom economy.

Microwave-promoted Mitsunobu reactions

Applications of microwave-promoted Mitsunobu reactions are very uncommon since Mitsunobu reactions are rarely heated. In a rare report, Kappe's group looked at a two-step protocol to deracemize sulcatol, the aggregation pheromone produced by the male ambrosia beetle.[32] Thus, the racemic acetate of sulcatol was resolved using *C. antartica B* lipase into the *(R)*-alcohol (**24**) and the *(S)*-acetate (**25**). The alcohol was then converted into the corresponding epimerised acetate (**25**) using microwave Mitsunobu conditions. These reactions, carried out on 1 mmol scale, were complete in 5 minutes with greater than 99% conversion and no loss of stereochemical integrity (data determined by GC analysis). In a two-step reaction sequence involving a Mitsunobu reaction followed by a Claisen rearrangement, Moody and Jacob found that both steps could be carried out in good yields using a high temperature microwave reaction.[33] Lastly, a series of thiouracil derivatives were alkylated at the thiol position using a microwave assisted Mitsunobu reaction.[34] After DEAD was added at 0 °C, the combined reaction mixture was heated in a microwave for 10 min at 40 °C.

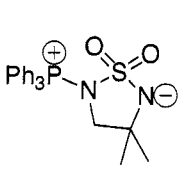


Catalytic Mitsunobu Reactions – a frontier to be explored

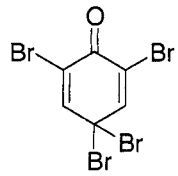
Catalytic Mitsunobu reactions in which substoichiometric amounts of phosphine or azodicarboxylate are used require much more work to find a workable solution. Some initial work in this area has been carried out by Toy and his group.[35] Use of stoichiometric iodosobenzene diacetate as an oxidant to oxidize the reduced azodicarboxylate allowed the use of 10 mol% of DEAD or an equivalent reagent. How to use only catalytic amounts of phosphine in Mitsunobu reactions remains an unsolved problem.

Alternative activating agents

The sulfonamide betaine **26** has occasionally been employed as a surrogate for TPP/DEAD in Mitsunobu reactions in solution and on solid support.[36] Tamaka *et al.* have employed 2,4,4,6-tetrabromo-2,5-cyclohexandione (**27**) as a DEAD equivalent.[37] The couple has been used to convert alcohols and THP ethers into the corresponding bromides. Use of the reagent combination in the presence of zinc(II) azide leads to the efficient formation of azides from alcohols in 70% or higher yields.[38]



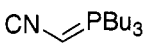
26



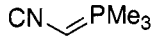
27

The sulfonamide betaine **26** was useful for the preparation of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones in cases were the traditional Mitsunobu conditions failed.[39]

Two other important reagents developed in Tsunoda's group are the novel TPP/DEAD surrogates CMBP (**28**) and CMMP (**29**).[40] These reagents tend to give equivalent or superior results in many of the common applications of the Mitsunobu reaction. CMBP or CMMP frequently require elevated reaction temperatures (e.g., refluxing benzene).



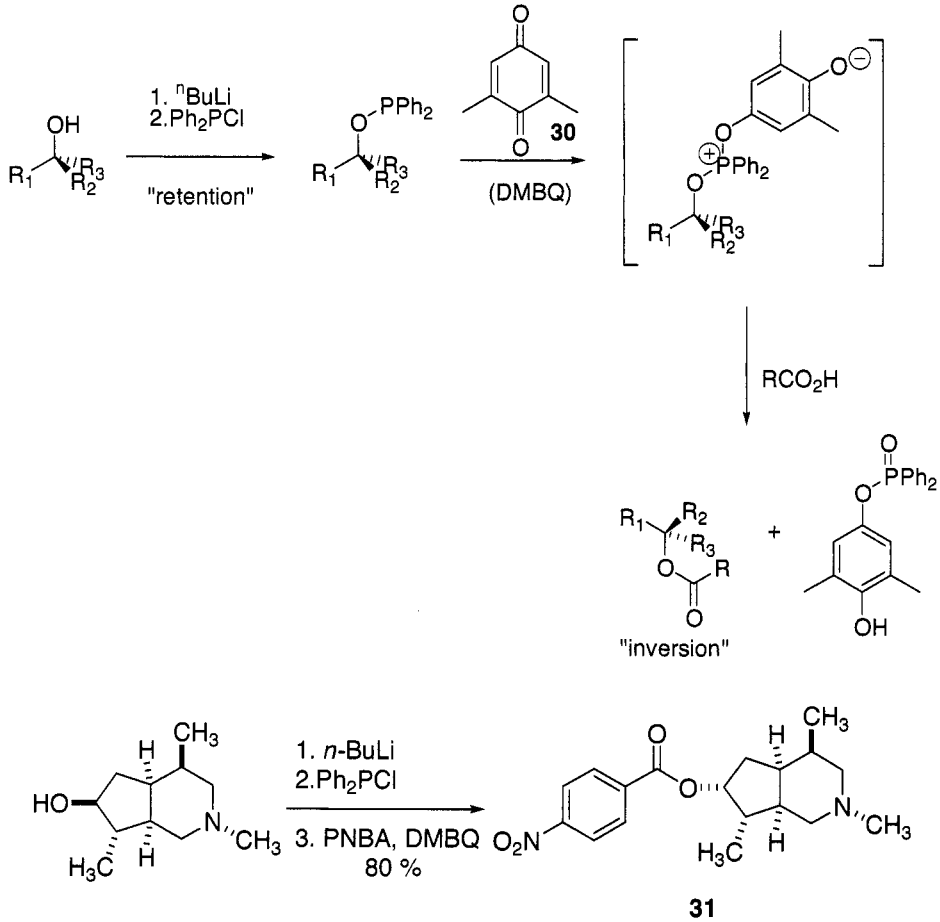
CMBP (**28**)



CMMP (**29**)

Recently, Mukaiyama's group reported a new approach to convert tertiary alcohols into carboxylates using diphenylphosphorous chloride and

2,6-dimethyl-1,4-benzoquinone (DMBQ, **30**).[41] The basic approach is summarised in the figure below. This methodology has been extended to the preparation of ethers as well. Kibayashi *et al.* employed this methodology to prepare **31**, an advanced intermediate in their synthesis of (–)-incarvilline.[42]



31

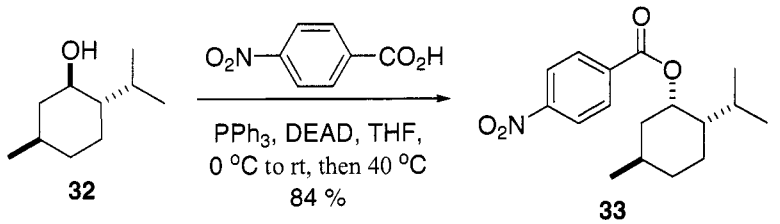
6.3.4 *Synthetic Utility*

Applications: Inversion of alcohols—intermolecular

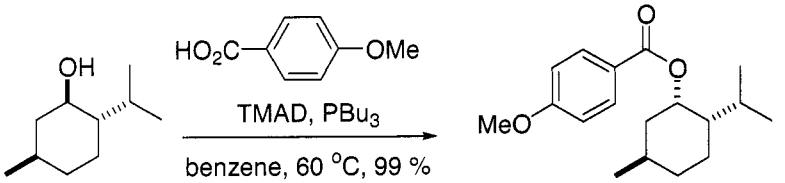
The inversion of secondary alcohols into the corresponding esters, followed by hydrolysis of the ester intermediate into the inverted alcohol, has been one of the most commonly used applications of the Mitsunobu reaction during the last forty years. After the initial discovery by Mitsunobu, this method has been used hundreds of times to invert alcohols in all kinds of organic molecules. Intermolecular and intramolecular inversion reactions are possible, although the latter reaction to make lactones is used much less

frequently. Typically, most carboxylic acids (acetic, benzoic, benzyl, trifluoroacetic, *etc.*) can be used in the reaction. Triphenylphosphine or tributylphosphine (less frequently) are usually partnered with DEAD or DIAD in the reaction. The reaction can be scaled up to kilogram quantities if desired, although purification issues to remove triphenylphosphine oxide and reduced hydrazine byproducts would have to be addressed on a case by case basis.

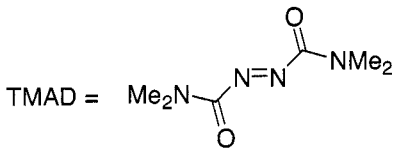
Sterically more hindered alcohols can be problematic. In 1991, Martin and Dodge showed that *para*-nitrobenzoic acid (PNBA) can be used as an effective nucleophile for more hindered alcohols; the inversion of the alcohol in (–)-menthol (**32** to **33**) is shown below.[43] A more detailed experimental procedure is given in the experimental part of this review. In a similar manner, (–)-menthol (**32**) was epimerised using the TMAD (*N,N,N',N'*-tetramethylazadicarboxamide)/tributylphosphine pairing developed by Tsunoda and coworkers to yield ester **34** in 99% yield.[44,45]



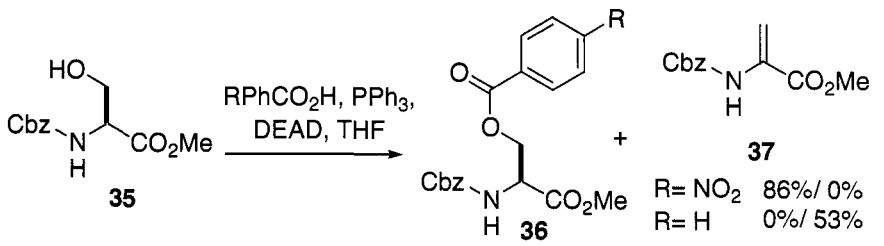
32 **33**



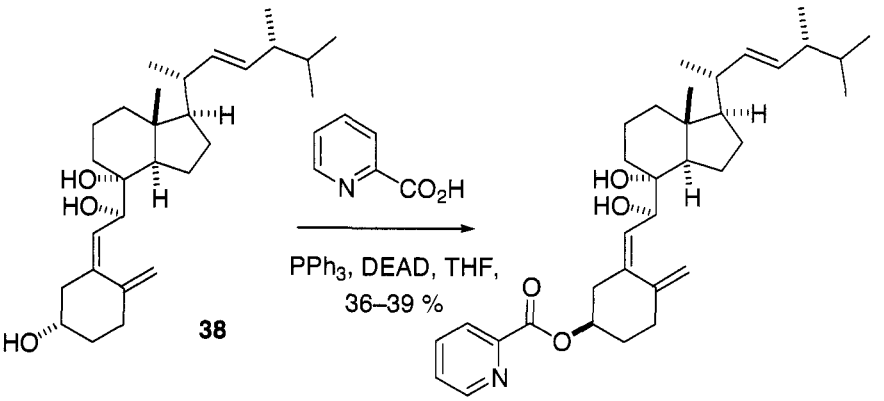
32 **34**



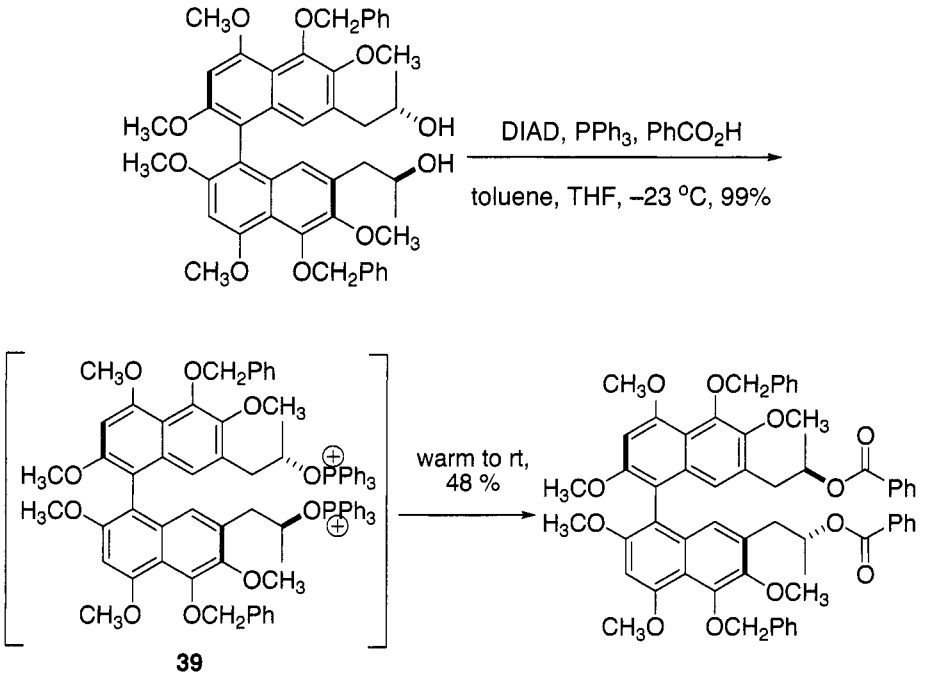
Alcohols that can form conjugated olefins sometimes eliminate under the standard Mitsunobu conditions to provide undesired side products instead of the ester product. In the case of a protected serine derivative **35**, para-nitrobenzoic acid gave preferentially the desired product **36**, whereas the use of benzoic acid gave only the elimination product **37**.[46]



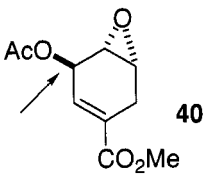
In a similar manner, acid labile compounds can be sufficiently sensitive to the carboxylic acids used in the Mitsunobu reaction that dehydration or other degradation pathways can become competitive. In a particularly sensitive case, dihydroxyvitamin-D_3 related triol **38** was selectively epimerised using picolinic acid.[47] Use of the more standard p-nitrobenzoic acid conditions led to the exclusive formation of dehydration products. Sammakia and Jacobs developed a mild copper acetate mediated methanolysis of the picolinate esters into the corresponding methyl esters.[48]



Coleman and Grant ran into difficulties during an attempted double Mitsunobu reaction for the synthesis of the pyrelenequinone natural product calphostatin.[49] Careful study of the reaction suggested that formation of the bis-oxyphosphonium intermediate **39** was required for a successful double Mitsunobu reaction. Otherwise, competing side reactions including intramolecular cyclizations led to poorer yields. The presumed bis-oxyphosphomium intermediate was obtained by running the reaction at a lower temperature for several hours before warming the reaction up. At the lower temperature, S_N2 displacement appears to be rate determining, thus allowing complete formation of the needed intermediate.

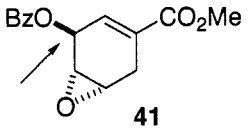


The figures below list many examples of alcohol inversion using the Mitsunobu reaction. Examples incorporating a variety of carboxylic acids are shown to give an idea of the wide range of acids that can be used. Typical reaction conditions and yields are provided when available. Examples **40** through **43** indicate that epoxides and conjugated esters are stable under the standard Mitsunobu conditions.[50–53] Quibell and coworkers prepared a series of peptidomimetic cysteine proteinase inhibitors (**44**) incorporating substituted prolines.[54] As such, the secondary alcohol was inverted in the presence of formic acid. The subsequent hydrolysis, carried out in the presence of strong acid and a large excess of allyl alcohol, gave the inverted alcohol in 41% yield. A more unusual inversion reaction takes place by using a 1,2,5-thiadiazoles as the nucleophilic reaction partner; in this context, azabicycle **45** was prepared in 46% yield.[55] A classic application of the Mitsunobu reaction from Bose's laboratory (to make **46**) is shown along with the preparation of the nitrobenzoate of *tert*-butyldimethylsilyl protected 17a-dihydroequilenin (**47**), an important non-uterotrophic component of Premarin®.[56,57]Interestingly, Mitsunobu reactions of steroid derivatives frequently work better in benzene; in this particular case the reaction was heated.



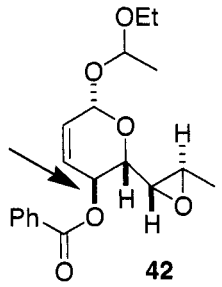
40

PPh_3, DIAD,
AcOH
Ref: Rigby[50]



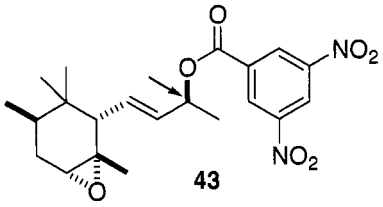
41

BzOH, PPh_3, DEAD
THF, 0 °C-->rt, 88 %
Ref: Schreiber[51]



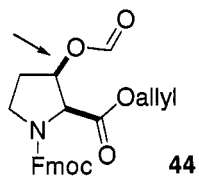
42

$PhCO_2H$, PPh_3,
DEAD, THF, 99 %
Ref: Mori[52]



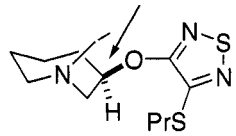
43

3,5-dinitrobenzoic acid,
PPh_3, DEAD,
Ref: Fuganti[53]



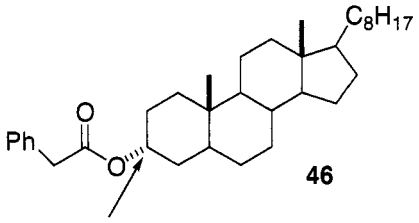
44

Formic acid, PPh_3, DIAD,
THF, 0 °C-->rt, ~90 %
Ref: Quibell[54]



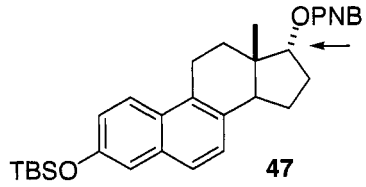
45

PPh_3, DEAD,
THF, 0 °C-->rt, 46 %
Ref: Ward[55]



46

$PhCH_2CO_2H$,
PPh_3, DEAD,
THF, 99 %
Ref: Bose[56]

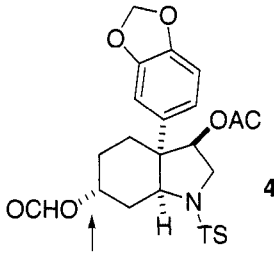


47

4-$NO_2C_6H_4CO_2H$,
PPh_3, DEAD,
PhH, 80 °C, 75 %
Ref: Dodge[57]

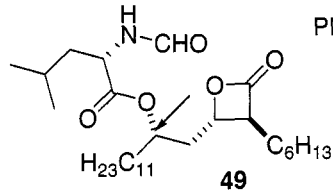
Nishimata *et al.* prepared intermediate **48** during their synthetic work on the *amaryllidacae* alkaloids crinanine and pretazettine.[58] The preparation of Orlistat (**49**), the active pharmaceutical ingredient in Xenical®, involves a Mitsunobu reaction between a hydroxy-β-lactone and *N*-formyl-(*L*)-leucine.[59] A larger scale inversion involving para-nitrobenzoic acid was used in the synthesis of BILN 2061 (**50**), a potent HCV protease inhibitor.[60] The alcohol

of the bicyclic lactam (**51**) was inverted using *para*-nitrobenzoic acid under the standard Mitsunobu conditions in 80% yield.[61] An example from Nicolaou's group to prepare **52** shows that more functionalised carboxylic acids can be used as well.[62] Additional ester formations in the context of nucleoside chemistry are shown with examples **53** and **54**. Thus, protection of the primary hydroxyl in the nucleoside derivative **53** introduces the 4-benzyloxybutyric acid protecting group.[63] This group can be removed under hydrogenation conditions. Fluoridine derivative **54** was prepared as a potential bioreductively activated prodrug of 5-fluoro-2′-deoxyuridine, an anticancer drug.[64]



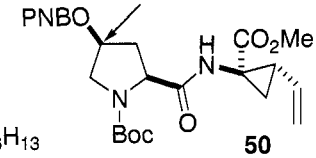
48

Formic acid, PPh_3, DEAD, THF, rt, 30 min, 99%
Ref: Nishimata[58]



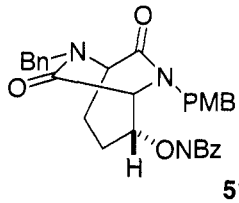
49

N-Formylleucine
PPh_3, DEAD, 83%[59]



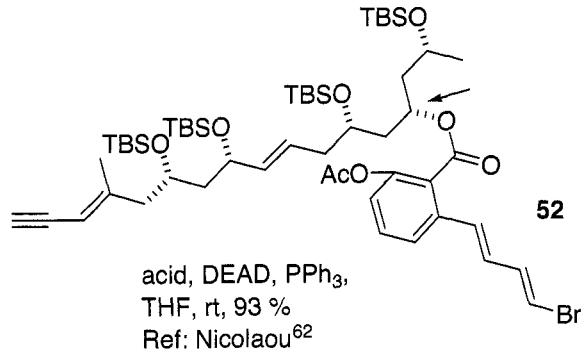
50

$4\text{-}NO_2C_6H_4CO_2H$, PPh_3, DIAD, THF, 0 °C, 88%[60]



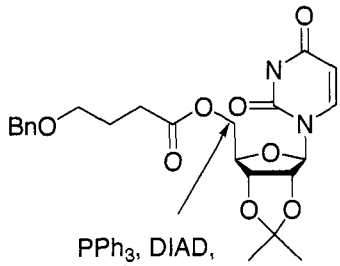
51

$4\text{-}NO_2C_6H_4CO_2H$, (NBzOH), PPh_3, DIAD, THF, 0 °C, 80 %[61]



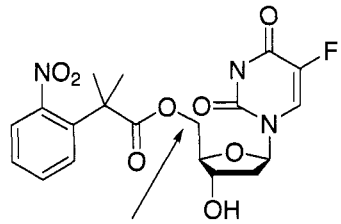
52

acid, DEAD, PPh_3, THF, rt, 93 %
Ref: Nicolaou[62]



PPh_3, DIAD, Et_2O, 90 %

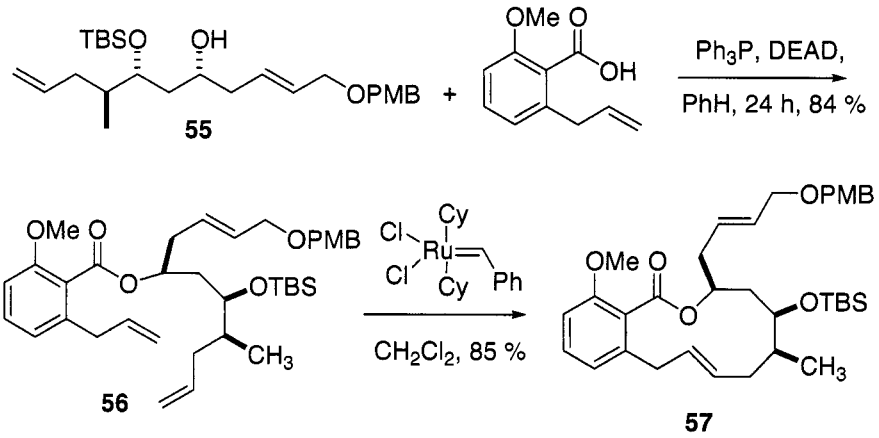
53



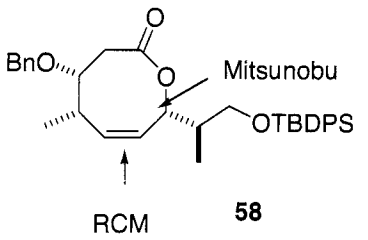
PPh_3, DEAD, dioxane, rt,, 57 %

54

In recent history, a two step process incorporating a Mitsunobu esterification followed by a ring-closing metathesis has proven to be useful for the synthesis of a number of natural products. The protocol has been particularly effective for the synthesis of larger macrocycles. A couple of key steps in the Smith and Zheng synthesis of (–)-salicylhalamide A are outlined below (conversion of **55** into **57**).[65] Labrecque *et al.* took the same approach in their syntheses of salicylhalamides A and B, while De Brabander and his group followed a similar approach in their synthesis of salicylhalamide analogs.[66,67] Other noteworthy applications of this approach to prepare macrocylic lactones include work by Fürstner *et al.* to prepare *(R)*-(+)-lasidiplodin, zeranol and truncated salicylhalamides.[68]

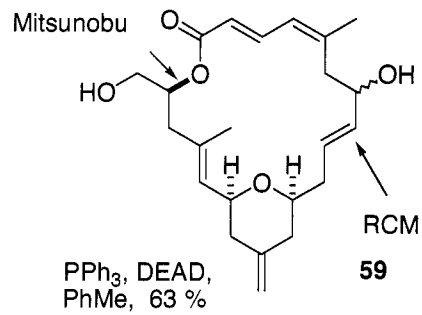


Other applications of the Mitsunobu/RCM approach are shown in the figure below. The respective arrows indicate the use of the Mitsunobu reaction to prepare the acyclic precursor and the olefin formed in the ring-closing metathesis reaction. The first example shows an advanced intermediate (**58**) in the preparation of octalactin ketone.[69] McLeod and coworkers employed a Mitsunobu reaction to set up an RCM precursor for the preparation of a key intermediate (**59**) for the synthesis of (–)-dactylolide.[69,70] An alternative approach towards (+)-zampanolide and (+)-dactylolide was taken by Smith *et al.*; their approach, which is not shown, attached a diethylphosphonacetic acid moiety to an alcohol via a Mitsunobu reaction and yielded the desired macrocycle after deprotonation and reaction with a pendant aldehyde via an intramolecular olefination reaction.[71]



58

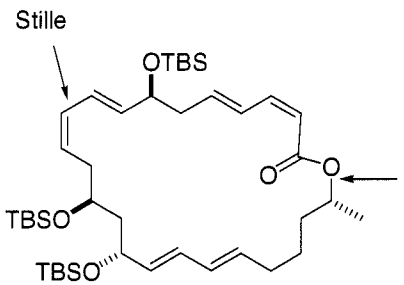
PPh_3, DEAD,
Et_2O-PhMe (2:1), 68 %



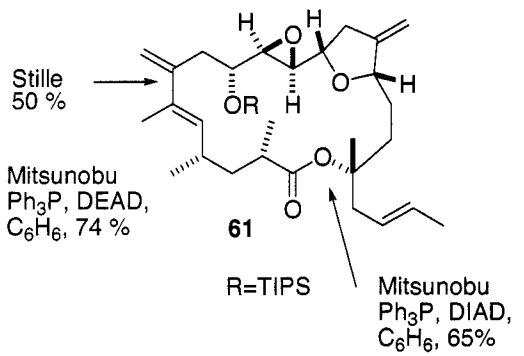
PPh_3, DEAD,
PhMe, 63 %

59

Other approaches to make macrocyclic ring systems exist as well. Smith and Ott prepared the central framework of (–)-macrolactin A by using a Mitsunobu reaction to prepare a linear precursor for the final ring closure reaction with a Stille reaction.[72] The Mitsunobu reaction proceeded in 74% yield; the Stille reaction, in contrast, took seven days and provided the desired macrocyclic intermediate **60** in 42% yield. In an inverse approach, Williams and Meyer prepared (+)-amphidinolide K by preparing a seco-acid macrolactonisation precursor via Stille reaction and then using the Mitsunobu reaction to close the ring to form **61**.[73]



60

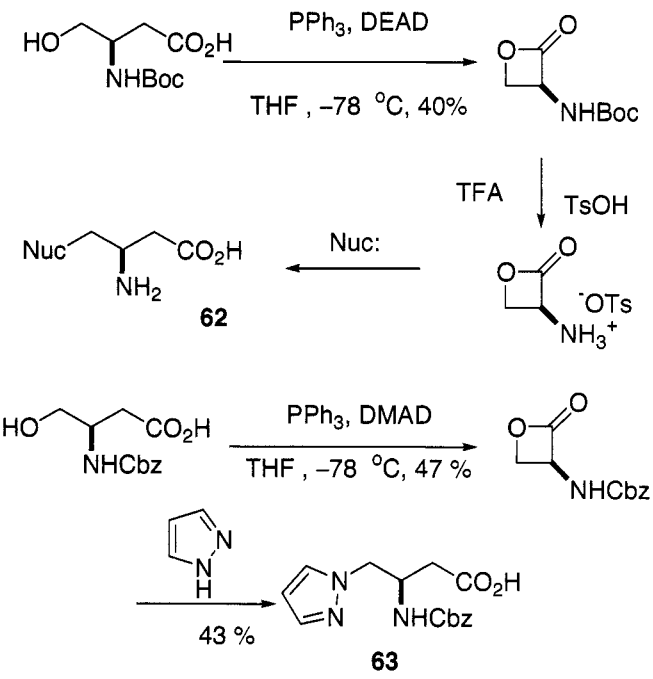


61

Applications: Inversion of alcohols—intramolecular lactone formation

As already mentioned, applications of the Mitsunobu reaction in lactone formation are significantly less common. Like so many other applications of the Mitsunobu reaction, the application of the Mitsunobu reaction for the preparation of lactones was first reported by Mitsunobu's group.[74] Later on, Mitsunobu's group used the reaction to prepare colletodiol.[75] Since then the scope of the reaction has been expanded to include the well known application of the Mitsunobu reaction for the preparation of amine protected (*S*)-3-amino-2-oxetanones derived from the correspondingly protected serine precursor; this protocol was initially discovered by Vederas and

coworkers.[76,77] Nucleophilic opening of the oxetane intermediates then provides access to modified α-amino acids **62** and **63**. The two examples below are taken from *Organic Synthesis* procedures. More recently, Olma and Kudaj have examined the ring-closure of α-alkylserine derivatives into the corresponding oxetanes.[78] In their hands, DEAD was necessary to obtain good cyclisation yields. DIAD worked only for the Mitsunobu reaction of *N*-Boc-α-methylserine (60% yield). In related work, Moura and Pinto prepared a series of β-*N*-methylamino-*L*-alanine derivatives from the CBz protected Mitsunobu derived oxetanes by using various primary and secondary amines as nucleophiles to open the serine lactone.[79] Malic acids can also be used in the preparation of β-lactones.[80] Application of the reaction can be carried out on much larger scale, as shown by the preparation of a key intermediate for the synthesis of Nelfinavir®, a potent HIV protease inhibitor.[81]

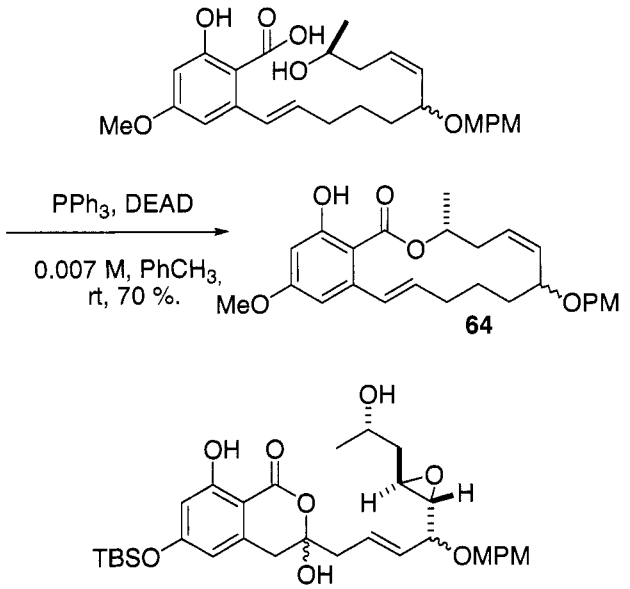


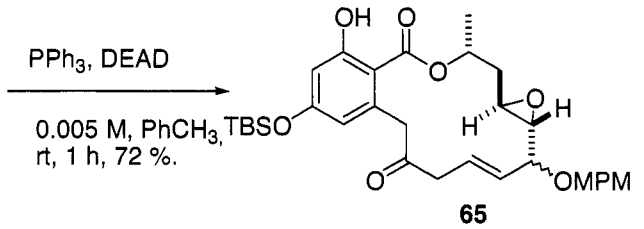
The Mitsunobu reaction has occasionally been used for the preparation of macrocyclic lactones. The figure below shows two examples from the literature (**64**, **65**).[82,83] Macrocyclic lactone **66** was prepared as a potential inhibitor of BACE, an important contemporary Alzheimer's disease target.[84] Huang *et al.* prepared lactone **67** as an intermediate for the synthesis of Geissman–Waiss lactone.[85] Shimano *et al.* used the intramolecular Mitsunobu reaction to prepare a medium-ring lactone intermediate **68** in their synthesis of the antifungal dilactone UK-2A.[86] The larger lactone found in

(+)-leucascandrolide A was prepared via a Mitsunobu reaction as well (see **69**).[87a] A subsequent Mitsunobu esterification was also used in this total synthesis by Patterson and Tudge. Couladourous *et al.* employed a Mitsunobu macrolactonisation in their synthesis of combrestatin D.[87b] In this synthesis, the *seco*-acid **70** was added over a period of 7 hrs to a heated solution of excess TPP/DEAD in toluene. A final concentration of 2.5 mM was achieved during the reaction. The next example (**71**) is one of a series of morpholine diones prepared by lactone formation via the Mitsunobu reaction.[88] The *cis/trans* relationship of the two alkyl substituents could be varied as needed by changing the Mitsunobu reaction conditions in terms of addition rates or the use diphenyl-(2-pyridyl)phosphine; thus it was possible to prepare all four isomers of the compound.

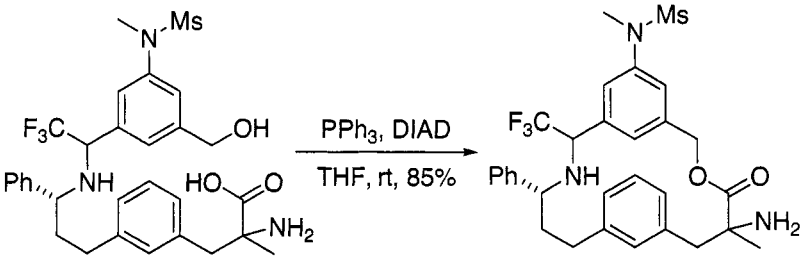
Additional applications of macrolactone formation via the Mitsunobu reaction can be found in the context of DNA primase inhibitor Sch642305,[89] histone deacetylase inhibitor FK228,[90] marine metabolite palmerolide A,[91] (+)-tedanolide,[92] racemic phomactin,[93] xestodecalactone A,[94] FR-901375,[95] (–)-laulimalide,[96] and lobatomide.[97]

As might be anticipated, each of these reactions is unique in the sense that macrocycles of significant variation and complexity were prepared. As such, these reactions tend to be variable in terms of the actual experimental conditions and yields. Frequently, the reactions are run on very small scale due to the limited availability of starting materials.

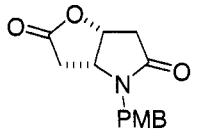




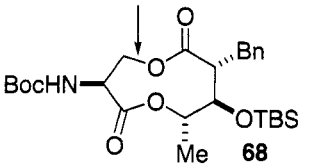
65



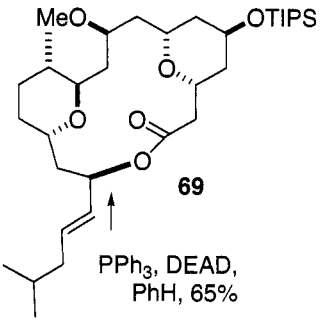
66



67



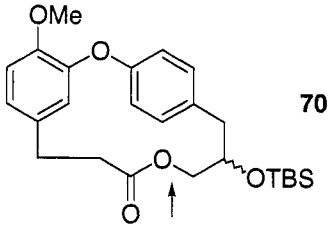
68



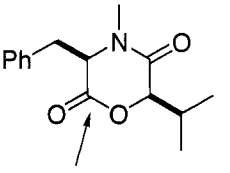
69

PPh3, DEAD, THF, 0 °C-rt, 96%. PPh3, DIAD, 87%

PPh3, DEAD,
PhH, 65%



70



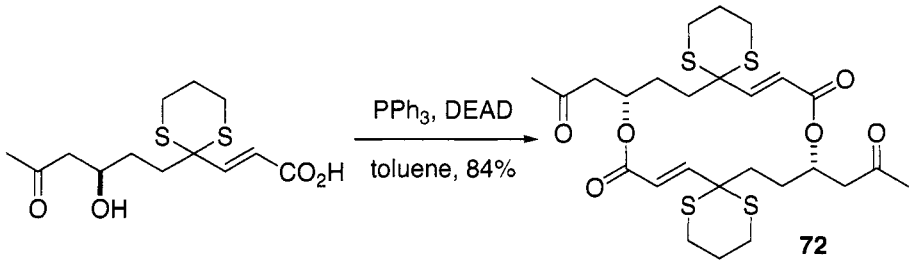
71

PPh3,DEAD, toluene, 45 °C, 90 %.

PPh3,DEAD, THF, rt, 54 %.

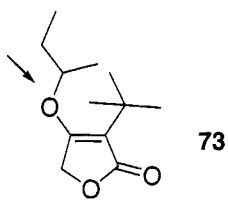
More interesting, however, is the potential application of the Mitsunobu reaction in the preparation of symmetric lactones from 2-hydroxyacid pieces. Such an approach would allow preparation of a number of C-2 symmetric natural products. Seebach and Searing employed such an

approach for the preparation of (*R,R*)-vermiculin intermediate **72** as shown below.[98]



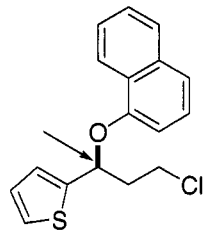
Applications: Ether formation

Mitsunobu and Wada first reported the use of the Mitsunobu reaction in the preparation of ethers in 1972.[99] Since then, the Mitsunobu reaction has become a useful alternative to the reaction of phenols with alkyl halides. Other sufficiently acidic alcohols with a p*K*a of less than 13 may also react under the Mitsunobu reaction conditions. Interestingly, unactivated, less acidic alcohols will form ethers when reacting in an intramolecular manner. The figures below show a number of applications of the Mitsunobu reaction in the preparation of alkyl and aryl ethers.



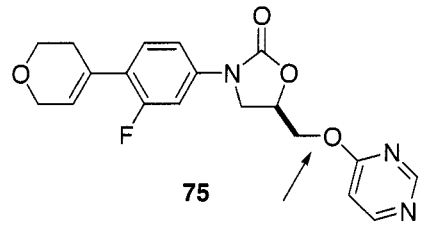
73

(1-methyl)butan-1-ol
PPh_3, DEAD
THF, rt, ON, 75%
Ref: Bajwa[100]



74

1-Naphthol,
PPh_3, DEAD
THF, 0 °C-->rt, 88%
Ref: Gallagher[101]

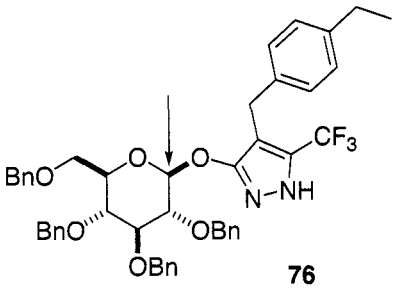


75

4-hydroxypyrimidine, PPh_3, DIAD
49%
Ref: Gravestock[102]

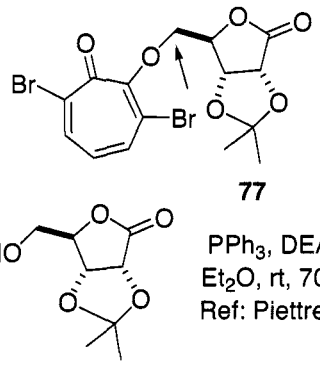
First, the table immediately below shows a series of phenol based Mitsunobu reactions. As can be seen from the examples, a large variety of alcohol partners are tolerated in the reaction. In addition, naphthyl (**74**), enol and heteroaryl alcohols (e.g., **75** and **76**) also readily participate in the reaction. Acid sensitive ascorbates (example **73**) and tropones (example **77**) are viable Mitsunobu reaction partners as well. Less common reactions such as an intramolecular Mitsunobu cyclisation of a phenol onto a hydroxamide functionality to prepare 1,2-benzisoxazolin-3-ones are also possible (example **78**). Compound **79**, an intermediate in the synthesis of a series of tumor

necrosis-A converting enzyme inhibitors, shows that macrocyclic phenol ethers can be prepared as well using the Mitsunobu reaction.



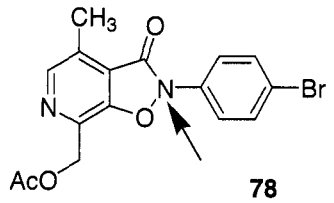
76

2,3,4-tetrabezyl-D-gluco-pyranose, PPh_3, DEAD, toluene THF, rt, 72 %
Ref: Ohsumi[103]



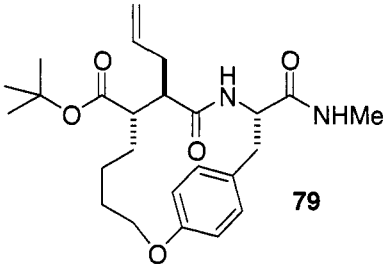
77

PPh_3, DEAD
Et_2O, rt, 70 %
Ref: Piettre[104]



78

PPh_3, DEAD
THF, 0 °C-->rt, 82 %
Ref: Shi[105]

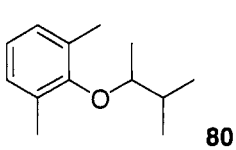


79

PPh_3, ADDP
THF/benzene
Ref: Holms[107]

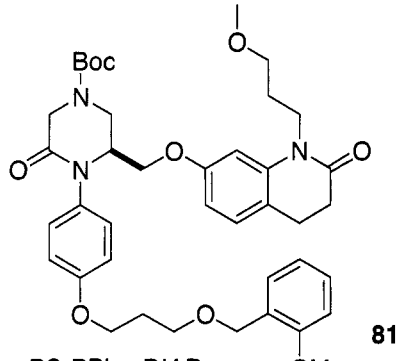
The preparation of aryl sec-alkyl ethers is often problematic without the use of sonication or polymer supported reagents. Arunachalam *et al.* report that the sluggish reactivity of secondary alcohols under the standard Mitsunobu conditions employing TPP/DIAD can be improved by the addition of a stoichiometric amount of triethylamine.[106] Larger quantities of added base or other bases did not improve yields of **80** any further. The standard TPP/DIAD reaction conditions provided the product in approximately 10% yield. Powell *et al.* prepared a series of ketopiperazine based renin inhibitors **81** using polymer supported PS-PPh_3 and DIAD.[107] Carbohydrate derivative **82** was prepared in a 4:1 α/β anomeric ratio in 54% yield using the standard TPP/DEAD Mitsunobu reaction conditions.[108] Compound **83,** a member of a series of non-peptide quinolone GnRH receptor antagonists, was readily prepared in good yield by coupling the

sufficiently acidic, vinylogous carbamic acid phenol with the Boc-piperidine derivative **84**.[109] Large scale applications of the Mitsunobu reaction are periodically seen in the literature; one recent example involves the coupling of 6-methylamino-2-pyridineethanol **85** with a phenol derivative on a 50 kg scale to prepare **86**. In this particular case, chromatography was not efficient from a purification or cost perspective. Saponification of the methyl ester gave an intermediate that was separable by precipitation from the Mitsunobu reaction byproducts; further purification gave the vitronectin receptor antagonist in good purity and 66% yield for the two steps.



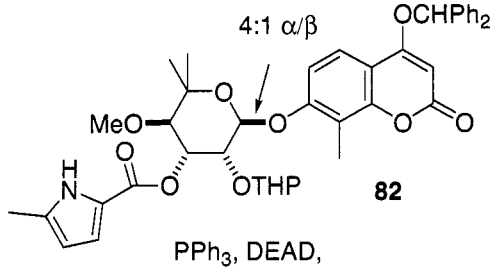
80

PPh_3, DIAD, TEA
THF, 0 °C-- >rt, 81 %
Ref: Manivel[107]



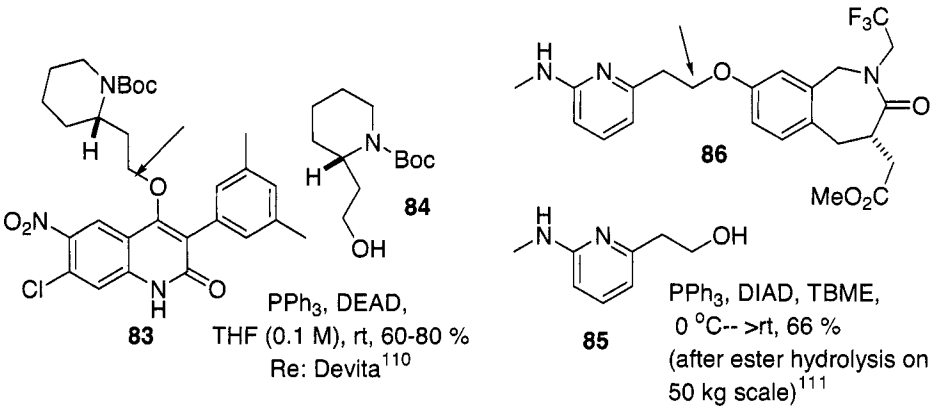
81

PS-PPh_3, DIAD,
CH_2Cl_2, 0 °C-- >rt, 38 %
Ref: Powell[108]

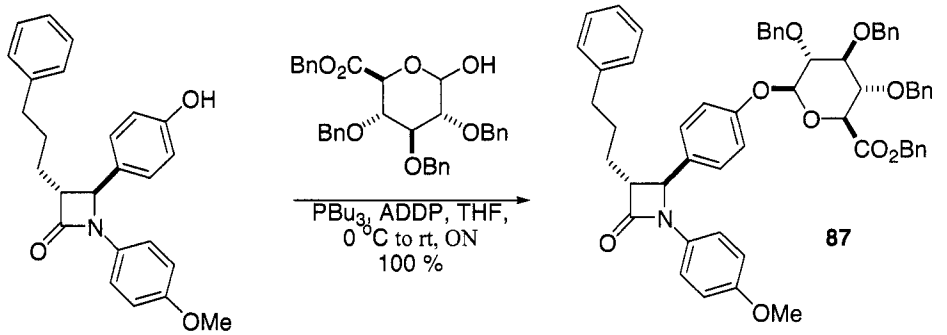


82

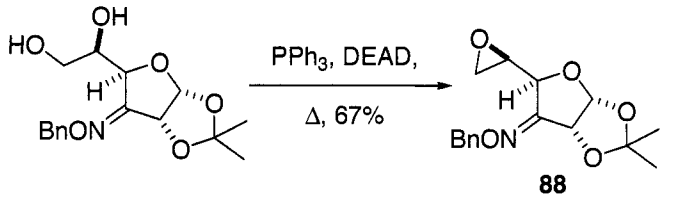
PPh_3, DEAD,
CH_2Cl_2, rt, 54 %
Ref: Musicki[109]

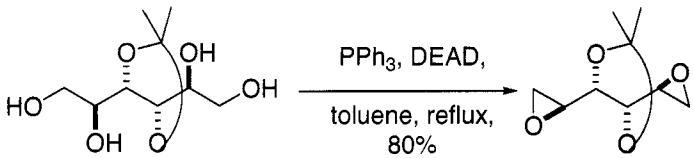


Vaccaro *et al.* at Schering–Plough employed the ADDP/PBu_3 reagent combination developed by Tsunoda for the preparation of a series of sugar-substituted 2-azetidinones. For example, the preparation of cholesterol absorption inhibitor **87** is shown below.[112–114].



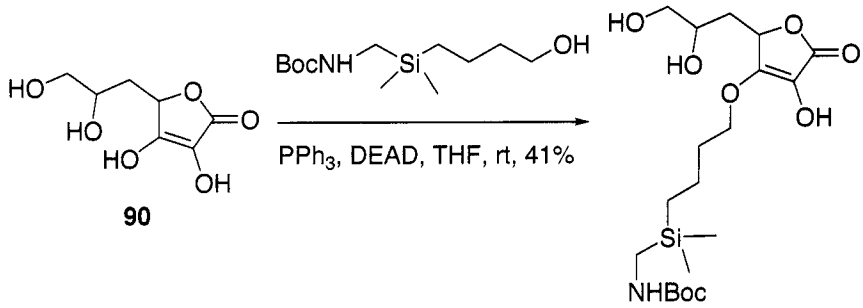
Epoxides can be readily formed using the standard Mitsunobu reaction conditions. A recent example (**88**) from the literature is shown below.[115] The reader is referred to the cited paper for additional examples. Bis-epoxides such as **89** were useful in the preparation of a series of cyclic urea based HIV protease inhibitors.[116]





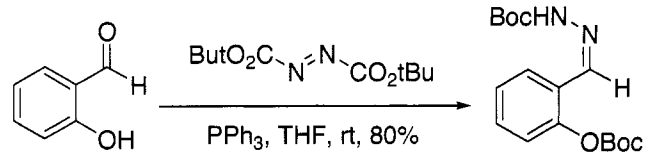
89

In a related application of a phenol-like ether formation via Mitsunobu reaction, Deleris *et al.* prepared a series of *L*-ascorbic acid derivatives using the unprotected acid.[117] The reaction was selective for the 3 position of ascorbic acid **90**, the most acidic of the four alcohol substituents of the acid. Use of the *N,N,N',N'*-tetramethylaza-dicarboxylate/tributylphosphine reagent combination did not improve the yield of the reaction.



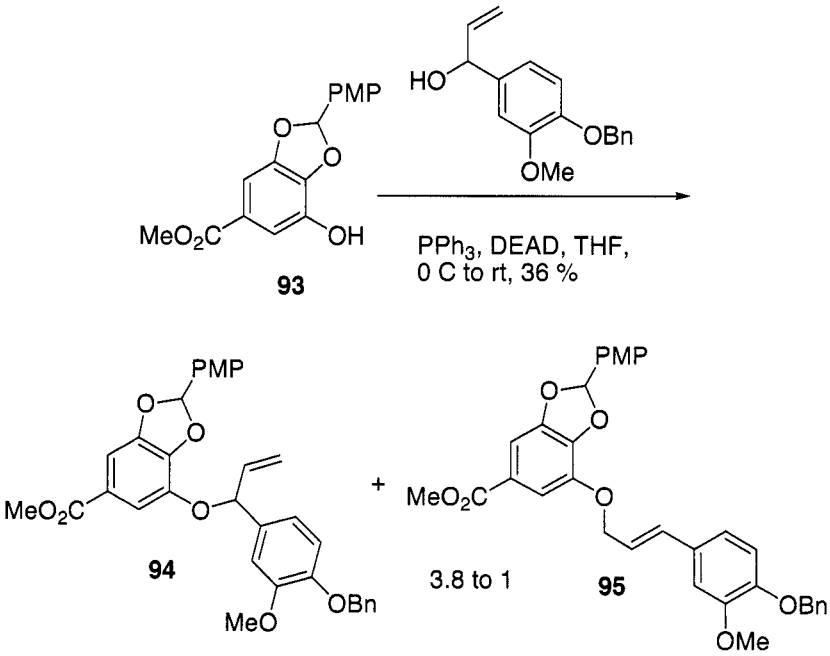
90

An exception to the expected ester formation of a phenol and a carboxylic acid is found in the case of salicylaldehydes. Girard *et al.* found that salicylaldehydes (**91**) preferentially form hydrazones like **92** when DEAD or related azadicarboxylates are employed in the Mitsunobu reaction. The hydrazone formation occurs with or without a carboxylic acid coupling partner. If DBAD is used during the reaction, the neighboring alcohol is "protected" as the boc ester during the reaction. This presumably occurs through Boc transfer from DBAD via a tetrahedral intermediate. The subsequent hydrazone formation can then proceed via a concerted or nonconcerted reaction with the reactive triphenylphosphonium boc hydrazide species that is formed after the collapse of the tetrahedral intermediate.

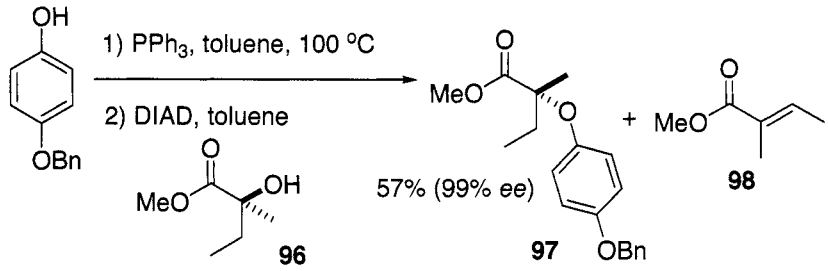


91 92

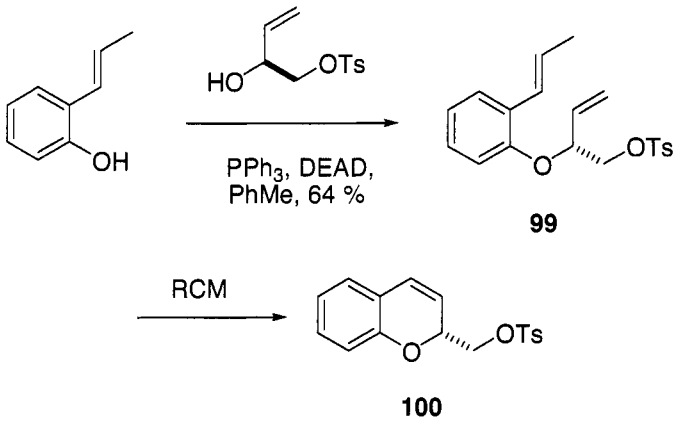
In some cases, allyl substituted alcohols react via an S_N2 or S_N2' mechanism under the standard Mitsunobu reaction conditions. Benzyllic alcohol **93**, for example, gave the isomeric ethers **94** and **95** in a 3.8 to 1 ratio.[119,120]



Mitsunobu reactions of tertiary alcohols are relatively uncommon. Shi *et al.* employed the reaction to prepare a series of chiral tertiary chiral aryl ethers.[121] Not surprisingly, these reactions required more forcing conditions than the typical room temperature conditions. Yields, typically in the 50% range, were accompanied by a fair amount of elimination byproduct and inversion of stereochemistry. Best results were obtained by adding a toluene DIAD solution to a preheated mixture of the remaining reaction partners. Thus, reaction of tertiary alcohol **96** gave ether **97** in 57 % yield, along with elimination product **98**.



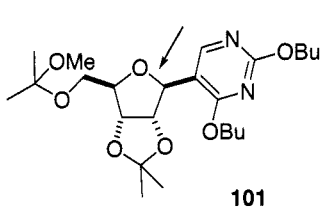
The intermolecular Mitsunobu alkylation can be followed by a number of other reactions to make larger cyclic structures. The example below shows a phenol alkylation to make a chiral precursor for the synthesis of repintonan (BAY-3702), a high affinity 5-HT_{1A} receptor agonist in clinical trials as an ischemic stroke treatment.[122] After the initial Mitsunobu reaction, the alkylated intermediate **99** is converted into the chromene **100** according to a protocol initially developed by Grubbs and Chang.[123]



99

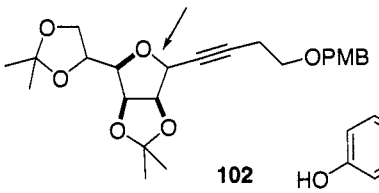
100

Intramolecular alkylations of alcohols via the Mitsunobu reaction work quite well. The figure below lists a number of recent examples. Hanessian and Machaalani completed an efficient, stereocontrolled synthesis of α- and β-pseudouridines, ubiquitous uridine derivatives found in bacterial and mammalian r-RNA and t-RNA, with a Mitsunobu cycloetherification to produce protected β-pseudouridine precursor **101** in 70% yield.[124] A similar intermediate was prepared by Hanessian *et al.* in the total synthesis of malayamycin A.[125] Subsequent removal of the alcohol protecting groups provided the natural product. Ley and his group prepared a series of chiral 2,5-disubstituted tetrahydrofurans **102** via a Mitsunobu cyclization in excellent yields.[126] An interesting large scale application of the Mitsunobu reaction takes place in the selective preparation of the tetracyclic selective estrogen receptor modulator **103.**[127] Of the three possibly reactive phenols only one is situated to undergo the intramolecular reaction to form the seven-membered ether. Another example of an intramolecular phenol cyclisation is shown for the preparation of imidazopyridine derivative **104.**[128] The spirocyclic aminochroman derivative **105** was prepared in 93% yield from the corresponding diol in refluxing toluene.[129]



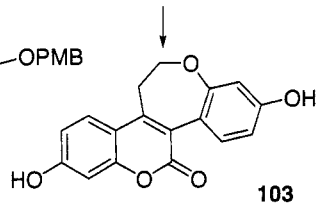
101

PPh_3, DIAD
THF, 70 %
Ref: Hanessian[124]



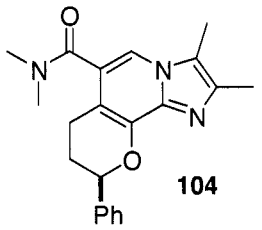
102

PPh_3, DEAD
THF, rt, 1 h, 93 %
Ref: Ley[126]



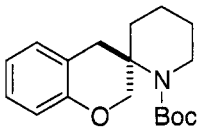
103

PPh_3, DIAD
THF, 20 °C 18 h, 97 %
Ref: Li[127]



104

PPh_3, DIAD
CH_2Cl_2, rt, 3 min, 42 %
Ref: Palmer[128]

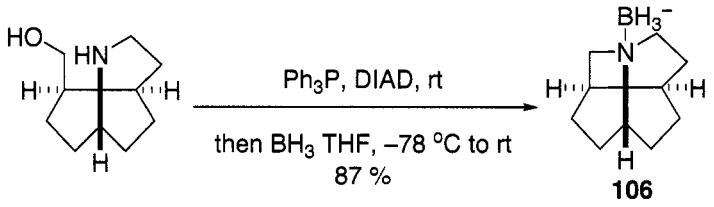


105

PPh_3, DEAD
toluene, reflux, 93 %
Ref: Pave[129]

Applications: Alcohol into amine conversion

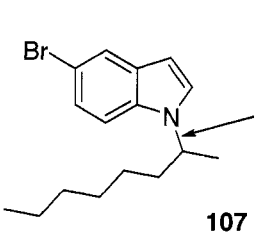
Sometimes, unactivated alcohols can be converted directly into amines. Denmark *et al.* were pursuing the synthesis of the structurally interesting fenestranes when they employed an intramolecular Mitsunobu reaction to form compound **106** in 87% yield as the borohydride derivative.[130]



106

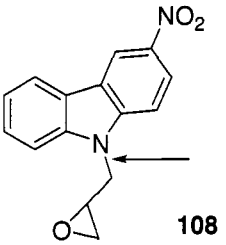
Bombrun and Casi were interested in preparing alkylated indole and carbazole derivatives; they found that the traditional TPP/DEAD approach for the alkylation of 5-bromo-1*H*-indole with benzyl alcohol or glycidol failed.[131] Use of the TMAD/PBu_3 or CMMP reagents developed by Tsunoda gave yields of 20–88%. The Mitsunobu reactions of the carbazoles proved to be even more unpredictable, with yields depending on which amine and alcohol were used under which redox conditions. Examples incorporating an indole (**107**) and carbazole (**108**) are shown below. Prudhomme and

coworkers were interested in the preparation of novel rebeccamycin analogs.[132] As such they were able to introduce the glucopyranose moiety as shown below for rebeccamycin analog **109**. A similar strategy was employed by Ohkubo *et al.* for the preparation of a number of indolocarbazole derivatives related to rebeccamycin.[133] Lastly, Chong and Wu completed a very efficient synthesis of (+)-crispine **110** in three steps.[134] An intramolecular Mitsunobu cyclization closed the final ring.



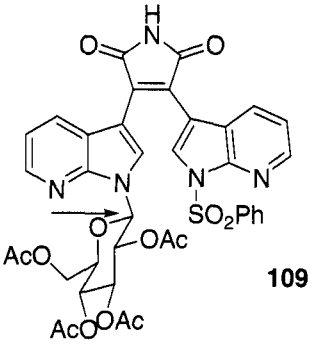
107

CMMP, toluene,
110 °C, 15 h, 93 %
Ref: Casi[131]



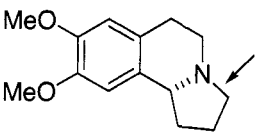
108

PPh_3, DEAD
THF, 40 °C, 95 %
Ref: Casi[132]



109

2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranose
PPh_3, DEAD
THF, –78 °C, 65%
Ref: Prudhomme[133]



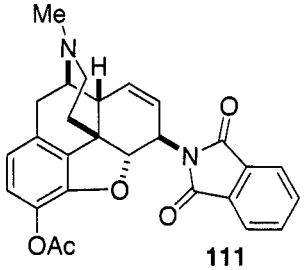
110

PPh_3, DEAD
57% (inc.
preceeding hydroboration)
Ref: Chong[134]

More typically, activated amines in the form of amides or sulfonamides are employed as coupling partners in the Mitsunobu reaction. Amides, sulfonamides, lactams, imides, azides, and more esoteric acidic amine derivatives work well in this context. The figures below list a significant number of amine derivatives that have been used in the Mitsunobu reaction. Phthalimide, originally employed by Mitsunobu's group many years ago, remains one of the most important amine surrogates for use

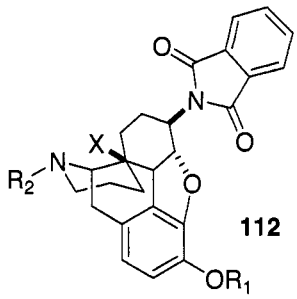
in the Mitsunobu reaction.[135] A solid-supported phthalimide reagent has been developed as well; in this context, the alcohol reacts with the supported reagent and becomes attached to the resin.[136] After removal of excess TPP/DEAD and the redox byproducts by resin washing, the desired amine is obtained from the resin by the traditional hydrazine cleavage.

MacDougall and Cashman *et al.* prepared a number of analogs of morphine-6-glucuronide.[137] As such, the amine intermediate **111** was prepared using a phthalimide Mitsunobu reaction. The free phenol was protected as the acetate ester prior to the Mitsunobu reaction since the phenol is more reactive than the vinyl alcohol under the reaction conditions. Other diverse examples employing phthalimide are listed below as well (**112–115**).[138–141]



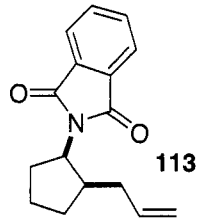
111

PhthNH, PPh_3, DEAD
72 % (after acetate removal)
Target: morphine glucuronide
Ref: Macdougall[137]



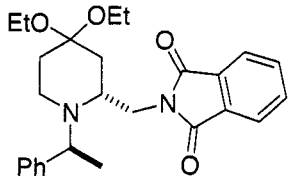
112

PhthNH, PPh_3,
DEAD
THF, rt
Ref: Makleit[138]



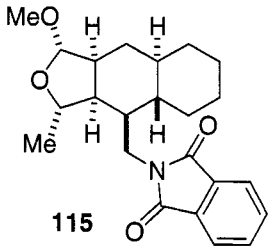
113

PhthNH, PPh_3,
DEAD
THF, rt, 2 d.
Ref: Hegedus[139]
63 % after H_2NNH_2



114

PhthNH, PPh_3, DEAD
THF, 0 °C, 3.5 h, 73 %
(0.2 mol scale)
Ref: Lau[140]

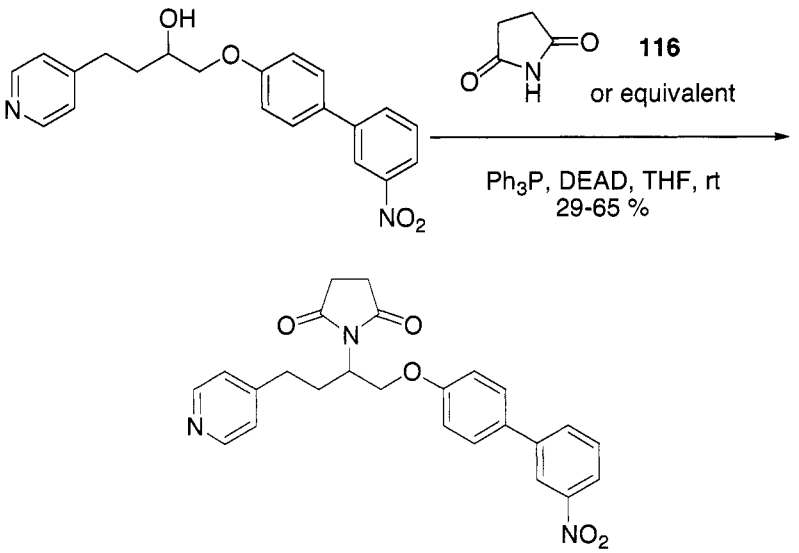


115

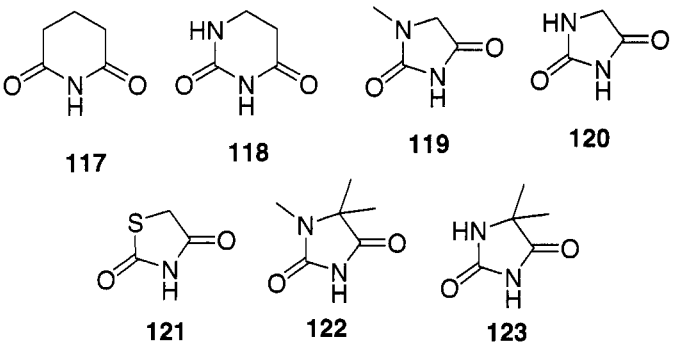
PhthNH, PPh_3, DEAD
THF, 0 °C-->rt, 99 %
Ref: Takadoi[141]

In analogy to the phthalimide Mitsunobu reaction above, a number of other imides also participate in the Mitsunobu reaction. For example, various imides (**116** to **123**) were examined by Alcarez *et al.* in their search for novel

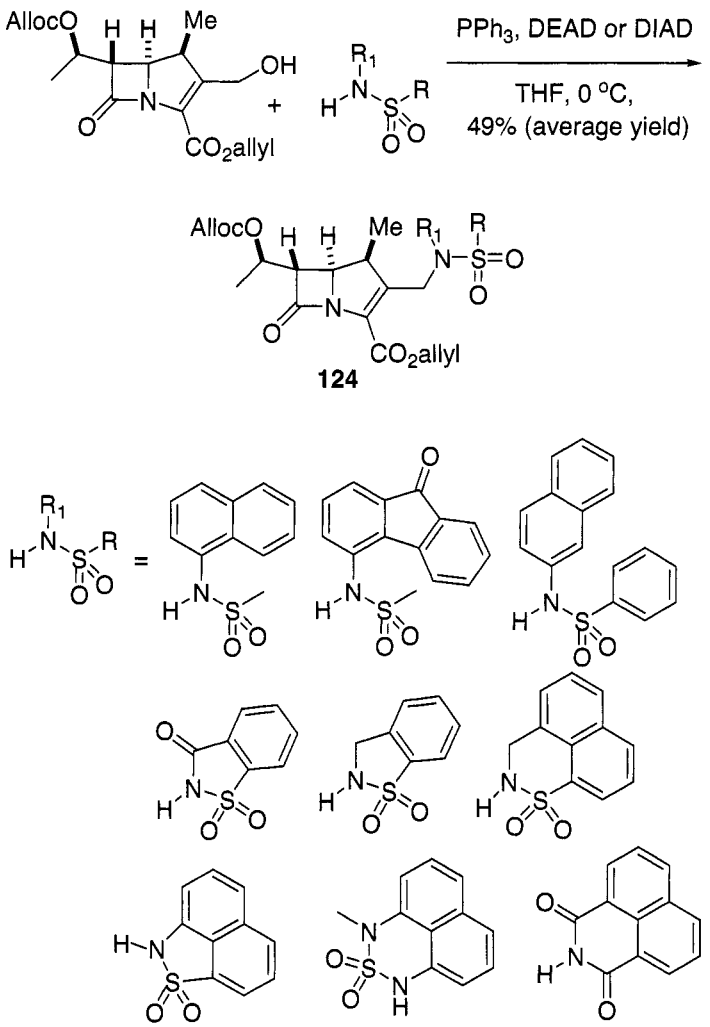
P_2X_7 receptor antagonists.[142] The Mitsunobu reactions were generally carried out in THF at room temperature and provided the desired substituted imides in 29–65% yield. The substrates that were prepared are summarised in the figure below.



Reaction partners:

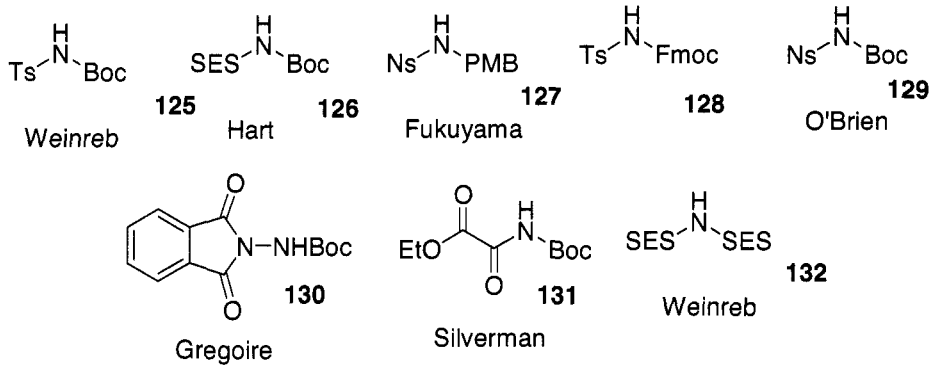


Activated sulfonamides and other activated amines were used in a series of Mitsunobu reactions to prepare analogs of 2-(sulfanamido)methyl carbapenems (**124**) as potential anti-MRSA compounds.[143] The basic reaction scheme and some of the activated amines that were used are shown in the figure below. Additional examples can be found in the original paper.

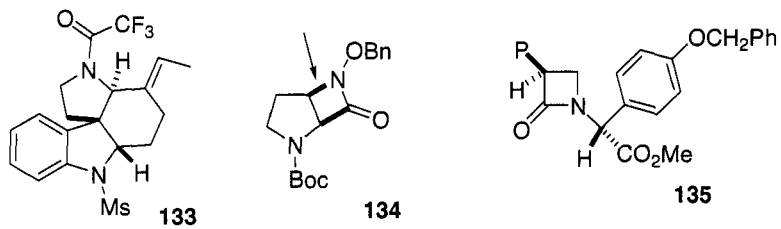


The bis-protected amine **125**, first employed by Weinreb *et al.*, can be selectively deprotected after the Mitsunobu reaction to provide a Boc or Ts protected amine intermediate.[144] More recently, Hart and Campbell have used the 2-(trimethylsilyl)ethyl-sulfonyl (SES) protected boc amine **126** as the nucleophilic partner in the Mitsunobu reaction.[145] Selective removal of the SES group with TBAF provides the corresponding boc protected amine, whereas 6 N HCl provides the corresponding amine HCl salt. The protected sulfonamide equivalent **127** was first reported by Fukuyama.[146] The tosyl/fmoc amine derivative **128** used by Murphy and others surprisingly loses the fmoc group under the standard Mitsunobu reaction conditions.[147] Phthalimide variants of activated hydrazines (e.g., **130**) are also possible.[148] Thus, addition of a Boc group to the primary amine of aminophthalimide

produces an activated hydrazine equivalent that readily undergoes the Mitsunobu reaction; subsequent removal of the phthalimide moiety can lead to alkylated hydrazines or a Boc protected hydrazine derivative. In a more unusual method of activation, Silverman *et al.* employed *N*-Boc ethyl oxamate **131** as a protected nitrogen equivalent.[149] The oxamate group, while readily removed with lithium hydroxide, gave a somewhat unstable intermediate product which the author preferred to hydrolyse to the BOC intermediate prior to purification. The bis-(β-trimethylsilylethanesulfonyl) imide **132** was prepared by Weinreb's group as well.[150] As expected Mitsunobu reactions with this activated amine work well. Selective deprotection to the mono-SES protected intermediate amine allows for further alkylation chemistry if so desired.



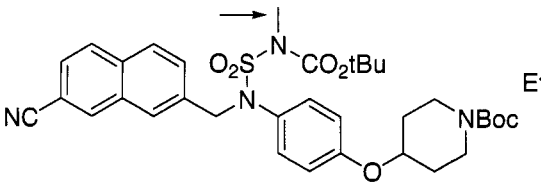
Activated amines such as the ones listed above have been frequently employed in the context of alkaloid total synthesis. The figure below lists a number of key intermediates (**133** to **135**) prepared via Mitsunobu reaction in the preparation of various alkaloids.[151–153] Many additional applications of the Mitsunobu reaction in alkaloid synthesis can be found in the slightly older review by Simon, Hosztafi, and Makleit.[154]



Activated amines have been used in the Mitsunobu reaction in other contexts as well. The figures below list a wide range of intermediates in medicinal chemistry and total synthesis that were prepared using diverse activated amine precursors.

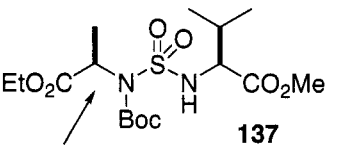
Examples **136** and **137** used Boc-protected sulfonamides to prepare alkylated sulfonamides. The chiral cyclopentene derivative **138** was prepared using a nitrosulfonamide activated amine equivalent. In an intramolecular cyclisation approach, Bell *et al.* prepared a series of 1-heterocyclic-3-aminopyrrolidines. The Mitsunobu reagents PBu_3 and DBAD were premixed prior to addition to the homoserine amide to provide, for example, compound **139**. This approach is similar to an already reported synthesis of *N*-arylpiperazinones by Weissmann *et al.*

A number of different nitrogen containing compounds have been prepared via intramolecular Mitsunobu cyclisation of an amine and an alcohol. For example, McAlpine and Armstrong prepared a tricyclic guanidinium model (**141**) of cylindrospermopsin using a pair of sequential Mitsunobu reactions. The Mitsunobu product **140**, arising from cyclisation of the Z diprotected guanidium moiety onto a primary alcohol is shown below. Subsequent deprotections are followed by another intramolecular Mitsunobu cyclisation between the former TBS protected primary alcohol and the external amine of the guanidine to form **141**.



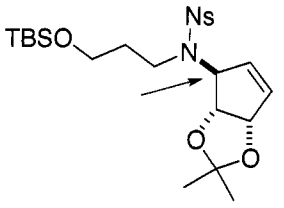
MeOH, PPh_3,
DEAD
THF, rt, 87%
Ref: Hirayama[155]

136

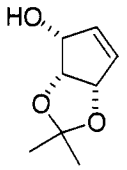


137

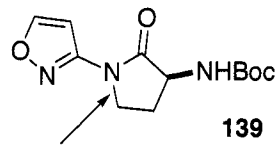
ethyl lactate,
PPh_3, DEAD
THF, rt, 81 %
Ref: Hanson[156]



138

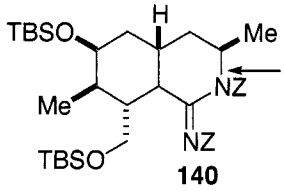


PPh_3, DIAD
THF, reflux,
77 %
Ref: Grubb[157]



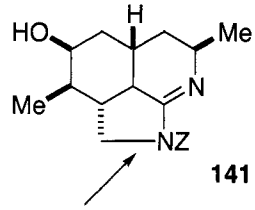
139

Intramolecular cyclisation
PBu_3, DBAD, THF (preformed)
then, SM, THF, 0 °C, 79%
Ref: Bell[158]



140

Intramolecular cyclisation
PPh_3, DIAD, 63 %
Ref: Armstrong[159]



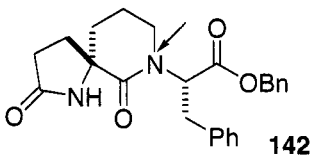
141

Intramolecular cyclisation
PPh_3, DIAD, 27 %
Ref: Armstrong[159]

A novel spirocyclic amino acid (**142**) was prepared by Moeller *et al.*[160] In a different approach, DeMong and Williams prepared a precursor (**143**) of the interesting, non-proteinogenic amino acid capreomycidine.[161] Removal of the chiral oxazinone and the Boc/Cbz protecting groups delivered the amino acid. In another Mitsunobu cyclisation, 1*H*-2,3-benzoxazines such as **144** can be prepared via cyclisation of the corresponding hydroximo alcohols.[162] The catalytic 4-nitrobenzoic acid increases formation of the product; without added acid, an approximate 1:1 mixture of starting material and product is obtained. α-Amino acids remain an important area of ongoing research. Van Boom *et al.* used a nitrosulfonyl activated amine to form an aziridine (**145**) upon reaction with a primary terminal alcohol.[163] The ensuing OBO protected aziridines were then opened with acetylide nucleophiles to produce alkynyl substituted α-amino acids after deprotection. O'Brien *et al.* employed another variant of the Fukuyama protocol to prepare chiral cyclohexane derivative **146** in good yield.[164] In a study focused on the synthesis of 1-deoxymannojirimycin analogs, Compernolle used a Mitsunobu cyclisation of a tosylated amine to prepare the highly functionalised cyclohexane derivative **147**. Purification issues, however, required conversion of the free alcohol into the corresponding

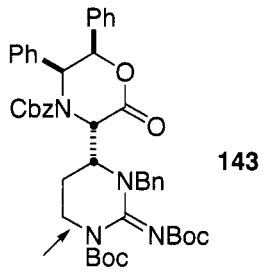
acetate in order to obtain a pure reaction product.[165] Reaction of 2′-deoxy-3′,5′-di-*O*-acetyl-5-fluorouridine using TPP/DEAD gave the coupled nucleoside derivative **148**. Compound **149**, a key intermediate in the preparation of BN-80927, an homocamptothecin analog active against topoisomerases I and II, was prepared via alkylation of the DE pyridone fragment with the lefthand AB ring system.[166] A subsequent Heck reaction forms the middle C ring. This approach has also been used by Bigg and others to prepare camptothecin and homocamptothecin analogs.[167]

In another modern application of the Mitsunobu reaction, Blechert *et al.* used the reaction to prepare chiral diene **150**; this compound was ideally set-up for a ring-closing metathesis reaction to prepare an advanced intermediate for the synthesis of (–)-halosaline.[168]



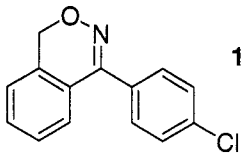
142

Intramolecular cyclisation
(1) PPh_3, DIAD,THF, rt, 12h
(2) CAN, CH_3CN, H_2O, rt, 2h
53 % (2 steps)
Ref: Moeller[160]



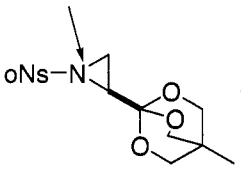
143

Intramolecular cyclisation
PPh_3, DIAD, THF, 0 °C, 87 %
Ref: Williams[161]



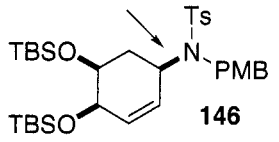
144

Intramolecular cyclisation
PPh_3, DEAD, cat. 4-$NO_2C_6H_4CO_2H$,
THF, rt, 82 %
Ref: Kai[162]



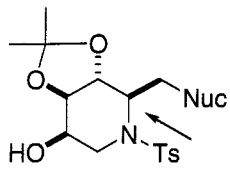
145

aziridine formation
PPh_3, DIAD, THF, 0 °C, 98 %
Ref: van Boom[163]



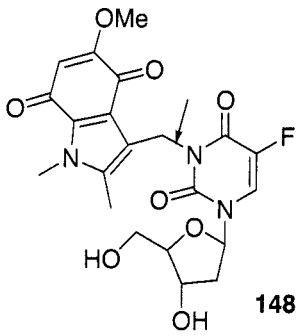
146

amine synthesis
PPh_3, DIAD, THF, rt, 91 %
Ref: O'Brien[154]



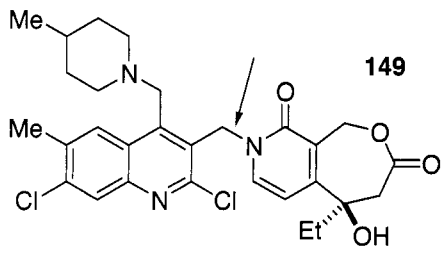
147

amine synthesis
PPh_3, DEAD, THF, rt, 5 d, 45 %
isolated as the acetate derivative
Ref: Compernolle[165]



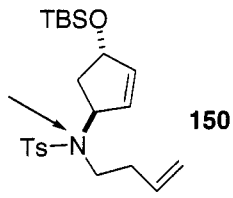
148

N-alkylation
PPh_3, DEAD, THF, 0 °C, 32 %
(after hydrolysis)
Ref: Nishimoto[166]



149

pyridone alkylation
PPh_3, DIAD, dioxane, rt, 50 %
Ref: Bigg[167]

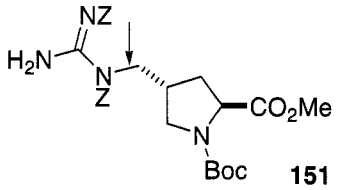


150

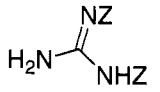
N-tosylbutenylamine
PBu_3, ADDP, PhH, rt, 87 %
Ref: Blechert[169]

Since the use of activated amines in the Mitsunobu reaction is very extensive, additional examples are listed in the figure below. Mitsunobu reactions that incorporate protected guanyl units work very well. Proline derivative **151** was prepared from a doubly protected guanyline equivalent in 80% yield.[170] Benzimidazoles can be readily alkylated with a number of different alcohols. In the context of non-steroidal progesterone receptor

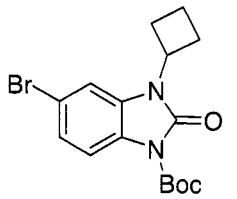
agonists, a series of bromobenzimidazoles were prepared. Alkylation of the nitrogen occurs in a 30–80% yield range for a variety of alcohols. A high-yielding example for the alkylation of a benzimidazole with cyclobutanol to give alkylated benzimidazole **152** is shown as an example.[171] Haidle *et al.* were interested in the preparation of 1-alkyl-4-aminopyrazoles as an isosteric replacement for an aniline functionality.[172] While these compounds have rarely been prepared via Mitsunobu reaction, the *N*-alkylation of the pyrazole nitrogen proceeds in 70–90% yield for a diverse group of alcohols. The reaction works quite well for the preparation of branched aminopyrazoles by reaction with secondary alcohols; an example using *tert*-butyl-3-hydroxypyrrolidine carboxylate is shown below (to prepare **153**). Piperazic acid derivative **154** was prepared via Mitsunobu cyclisation.[173] Subsequent manipulations allow the preparation of selectively protected esters of the piperazic acids. A nice application of the aza-Mitsunobu was utilised by Gin's group to prepare the pyrrolidine ring of an advanced intermediate (**155**) for the synthesis of two batzelladines.[174] Mishra and Panda prepared a series of benzannulated heterocylic compounds incorporating medium-sized rings (**156**).[175] Another example of a fused medium-sized ring prepared via an intramolecular cyclization can be found in tricyclic pyridone **157**.[176]



151

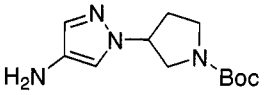


PPh_3, DIAD
THF, rt, 24 h, 80 %
Ref: Poitier[170]

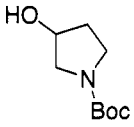


152

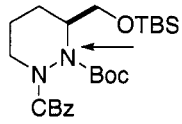
cyclobutanol,
PPh_3, DIAD
THF, rt, 30 min, 88 %
Ref: Zhang[171]



153

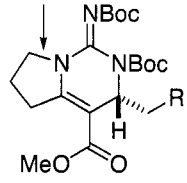


PPh_3, DBAD
THF, rt, 87 %
Ref: Haidle[172]



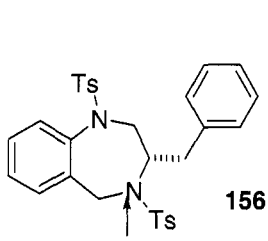
154

PPh_3, DEAD
THF, reflux, 0.5 h, 86 %
Ref: Williams[173]



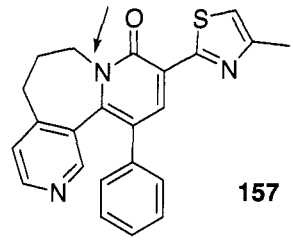
155

R=$(CH_2)_6CH_2CH_2OTBDPS$
PPh_3, DIAD
PhMe, 93 % %
Ref: Gin[174]



156

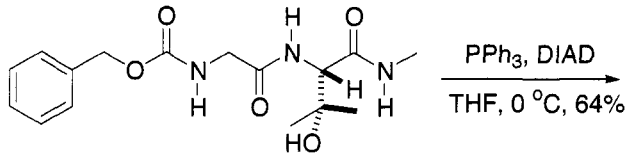
PPh_3, DEAD
THF, 0 °C-->rt, 77 %
Ref: Panda[175]

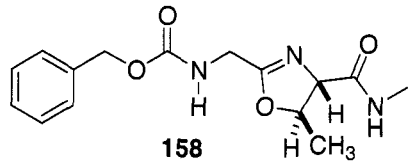


157

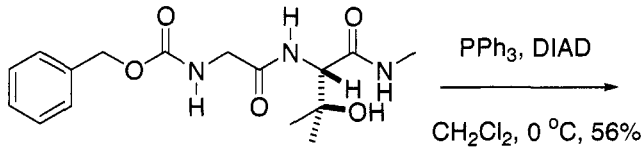
PPh_3, DEAD
THF, 84 %
Ref: Gibson[176]

Wipf and Miller reported a number of approaches for the preparation of acid and base labile oxazolines and thiazolines (e.g., **158**).[177] The Mitsunobu reaction or Burgess' reagent proved to be the most effective methods for the preparation of these heterocycles, but the Burgess reagent was much general in its applicability. In some cases, competitive aziridine (**159** to **160**) or elimination reactions (**161** to **162**) dominated under the Mitsunobu reaction conditions (*vide infra*).

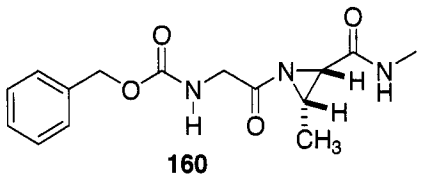




158

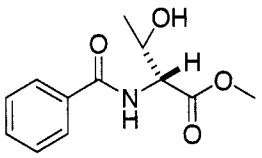


159

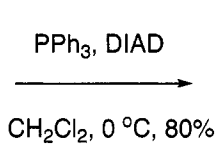


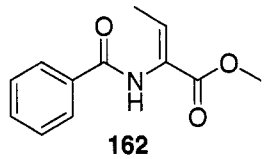
160

Burgess Reagent gave the oxazoline in 62 % yield.



161

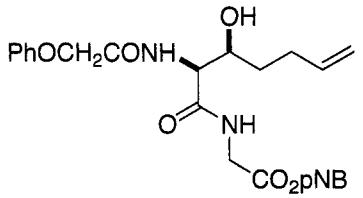




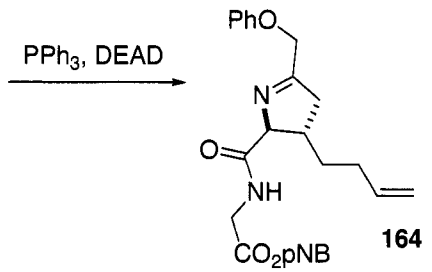
162

Burgess Reagent gave the oxazoline in 85 % yield.

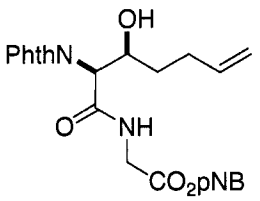
In some cases, the presence of proximal nucleophilic groups can lead to undesired products. In synthetic work towards the antibiotic loracerbef, Zhang *et al.* found that intermediate **163** preferentially formed oxazoline **164** instead of the desired β-lactam **166** because of the neighbouring group participation of the α-amido nitrogen.[178] Changing of the amino protection group to the phthalimide (**165**) eliminated the oxazoline formation, but introduced purification problems (i.e., TPP=O removal without chromatography). To advance the project, lower-cost phosphites were examined. Heated reaction conditions provided the desired product without epimerisation, with $P(OEt)_3$ giving the best overall results.



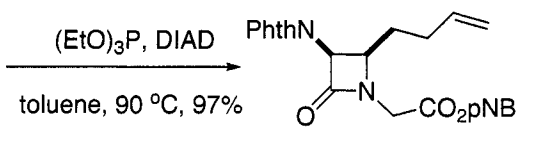
163



164

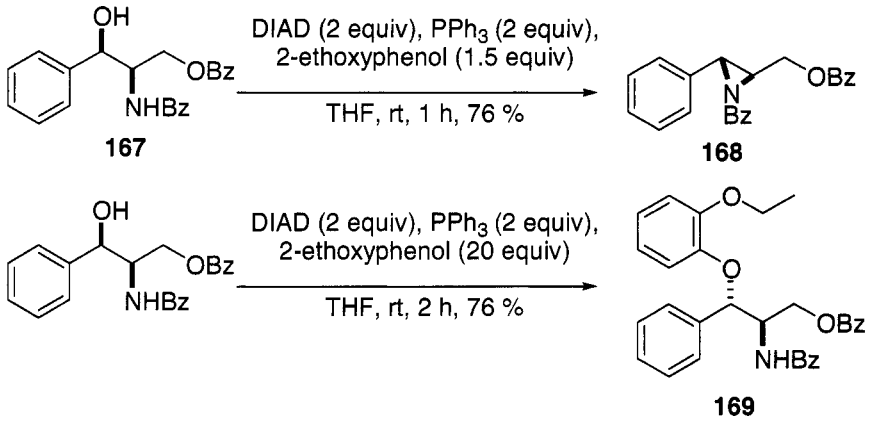


165



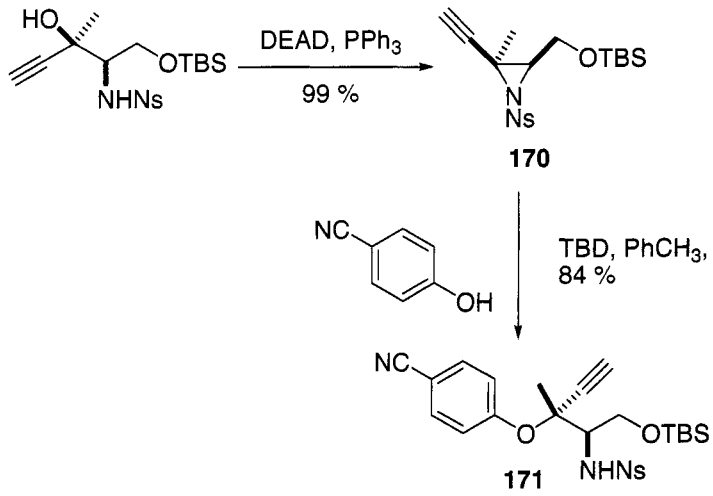
166

The Mitsunobu reaction has been extensively used for the formation of aziridines. Recently, Cossy *et al.* were interested in inverting the benzylic hydroxyl group in **167** to prepare a precursor of (*S,S*)-reboxetine.[179] At low concentrations of 2-ethoxyphenol (1.5 equiv), the aziridine **168** was formed instead of the desired inverted phenol derivative **169**. Increasing the concentration of 2-ethoxyphenol to 20 equiv led to the formation of the desired phenol ether in good yield. The Mitsunobu reaction has also been used for the preparation of amino acid derived aziridines; these compounds can then be used for the synthesis of pseudopeptides.[180]



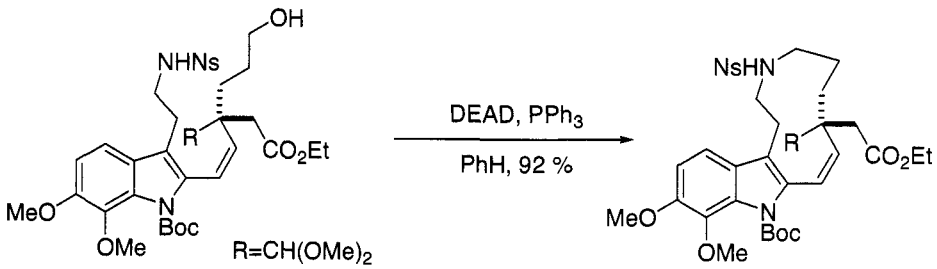
167 **168** **169**

Joullié's group developed a regio- and stereo-selective approach to prepare highly substituted aziridines like **170**.[181] Subsequent ring opening provided a variety of chiral phenoxy substituted quaternary ethers (e.g., **171**). The nucleophilic opening of the aziridines proceeds with thiols as well.



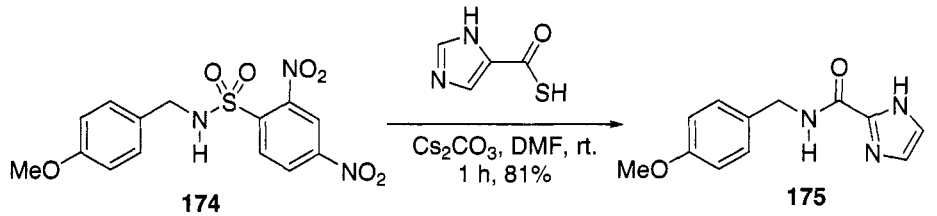
170 **171**

One of the most useful activated amine variants was developed by Fukuyama and coworkers.[182] The nitrosulfonamides shown below are easy to prepare and can be removed under relatively mild conditions (PhSH, K_2CO_3, DMF, rt). Fukuyama's group has used the sulfonamide protected amines in Mitsunobu reactions to prepare precursors for several alkaloid total syntheses. One very nice intramolecular application can be seen in the Fukuyama synthesis towards (–)-apsidophytine (**172** to **173**).[183] A number of additional examples employing similar ring-formation strategies to prepare medium and large rings can be found in recent syntheses of (–)-ephedranine,[184] (–)-tabersonine,[185] FR900482,[186] kainic acid (intermolecular),[187] (–)-strychnine,[188] (+)-vinblastine,[189] and many other examples. The reaction works equally well with the 2,4-dinitrobenzenesulfonamides.[190]



172 **173**

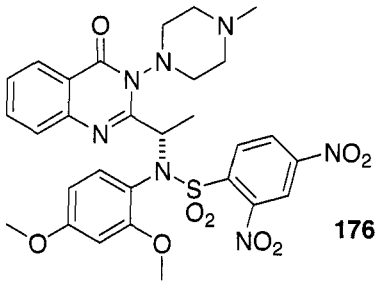
Tomkinson *et al.* developed a novel deprotection/amide formation sequence from Mitsunobu reaction products incorporating the 2,4-dinitrobenzenesulfonamide functionality.[191] Treatment of the sulfonamide derivative **174** with thiobenzoic acid or a substituted analog thereof in the presence of cesium carbonate in DMF led to the isolation of the amide product **175** in very good yields.



174 **175**

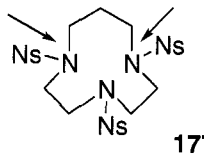
The Fukuyama variant has also been employed on solid support.[192] A particularly detailed examination of various phosphine/azadicarboxylate pairings was completed by Olsen *et al.*[193]

Additional examples of the Fukuyama–Mitsunobu variant are shown below. Lemoine *et al.* used the more activated dinitrosulfonamide amine equivalent for the Mitsunobu reaction to prepare **176**; the subsequent hydrolysis was carried out using mercaptoacetic acid.[194] Hovinen and Sillanpää found that azamacrocycles like **177** could be prepared under carefully controlled conditions.[195] In a similar context, azamacrocycle **178** was prepared in excellent yield using the tributylphopshine/DIAD pairing.[196] These conditions were better than TPP/DEAD or TBP/ADDP for this particular substrate class. The intramolecular Fukuyama–Mitsunobu reaction was of great use in the preparation of a series of heterocyclic peptidomimetics like the *D*-tryptophan-based example **179** shown below.[197]



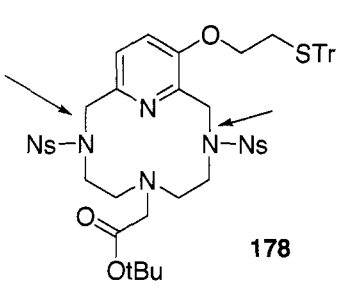
176

amine formation
PPh_3, DIAD, THF, rt
cleavage: $HSCH_2CO_2H$
Ref: Lemoine[194]



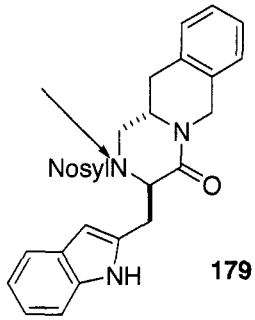
177

azamacrocycle
PPh_3, DIAD, THF, rt, 53 %
cleavage: PhSH, K_2CO_3
Ref: Hovinen[195]



178

azamacrocycle
PBu_3, DIAD, THF, rt, 93 %
cleavage: $HSCH_2CH_3$
Ref: Lemaire[196]

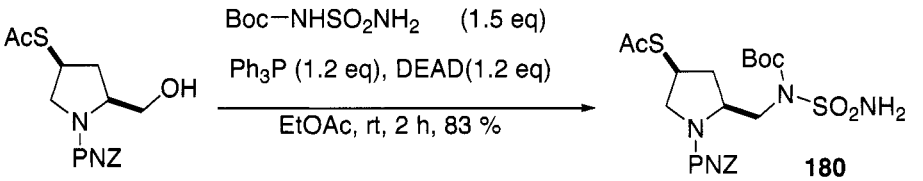


179

cyclic amine formation
PPh_3, DIAD, THF, rt
cleavage: PhSH, DBU, DMF
Ref: Goodman[197]

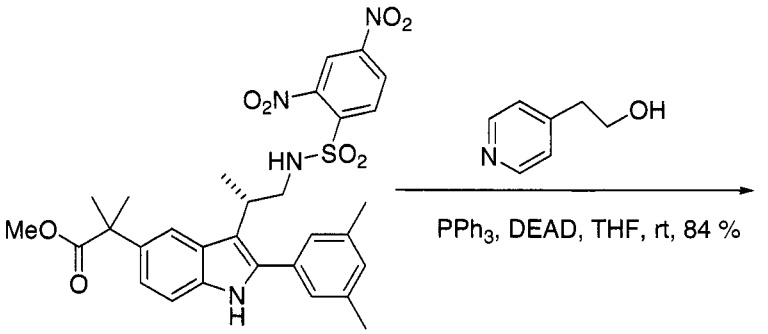
Activated amines have been employed in a number of larger scale applications. The first such example is drawn from a 50 kg synthesis of the

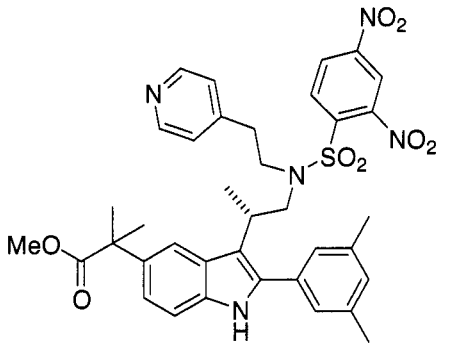
2-aminomethylpyrrolidin-4-ylthio-containing sidechain of the carbapenem antibiotic Doripenem.[198] This synthesis, which went through a number of experimental modifications, produced the desired Mitsunobu product **180** in 83% yield after recrystallisation. The DIAD was added dropwise as an EtOAc solution to a stirred mixture of the remaining reaction ingredients at room temperature. A 1000 L reactor was used during this process.



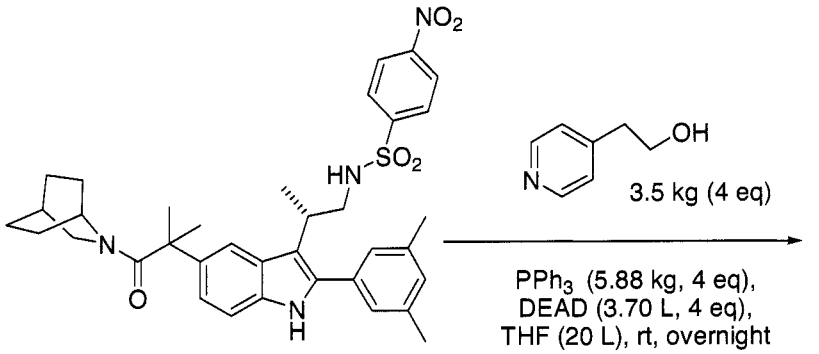
50 kg scale

During an exploration of practical syntheses of a GnRH antagonist, Farr *et al.* examined two key substrates for the Mitsunobu reaction.[199] Both reactions were carried out at kilo-scale. Typically, four equivalents of the pyridyl ethanol **181** were required to drive the reaction to completion. Since the dinitrosulfonamide product **182** proved to be labile during the hydrolysis of the methyl ester, further exploratory work was carried out with the p-nitrosulfonamide **183**. The nosyl group of the crude reaction product **184** was removed with thioglycolic acid. After an aqueous workup, the desired product **185** was obtained in 58% yield over three steps after recrystallisation from ethyl acetate. Eventually, this route was abandoned due to supply issues with the pyridyl ethanol and byproduct removal issues arising from the Mitsunobu reaction and the nosyl deprotection.



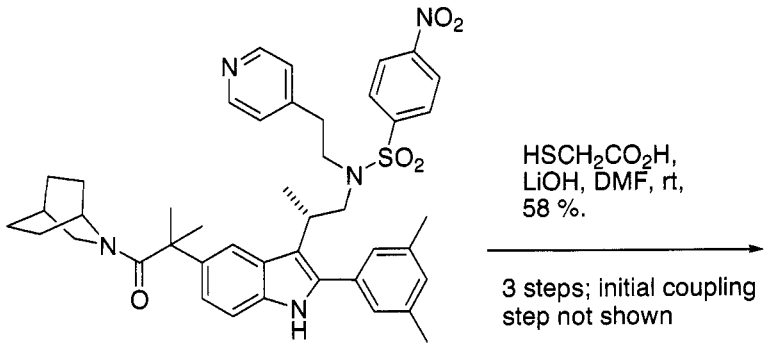


182

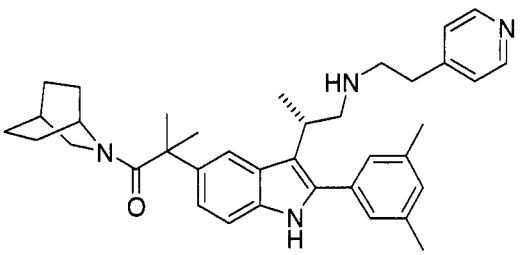


3.6 kg (5.61 mol)

183

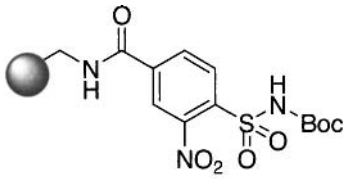


184

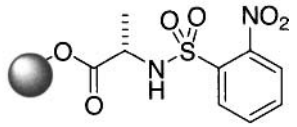


185

Activated amines tethered to solid supports have found ready application in the preparation of primary amines or Boc-protected amines. These approaches usually rely on doubly activated amines or a Fukuyama style approach. The figure below lists two amine synthesis precursors (**186, 187**); after Mitsunobu reaction, appropriate deprotection conditions yield the desired amines.[200,201] Additional examples for the synthesis of Fmoc-*N*-methyl amino acids are also known.[202]



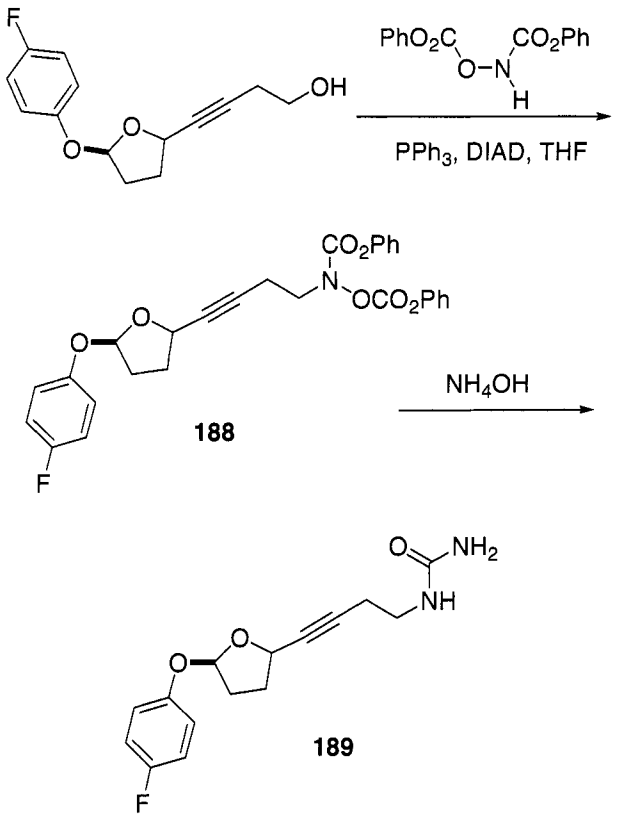
186



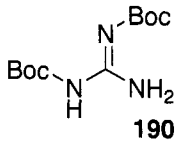
187

Activated hydroxylamines react as able nucleophilic partners in the Mitsunobu reaction to provide key intermediates for further elaboration. The 5-lipooxygenase inhibitor CMI-977 was prepared using two sequential Mitsunobu reactions.[203] After initial coupling of 4-fluorophenol to the lactone fragment, the homopropargyl alcohol was installed; this intermediate, upon reaction with the phenoxycarbonyl activated hydroxylamine equivalent gave intermediate **188**, which upon further reaction with ammonium hydroxide provided CMI-977 (**189**) in good yield.

Knight and Leese examined a number of bis-protected, activated hydroxylamine equivalents.[204] Useful protecting groups were: Z, alloc, troc, and teoc. Hydroxylamine equivalents incorporating two different protecting groups were also examined. All of these compounds underwent Mitsunobu reactions with simple alcohols to provide the alkylated adducts in 30–80% yield, with the lower yields arising from reaction with cyclohexanol.

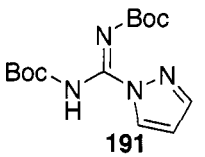


In addition to the activated amine species listed above, a multitude of less frequently used substituted, activated amines can introduce interesting nitrogen molecular fragments into drug candidates or natural products. The figure below shows a number of recent examples. Of particular note are the bis-protected guanidines **190** which preferentially react on the secondary amine.[205] The imidazole substituted guanidine **191** provides reactive intermediates subject to addition of a nucleophile to the imide nitrogen.[206] Benzotriazine-4-one **192** is another less commonly used activated nitrogen compound.[207] 3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one **193** is another rarely used Mitsunobu coupling partner.[208] Yields of this heterocycle in the Mitsunobu reaction tend to be low using the standard TPP/DEAD protocol. Imidazoles (**194**) can be alkylated with primary and secondary alcohols under modified Mitsunobu reaction conditions using tributylphosphine and TMAD or tributylphosphine/CMBP; the more traditional TPP/DEAD or TBP/ADDP conditions work in some cases, but usually with lower yields.[209]



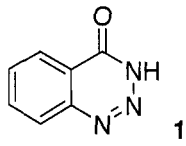
190

Ph_3P, DEAD, THF
Ref: Kozikowski[205]



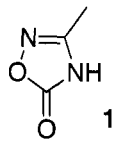
191

Ph_3P, DEAD, THF
Ref: Ogbu[206]



192

Ph_3P, DIAD,THF,
0 °C-->rt, 88 %
Ref: Casara[207]



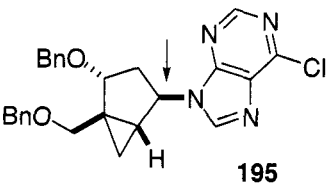
193

Ph_3P, DEAD, THF
30 %
Ref: Moormann[208]

194

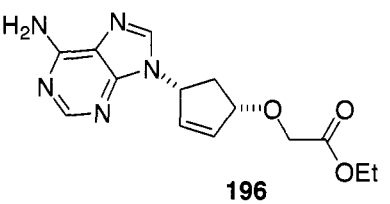
Bu_3P, TMAD
(10 eq each),
PhH, 0 °C--> 60°C
75-94 %
Ref: Kim[209]

A special subclass of amine formation reaction is the coupling of alcohols with purines to form nucleoside derivatives.[210] The application of the Mitsunobu reaction in this context is sufficiently expansive to warrant a mini-review in its own right, but due to space constraints only a limited number of recent examples are shown below (**195 – 198**).[211–214] The reader is referred to the references for additional information. Additional examples using N^3-benzoylthymine,[215] adenine,[216] deazapurine,[217] 6-azauracil, [218] and 3-benzoyluracil[219] have been reported in the literature as well. The preparation of racemic isonucleosides via the Mitsunobu reaction is also known. [220]



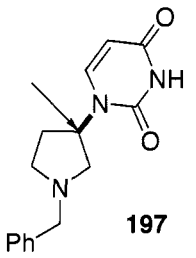
195

6-chloropurine
Ph_3P, DEAD, THF
Ref: Marquez[211]



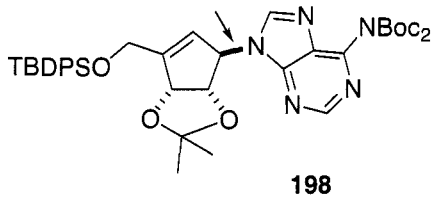
196

adenine
Ph_3P, DEAD,
THF,13 %
Ref: Levy[212]



197

uracil (benzoyl protected)
Ph_3P, DIAD, dioxane, reflux, 30 %
Ref: Brandi[213]

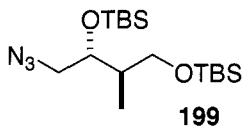


198

N^6-bisBoc-adenine,
PPh_3, DIAD
THF, 0 °C-->rt, 74-98 %
Ref: Strazewski[214]

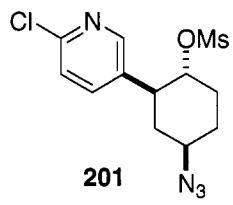
Appliactions: Alcohol into amine conversion via azides

Amines can be preapred via the Mitsunobu reaction by displacing the activated phosphonium intermediate with an azide species; subsequent reduction then provides the desired amine. The initially used toxic hydrazoic acid has been replaced by lithium or zinc azide.[221] In some cases, Shiori's reagent, diphenylphosphoryl azide (DPPA), can also be used as an azide source (see **199** and **200**). The table below lists a number of additional examples. During the preparation of the epatidine intermediate **201,** a small amount of elimination product arising from elimination of the activated axial alcohol was typically observed under the hydrazoic acid reaction conditions.[223] Wong *et al.* prepared tamiflu and phosphonate congeners thereof using the traditional Shiori's reagent approach (e.g., **202**).[226] For applications within the context of total synthesis, please see the nice Overman group total synthesis of (–)-sarain A.[227]



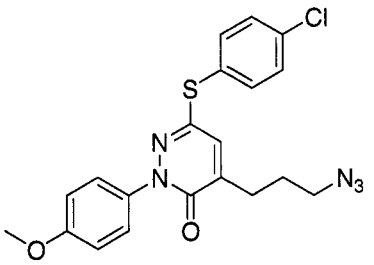
199

PPh_3, DIAD, THF
$(C_2H_5O)_2P(O)N_3$
93 %
Reference: Panek[222]

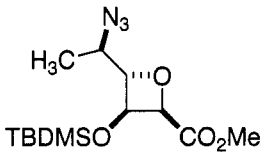


201

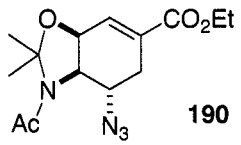
PPh_3, DEAD, THF
HN_3, 82 %
Ref: Maycock[223]



$Zn(N_3)_2$ 2Py,
PPh_3,Imidazole, DEAD,
CH_2Cl_2, 0 C to rt, 98%
Ref: Ujjainwalla[224]



PPh_3, DEAD, THF
$(C_2H_5O)_2P(O)N_3$
91%
Reference: Fleet[225]

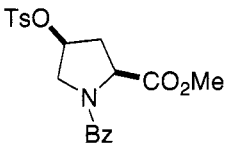


190

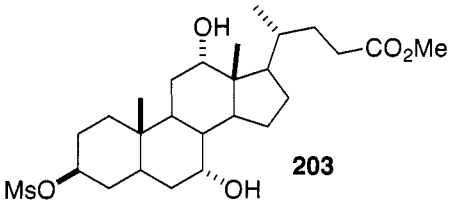
PPh_3, DIAD, THF
$(C_2H_5O)_2P(O)N_3$
Reference: Wong[226]

Applications: alcohol into sulfide conversion

The Mitsunobu reaction has found utility in the conversion of alcohols into the corresponding thioacetates and other sulfide derivatives. Methanesulfonic acid or toluenesulfonic acid produce the corresponding mesylate or tosylate derivates in good yield; these intermediates can then be displaced with other nucleophiles to produce new products with an overall retention of stereochemistry in the case of secondary alcohols.[228] The less acidic aliphatic thiols can be converted into the corresponding alkylthioethers by using TPP/ADDP and an equivalent amount of imidazole. Some examples of sulfides obtained from the Mitsunobu reaction are shown in the figures below. Of particular note is the preparation of compound **203**.[230] The Mitsunobu reaction selectively occurs at the C7-hydroxyl group. Zhao *et al.* carried out the sulfide alkylation of commercially available 2,3-*O*-isopropylidene-β-*D*-ribofuranoside and the fully protected homocystine with triethylphosphine in pyridine to give **204**.[235] Yields of the sulfides obtained in this manner ranged from 50–70%. In a different sulfur bond formation, Ishikawa *et al.* coupled a protected serine derivative with 1-thio-*N*-acetylglucosamine to prepare **205** using TBP and ADDP.[236] Chromene derivative **206** was prepared by the selective reaction of the benzylic alcohol of 4-(4-hydroxymethylphenyl)butan-1-ol in 46% yield using the standard Mitsunobu reaction.[237] One of the most interesting uses of the Mitsunobu reaction has been the installation of a thioacetate during total syntheses of racemic calicheamicinone by the Magnus and Clive groups respectively.[238, 239] The Magnus intermediate **207** shown below was obtained in 68% yield, whereas Clive *et al.* reported an even better yield of 94% for a closely related compound.

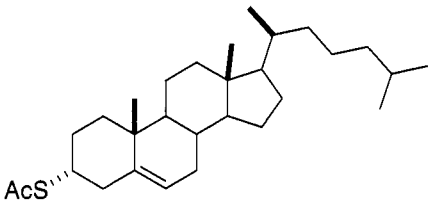


p-TolSO$_3$H, PPh$_3$,
DIAD,
PhH, 82 %
Ref: Anderson[229]

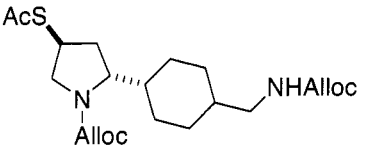


203

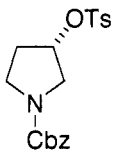
MeSO$_3$H,
PPh$_3$, DEAD,
THF, 90 %
Ref:Davis[230]



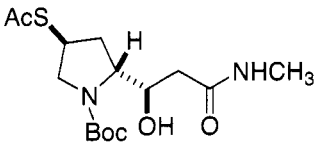
AcSH,
PPh$_3$, DIAD,
THF, 0 °C, 94 %
Ref:Volante[231]



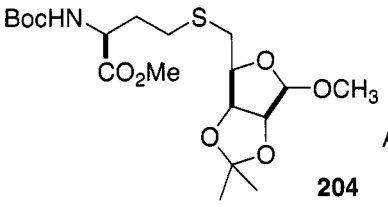
AcSH, PPh$_3$, DIAD
THF, 0 °C
Ref: Imamura[232]



Zn(OTs)$_2$,
PPh$_3$, DEAD,
PhH, rt, 60 %
Ref:Cardillo[233]

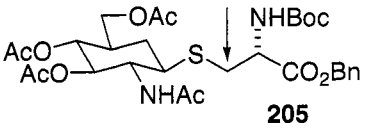


AcSH, PPh$_3$, DIAD
THF, - 20 °C
Ref: Armstrong[234]



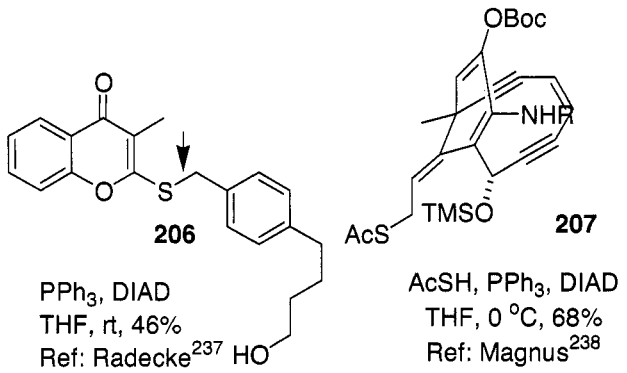
204

homocystine
PEt$_3$, pyridine, rt,
3 d, 50–70%
Ref Zhao[235]

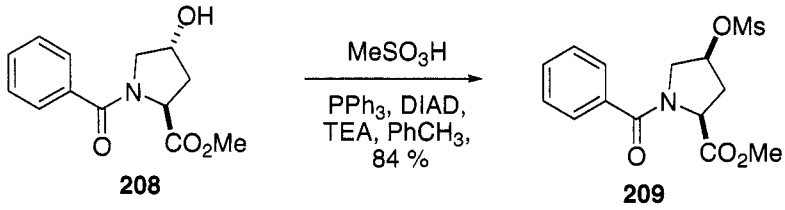


205

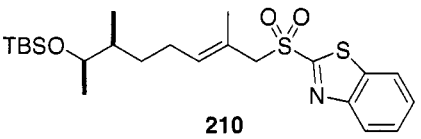
serine derivative, PBu$_3$, ADDP
THF, rt, 53%
Ref: Ichikawa[236]



A larger scale application of an alcohol into sulfide conversion was carried out by Anderson *et al.*[229] In their synthesis of an intermediate for the preparation of the ACE inhibitor Fosinopril, the trans-hydroxyproline derivative **208** was converted into the corresponding cis-mesylate derivative **209** in 84% yield. This reaction can be carried out on kilogram-scale. The TPPO and DIAD urea byproducts are usually filtered off after precipitation.

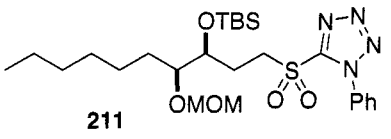


More recently, the Mitsunobu reaction has been used as part of a two-step process to prepare precursors for the Julia–Kocienski olefination reaction. In this context, a primary or secondary alcohol is treated with thiobenzimidazole or another equivalent sulfur source to provide a sulfide intermediate which is then oxidized using MOOPh (ammonium heptamolybdate) to provide the sulfone precursor for the Julia–Kocienski reaction. The following figure lists olefination precursors **210** through **213**, which were prepared following the two-step protocol mentioned above.[240–243] Information about the final target, if known, is also provided.



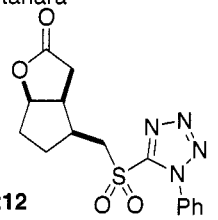
210

2-Mercaptobenzothiazole,
PPh_3, DIAD, THF, 98 %.
then: $(NH_4)_6Mo_7O_{24}$ (87 %)
Target: Cineromycin B
Ref: Kitahara[240]



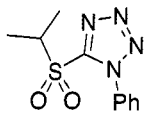
211

1-phenyl-1H-tetrazol-5-yl sulfide,
PPh_3, DIAD, THF, 98 %.
then: $(NH_4)_6Mo_7O_{24}$, followed by
TBS protection (91 % , 3 steps)
Target: microcarpalide
Ref: Ishigami[241]



212

1-phenyl-1H-tetrazol-5-yl sulfide,
PPh_3, DEAD, PhMe, 96 %.
then: $(NH_4)_6Mo_7O_{24}$ (90 %)
Target: 14-A_{4t}-Neuroprostane
Ref: Vidari[242]



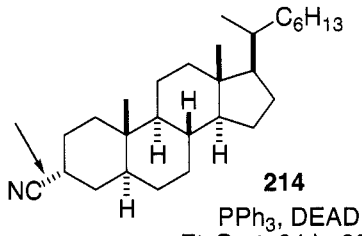
213

1-phenyl-1H-tetrazol-5-yl sulfide,
PPh_3, DEAD, THF, 81%.
then: oxone (85 %)
Target: (-)-spirotryprostatin B
Ref: Carreira[243]

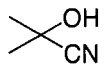
In a newer application of the Mitsunobu reaction in carbohydrate chemistry, Falconer *et al.* prepared glycosyl disulfides from a variety of glycosyl sulfides.[244] This particular reaction employs only DEAD as an activating agent. TPP or an equivalent thereof was not needed in this reaction.

Applications: Carbon–carbon bond formation

Carbon–carbon bond formations are possible using the Mitsunobu reaction. Typically, an activated, acidic carbon fragment with a pKa of less than 11 is needed. The most commonly used carbon fragments are lithium cyanide and acetone cyanohydrin. The latter method, initially developed by Wilk *et al.*, has been used most frequently. While simple alkyl alcohols gave acceptable results with the standard Mitsunobu reaction protocols, much better results were obtained for secondary alcohols and other more sterically demanding alcohols by using the TMAD/TBP or CMBP approaches pioneered by Tsunoda's group. Example **214** compares the different approaches on a steroid skelton.

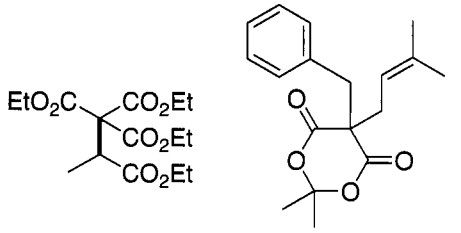


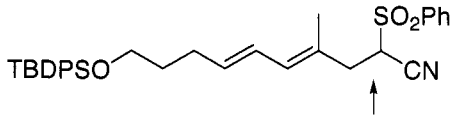
214



PPh_3, DEAD
Et_2O, rt, 24 h, 23%.
TMAD, PBu_3,
PhH, rt, 24 h, 6%
CMMP,
DME, 100 °C, 48 h, 73%

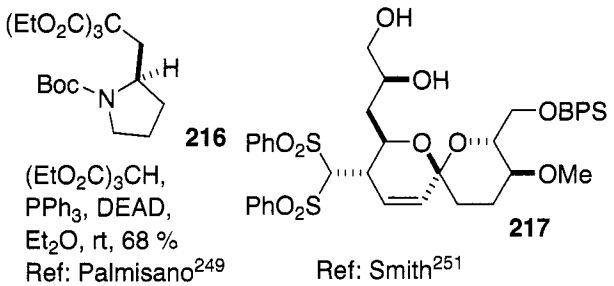
Other carbon–carbon bond formation reactions using the Mitsunobu reagents are very rare. Some isolated examples employing Meldrum's acid or derivatives thereof and triethylmethanetricarboxylate are shown below.[246,247] Falck *et al.* used phenylsulfonyl–acetonitrile to prepare **215** in their synthesis of curacin A.[248] An example (**216**) incorporating triethyl methanetricarboxylate from Palmisano's group is shown as well.[249] Additional examples for the reaction of simpler alcohols can be found in the earlier publication by the same group.[250] Bis(phenylsulfonyl)methane, a sufficiently activated methyl derivative that undergoes the Mitsunobu reaction, is equivalent to a methyl group if the sulfonyl substituents are subsequently removed. During the construction of the C1–C25 fragment of the spirastrellolides, Smith and Kim employed such a strategy to stereoselectively introduce a methyl group into compound **217**.[251] The yield for the combined Mitsunobu/reduction sequence was 65%.



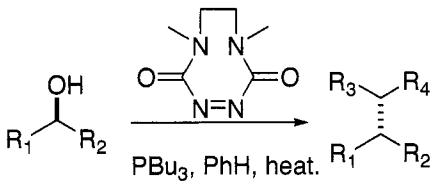


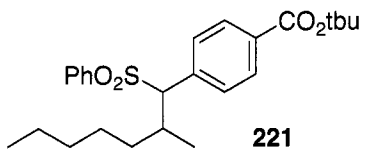
PPh_3, ADDP, PhH
87 %
Ref: Falck[248]

215



More recently, Tsunoda's group has extended their work on modified Mitsunobu reagents to include reagent combinations that allow for the use of less activated carbon nucleophiles.[252] A combination of tributylphosphine and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) proved to be successful for the reaction of malonates (**218**) and sulfone substituted methanes (**219**, **220**) (*vide infra*). As expected, the sulfones can be reductively removed with samarium iodide or other equivalent reagents to allow for entry into other functional groups. Additional applications employing TMAD/TBP and the CMBP or CMMP reagent were also developed. Use of the latter reagents allows use of arylmethylsulfones as reaction partners in the Mitsunobu reaction (see **221** below).[253] An application of this approach on solid-support has also been reported.[254]

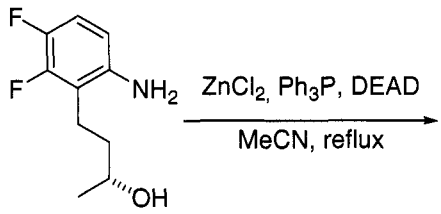




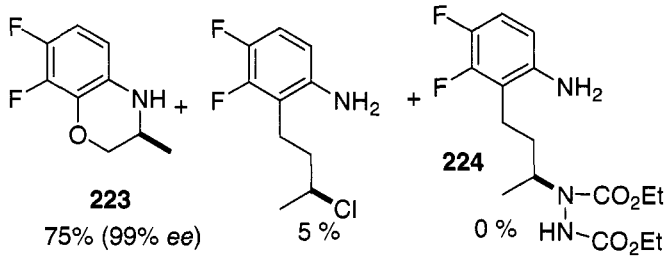
CMMP, toluene,
80 °C, 24 h, 88 %.

Applications: Halogenation

Alcohols can be converted into halides if lithium halides (F, Cl, Br, I) or MeI are used in the presence of TPP/DEAD. Kim and Kim were interested in the preparation of (*S*)-(–)-7,8-difluoro-3,4-dihydro-3-methyl-2*H*-1,4-benzoaxine (**223**), a key intermediate for the synthesis of the commercially available quinolone antibiotic levofloxacin. Initial attempts to cyclize **222** under the standard Mitsunobu conditions employing the TTP/DEAD conditions failed to give acceptable yields even when the reaction was refluxed for 1 h in benzene or acetonitrile. Addition of several equivalents of zinc chloride gave the desired cyclized product, some chlorinated intermediate, and none of the DEAD adduct **224**. The DEAD adduct was the major product under the standard Mitsunobu conditions. The stereochemistry of the obtained products, which indicates retention of stereochemistry, suggests that the reaction proceeded via a chloride intermediate.

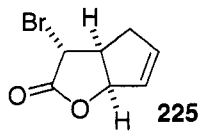


222



223 75% (99% *ee*) 5 % **224** 0 %

The preparation of bromide **225** was accomplished in 60% yield by Aggarwal *et al.*[256]



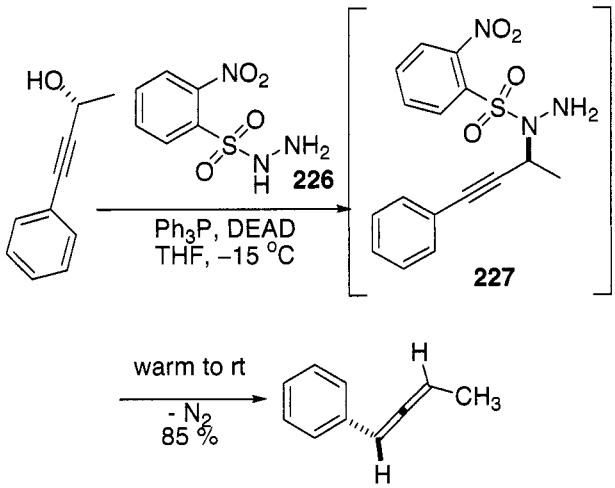
225

$ZnBr_2$, PPh_3, DEAD, 60%. Ref: Aggarwal[256]

6.3.5. Miscelaneous Synthetic Utility

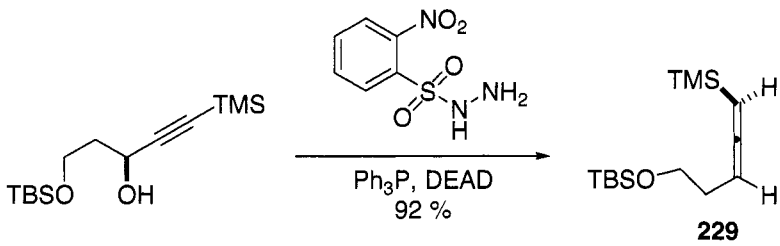
Allene synthesis

Myers and coworkers have developed a concise approach to stereospecifically convert propargyl alcohols into the corresponding allenes.[257] This approach employs 2-nitrobenzenesulfonylhydrazine **226** to react with the propargyl alcohol via the more acidic secondary nitrogen of the hydrazine to provide the reactive intermediate **227**. Upon warming to room temperature, the intermediate rearranges to the corresponding allene **228** with concomitant loss of nitrogen and arylsulfinic acid. A detailed procedure for the synthesis of (*tert*-butyldimethylsilyl)allene has been reported by Myers and Zheng.[258]



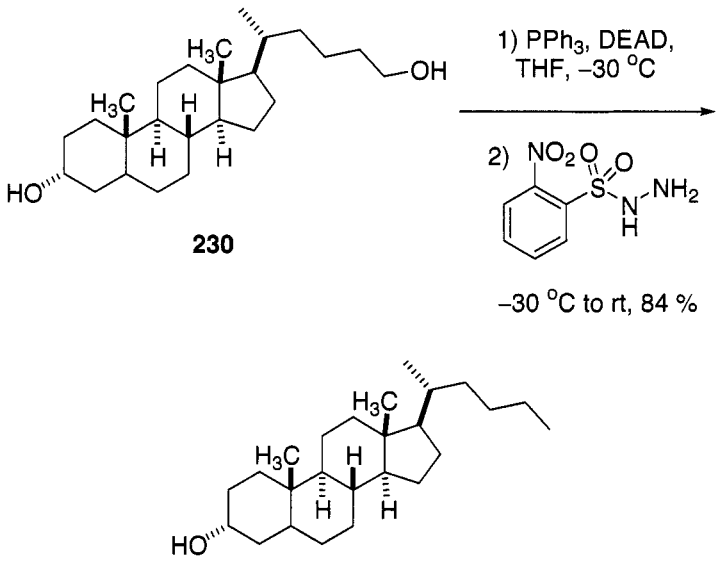
228

Carreira and Shepard have employed the Myers allene synthesis to prepare silyl substituted allenes **229** in greater than 90% yield as precursors for the stereoselective synthesis of exo-methylenecyclobutanes.[259]



229

Myers *et al.* have developed a variation of this protocol to reductively deoxygenate alcohols.[260,261] The premise of this approach relies on the efficient Mitsunobu reaction of an alcohol with *o*-nitrobenzenesulfonylhydrazine at –30 °C to make an intermediate hydrazine derivative; upon warming to room temperature, an *in situ* elimination of *o*-nitrobenzenesulfinic acid occurs to produce an unstable monoalkyl diazene, which further decomposes with loss of dinitrogen to give the desired deoxygenated product via a radical mechanism. As expected, alcohols with proximal cyclopropanes or appropriately situated double bonds undergo radical mediated ring-opening or cyclisation reactions during the attempted deoxygenation. Sterically hindered alcohols frequently do not undergo the Mitsunobu reaction under this protocol and therefore can't be reduced. A steroid based example led to the selective reduction of the primary alcohol of **230** to give **231** in 84% yield. Additional examples are given in the original paper.

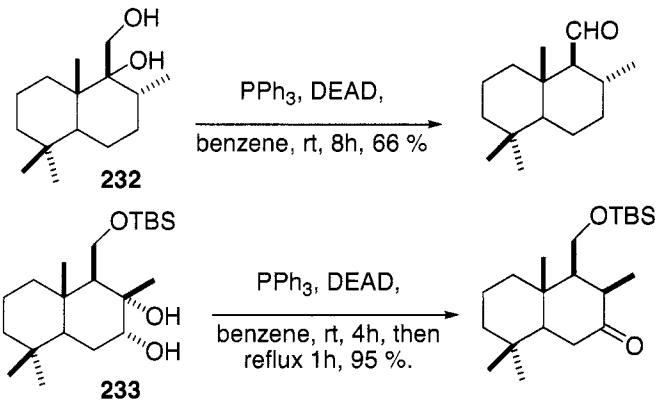


230

231

Unusual diol reactions

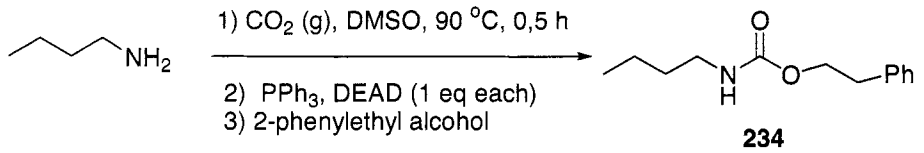
Acyclic and cyclic-*trans*-vicinal diols undergo Mitsunobu reactions to yield epoxides. A notable exception to this observation is seen with a vicinal diol pairing of a primary or secondary alcohol and a tertiary alcohol. In such an instance, the diol is converted into the corresponding aldehyde or ketone as shown below for examples **232** and **233**.[262]



Carbonates and Carbamates

Dialkyl carbonates can be prepared from alcohols and TPP/DEAD in the presence of gaseous carbon dioxide.[263] A carbon dioxide saturated solution of the alcohol is treated with TTP and DEAD before another equivalent of the same or another alcohol is added. The method is useful for the preparation of symmetric and unsymmetrical carbonates in 75–95% yield. The procedure works for the preparation of dithiocarbamates as well if an amine is initially reacted with carbon disulfide instead.[264]

The Mitsunobu reaction can be used in the preparation of carbamate esters as well (e.g., **234**).[265] The reaction proceeds via an in-situ carboxylation of an alkylamine with CO_2, followed by an *O*-alkylation with an alcohol in the presence of TPP/DEAD. Yields are typically in the 80–90% range. A solid-supported version in which Fmoc-(*L*)-phenylalanine is tethered to Wang resin via an ester has also been reported.[266] *In situ* deprotection with a tertiary amine to yield an *O*-ammonium carbamate intermediate in the presence of primary aliphatic alcohols and PBu_3/ADDP leads to the formation of the corresponding carbamates; the carbamates are typically obtained in 40–80% yield with variable purity after TFA cleavage from the resin.

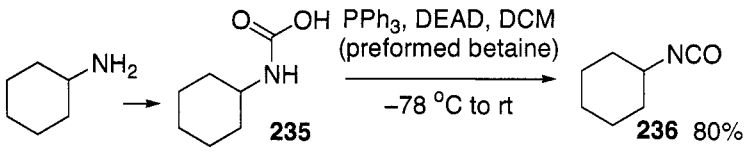


234

Isocyanates

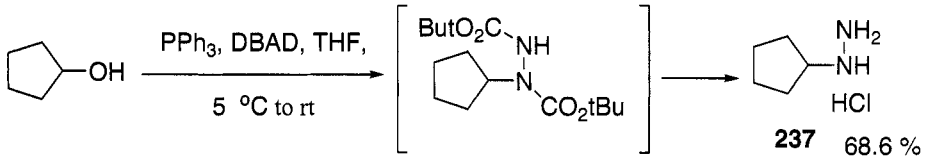
Isocyanates were prepared by reacting primary aliphatic amines or hindered aromatic amines with carbon dioxide gas at –10 °C in dichloromethane.[267]

The resulting carbamate salts **235** were then reacted with a freshly prepared solution of the activated betaine of TPP or TBP and DIAD to provide the isocyanates **236**. After completion of the reaction, as monitored by the IR stretch of the isocyanate, the desired products were obtained by fractional distillation or flash chromatography. Aniline, benzylamine and 2,6-diisopropylaniline gave no or very poor yields of the desired isocyanates under these reaction conditions. The poor yields in these reactions are due to formation of nonreactive intermediate carbamoylhydrazines or competing triazolinone formation; the latter arises from reaction of an activated arylisocyanate and the Mitsunobu betaine.



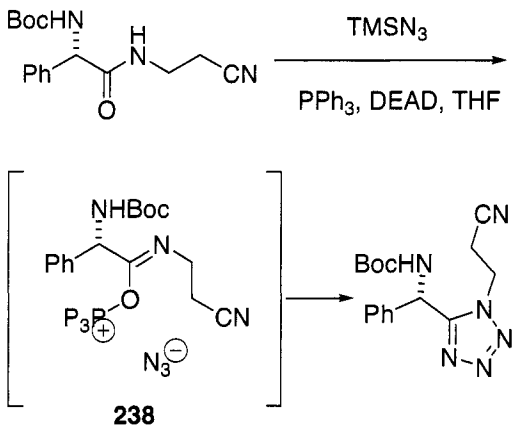
Hydrazines

The direct preparation of hydrazine derivatives is possible on kilogram scale as illustrated for the synthesis of cyclopentyl hydrazine hydrochloride (**237**).[268] After reaction of cyclopentanol with TPP and DBAD, the reaction intermediate obtained was hydrolysed to the hydrochloride salt in situ employing 6 N HCl.



Tetrazole syntheses

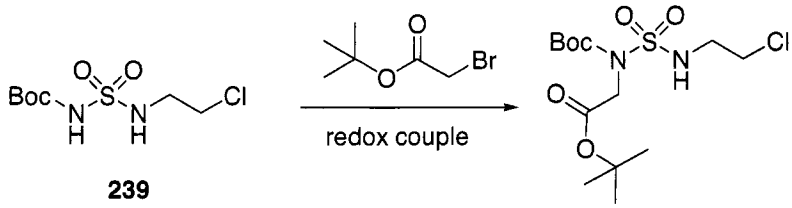
The Mitsunobu reaction has also been employed for the synthesis of substituted tetrazoles.[269] The reaction proceeds via a cyano compound in the presence of trimethylsilyl azide and the DEAD/TTP couple. The activated phosphonium intermediate **238** is thought to react with the azide to give the desired tetrazole derivative. The ethylcyano sidechain on the tetrazole can be removed with 2 N NaOH in THF.[270] This reaction has found application in the preparation of tetrazole based growth hormone sccretagogues.[271]



238

TPP/DIAD as a mild base

Montero *et al.* employed the TPP/DIAD and TBP/ADDP redox couples to prepare the Mitsunobu betaine as a base under mild conditions.[272] Deprotonation of the doubly activated sulfonamide **239** then produced the reactive anion that was alkylated in situ by a variety of alkyl bromides (benzyl, allyl, α-acetobromoglucose, *etc.*). Attempts to prepare the alkylated products via more traditional mineral base conditions using sodium or potassium carbonate gave much inferior yields of around 10%. The TBP/ADDP couple, as shown below, gave better yields in the alkylation chemistry; generally, the modest alkylation yields are around 40–60%.



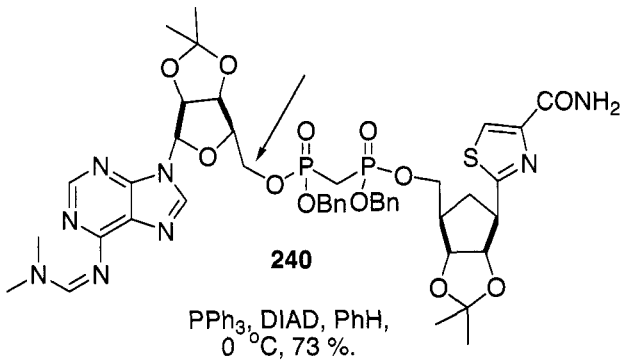
239

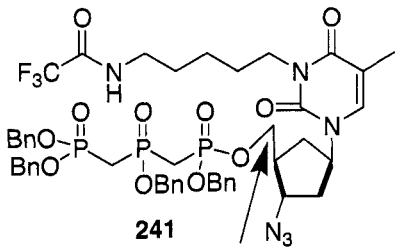
PPh_3, DIAD: 37 %
PBu_3, ADDP: 60 %

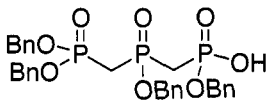
Phosphonate Esters

Phosphonate esters can be readily prepared from alcohols and phosphonic acid derivatives. The selective phosphorylation of the 5′-hydroxy groups of thymidine and uridine was originally reported Mitsunobu's group in 1969.[273] More recent examples include the modified derivative of the antitumor *C*-nucleoside tiazofurin (**240**) and an AZT triphosphate analog (**241**) shown below.[274,275] Ciufolini and coworkers employed a Mitsunobu inversion to

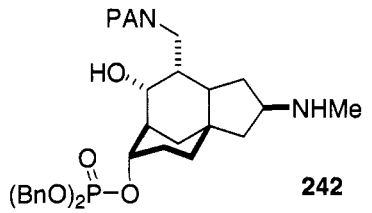
install a phosphonate ester moiety during the preparation of an advanced intermediate (**242**) for the total synthesis of FR901483.[276] This approach took advantage of earlier work in this area by Sorenson's group.







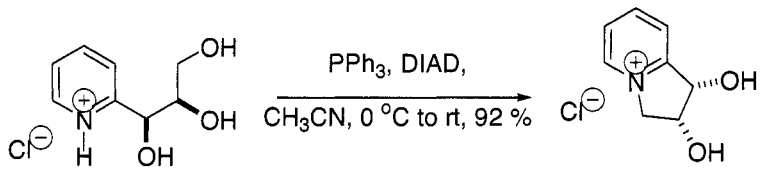
PPh_3, DIAD, 47 %.



$(BnO)_2P$-OH
$(4\text{-Cl-Ph})_3P$, DIAD,THF,
followed by CBz protection to
purify

Pyridinium Ion Reactions

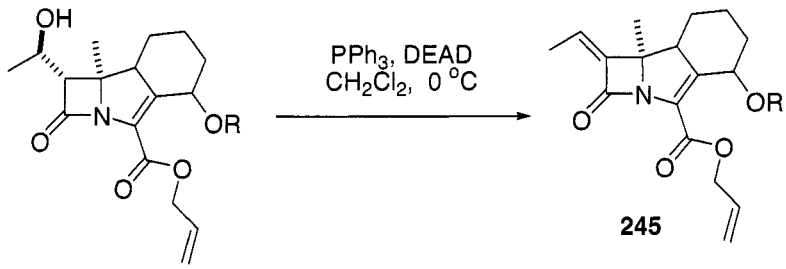
In an unusual application of the Mitsunobu reaction, the chiral pyridinium compound **243** was selectively cyclised to **244**, an advanced intermediate in the synthesis of 1-*epi*-*L*-entiginosine.[278] A similar approach has been used for the alkylation of pyridines and imidazoles to prepare the corresponding salts.[279]



243 **244**

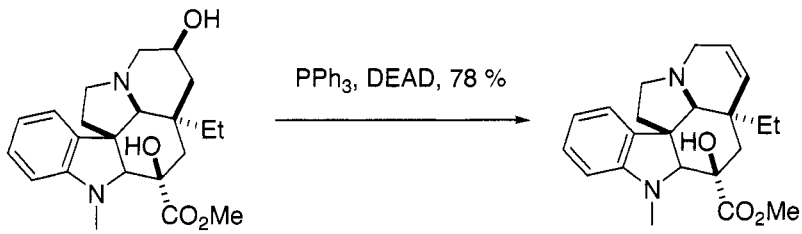
Dehydration Reaction

The Mitsunobu reaction can be employed as a dehydration method. In a synthetic approach towards broad-spectrum β-lactamase inhibitors of the trinem class, the Mitsunobu reaction was utilised to introduce an exocyclic double bond (**245**).[280] Other traditional dehydration methods did not work for this particular substrate.



245

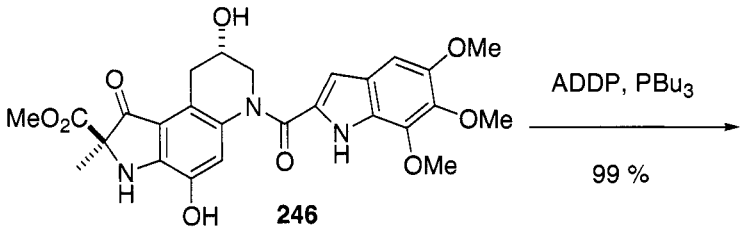
Boger *et al.* used the Mitsunobu reaction for the difficult elimination of a secondary alcohol during a recent synthesis of (–)-vindoline and related alkaloids.[281]

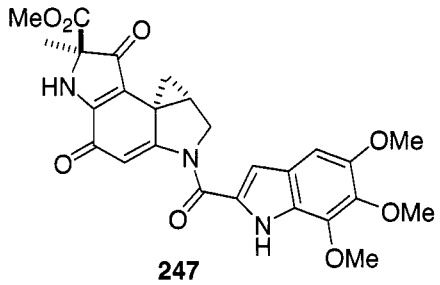


Neigboring-group participation

Neighboring group participation in Mitsunobu reactions occurs frequently if intermediate aziridinium or episulfonium cations can be formed. During such a process, subsequent attack by the nucleophile can lead to changes in ring size or products with retention instead of inversion at chiral alcohol centers.

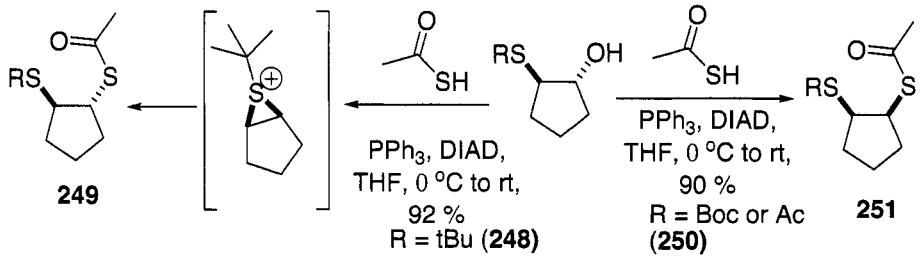
The total synthesis of (–)-duocarmycin and related compounds has made excellent use of neighboring group participation by a nitrogen.[283] Thus, treatment of **246** with tributylphosphine and ADDP gave the ring contracted compound **247** in 99% yield.





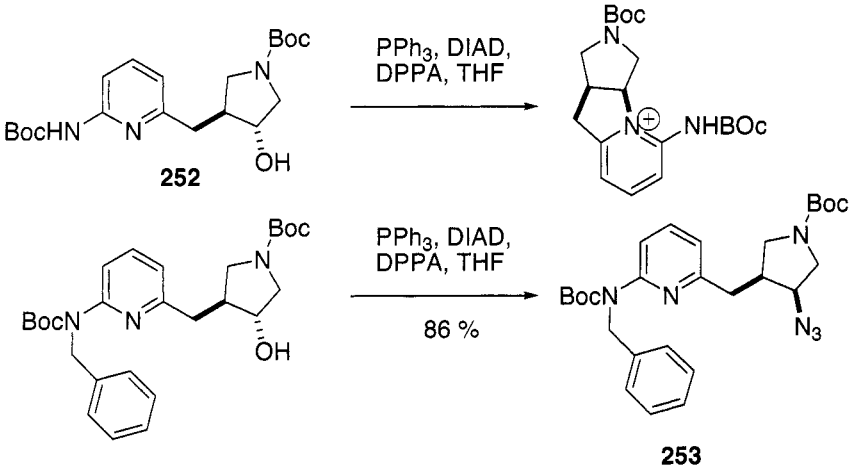
Other reports of intermediate aziridinium ions in Mitsunobu reactions have sporadically appeared in the literature. For additional examples, the reader is referred to the cited references.[284]

In a much simpler system, the outcome of a thioacetate Mitsunobu on a series of hydroxythiol derivatives depended on the nucleophilicity of the neighboring thiol group.[285] Thus, the *tert*-butylthiol compound **248** gave the trans compound **249** via an intermediate episulfonium ion, whereas the corresponding Boc or acetyl protected thiols **250** gave the desired cis derivatives **251**.



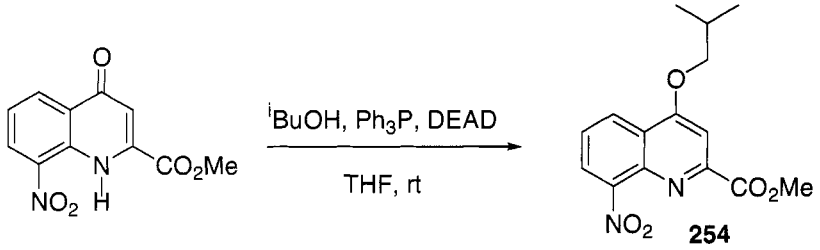
Silverman *et al.* found that the nitrogen protection groups played an important part in determining the nucleophilicity of a pyridine nitrogen.[286] In

an attempted reaction of bisboc protected pyridine **252** under the standard Mitsunobu reaction conditions for the azide introduction with DPPA, a cyclised pyridinium product was observed instead. Additional protection of the external nitrogen as the bisboc, dimethylpyrrole, etc. gave the actual desired azide substitution product **253**.



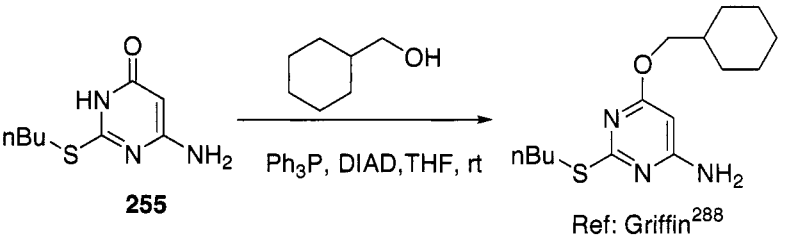
Ambident reactions

In some reactions, there may be more than one possible reaction site. Typical Mitsunobu reaction partners in such reactions include pyridones, sulfahydantoins, etc. A few examples are shown below. Quinoline **254** was prepared from the corresponding pyridone in good yield; reduction of the nitro group to the aniline was followed by condensation with another quinoline derivative to prepare quinoline based oligomers that form helical frameworks.[288]



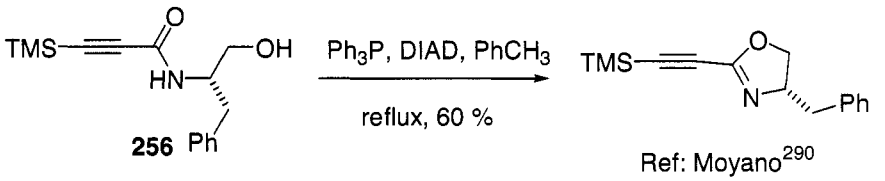
Additional examples of ambident Mitsunobu reaction partners are shown in the figure below. Pyridones (**255**) frequently alkylate at the oxygen position.[288] In related work, Font, Heras, and Villagordo prepared substituted pyridones as key intermediates for the preparation of pyrimidinyl aryl glycenes.[289] 2-Alkynyl-1,3-oxazolines were prepared from **256** following a

standard protocol for the preparation of chiral oxazoline ligands; these particular oxazolines were desired for some Pauson–Khand chemistry.[290] In phosphoramidite **257**, the O^6 position of the deoxyguanosine was selectively protected as the *p*-nitrophenethyl ether.[291] Sulfahydantoins (**258**) are preferentially alkylated on the amide oxygen instead of the more acidic sulfonamide nitrogen; the observed selectivity is attributed to neighboring-group participation of the amide ketone during the reaction.[292] *N*-(2-Hydroxyethyl)-thioureas (**259**) preferentially react via the sulfur atom to prepare 2-aminothiazolines.[293]



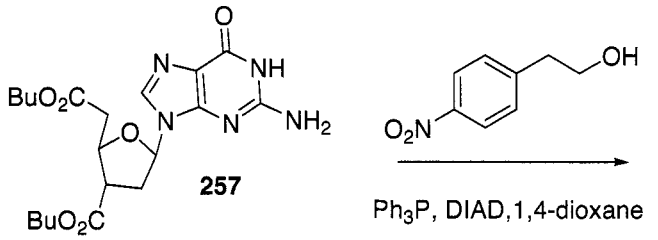
255

Ref: Griffin[288]

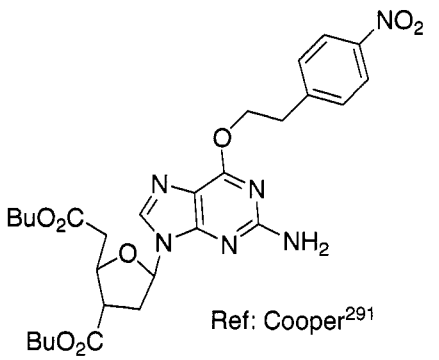


256

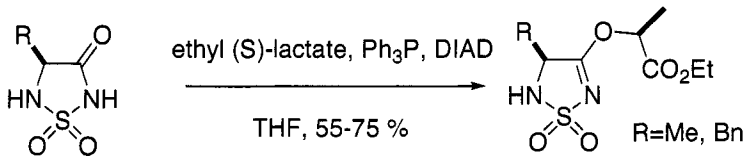
Ref: Moyano[290]



257

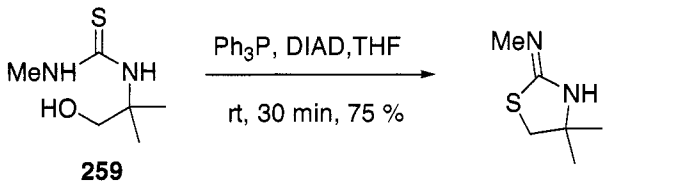


Ref: Cooper[291]



258

Ref: Toupet[292]



259

Ref: Cha[293]

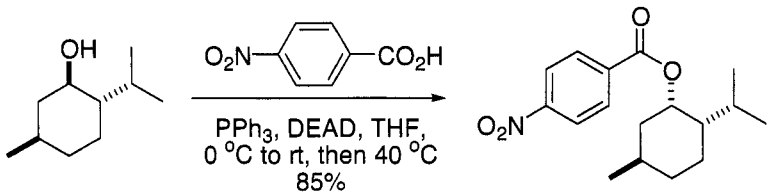
A complimentary approach to the commonly found *O*-alkylated major products in pyridone alkylations was found by Semple and coworkers in their preparation of Kappa Opioid receptor agonists.[294] In their hands, TBP and TMAD gave moderate to good yields of *N*-alkylated pyridone derivatives (**260**) as shown below. A solid supported variant of this reaction, in which the alcohol moiety was tethered to the solid support, was developed as well.

260

N vs O selectivity
typically, 85:15 to 99:1

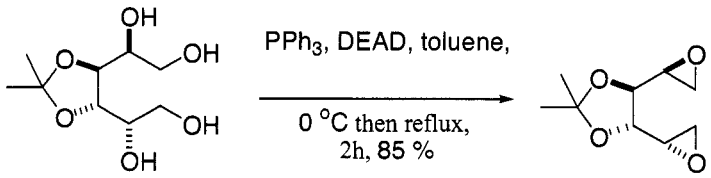
6.3.6 Experimentals

As expected, the organic synthesis literature is replete with thousands of potential experimentals. Since choosing among the many possibilities is difficult, this section will outline some of the procedures found in *Organic Syntheses*. A general procedure for the Mitsunobu inversion of sterically hindered alcohols was reported by Dodge, Nissen and Presnell.[295] This procedure is an optimised modification of the prior report by Martin and Dodge in 1991. Generally, sterically less hindered alcohols can be inverted using the same procedure, but the short segment at higher temperature can be omitted.



261

(1*S*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl-4-nitrobenzoate (**261**).
A 250 mL, three-necked, round-bottomed flask containing a magnetic stir bar is fitted with a nitrogen inlet, rubber septum and thermometer. After addition of (1*S*,2*S*,5*R*)-(–)-menthol (3.00 g, 19.2 mmol), nitrobenzoic acid (12.9 g, 77.2 mmol), triphenylphosphine (20.1 g, 76.6 mmol) and THF (150 mL, anhydrous) to the flask, the flask is immersed in an ice bath and diethylazadicarboxylate (12.1 mL, 77.0 mmol) is added dropwise at a rate such that the internal temperature of the reaction does not exceed 10 °C. Upon completion of the addition, the ice-bath is removed and the reaction is stirred at room temperature for 14 h; the reaction is then heated at 40 °C for an additional 3 h. Shorter reaction times (2–5 h) or omission of the heating segment lead to lower yields (65–75%). After cooling the reaction mixture to rt, diethyl ether (150 mL) is added, and the organic layer is washed twice with 100 mL of saturated aqueous sodium bicarbonate solution. After back-extraction of the aqueous washes with 100 mL of diethyl ether, the combined organic extracts are dried over sodium sulfate, filtered and concentrated on a rotary evaporator. Additional concentration under high vacuum (0.2 mm Hg, 30 °C, 3 h) provided a semi-rigid solid that was suspended in 40 mL of ether; after the suspension was allowed to stand overnight, hexanes (20 mL) was slowly added to precipitate out triphenylphosphine oxide. The oxide was removed by filtration and washed with 200 mL 50% (v/v) ether-hexanes. The filtrated was concentrated to a yellow oil using a rotary evaporator. The residue was dissolved in 10 mL dichloromethane, diluted with 40 mL of 8% ether-hexanes and further purified using flash chromatography (8% ether–hexanes) to provide 5.03 g (85.6%) of a pure white crystalline solid after concentration of the product column fractions.



262

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-L-mannitol (**262**).[296] A 1-L, two-necked, round-bottomed flask equipped with a nitrogen inlet, addition funnel, and a magnetic stir bar is charged with 3,4-*O*-isopropylidine-*L*-mannitol (14.5 g, 65 mmol), triphenylphosphine (42. 9, 163 mmol) and anhydrous toluene (160 mL). After cooling the reaction mixture in an ice-bath, neat diethyl azadicarboxylate (25.9 mL, 163 mmol) is added dropwise over a period of 20 min. After the addition is complete, the addition funnel is replaced by a reflux condenser, and the ice-bath is replaced with an oil bath. The reaction mixture is heated at reflux for 1–2 h, then cooled to room temperature and directly applied to a dry silica gel column. Elution with 30-50% ether/hexane provides the title compound in 9.4 g (78%) as a volatile oil after concentration.

In addition to the two experimentals shown above, a multi-gram scale phthalimide displacement, and the subsequent conversion of the intermediate imide into the corresponding amine with hydrazine is also covered in *Organic Syntheses*.[297]

6.3.7 References

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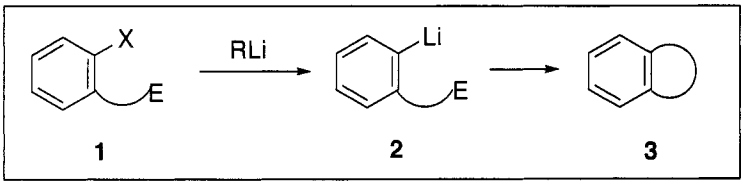
3.4 Parham Cyclization

Gordon W. Gribble

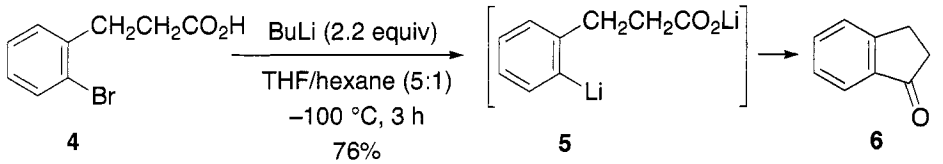
3.4.1 Description

The Parham Cyclization describes the generation by halogen–lithium exchange of aryllithiums and hetaryllithiums, and their subsequent intramolecular cyclization onto an electrophilic site, **1**→**2**→**3**.[1–8]

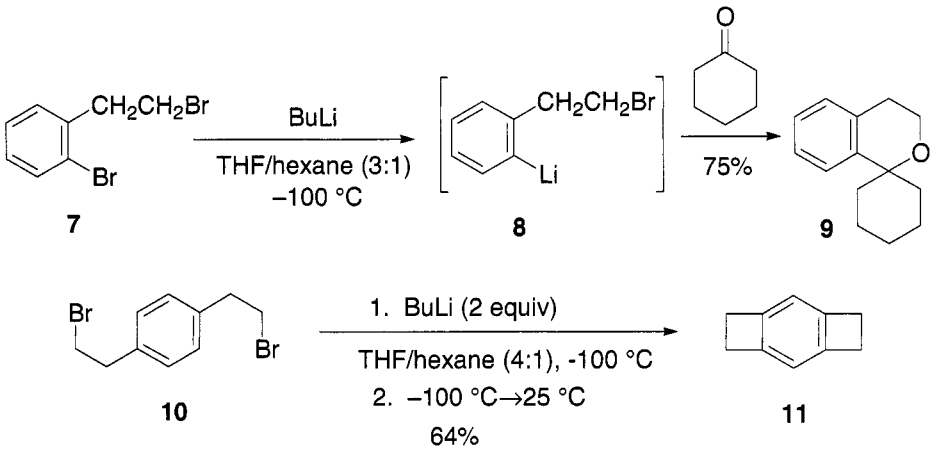


3.4.2 Historical Perspective

Following the initial discovery of the halogen-lithium exchange reaction by Gilman[9] and Wittig,[10] its further development by Gilman,[11] and a low temperature modification by Köbrich,[12] Parham extensively explored the generation and cyclization reactions of aromatic organolithium compounds in the presence of electrophilic groups.[1] An early example by Parham is the cyclization of 3-(2-bromophenyl)propanoic acid (**4**) to indanone (**6**).[13] In similar fashion, 4-(2-bromophenyl)butanoic acid is cyclized to tetralone in 76% yield.[1]



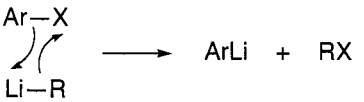
Parham also discovered that added electrophiles can be incorporated in the cyclization sequence. Thus, 2-bromophenethyl bromide (**7**) is selectively lithiated to afford **8**, which upon reaction with cyclohexanone affords spiro[cyclohexane-1,1′-isochroman] (**9**) in good yield.[14] It is also possible to execute twin Parham cyclizations, as in the synthesis of benzo[1,2:4,5]dicyclobutene (**11**).[15]



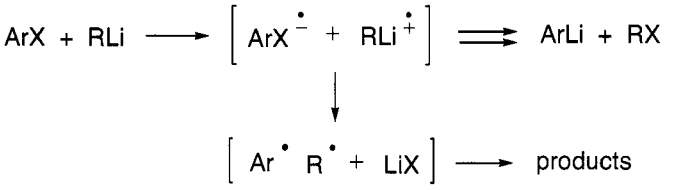
3.4.3 Mechanism

Despite its apparent simplicity, the halogen–lithium exchange reaction remains mechanistically intriguing.[3,16–23] Depending on the substrate and conditions, halogen-lithium exchange may involve a four-center transition state,[3,16,18,24] radical intermediates via a single-electron transfer (SET) mechanism,[3,16,20,25] or a nucleophilic mechanism perhaps via an "ate" complex.[3,16,18,19,21,23,26] These possibilities are summarized below. The experimental data and rationale for these mechanisms have been reviewed and summarized in great detail by Bailey and Patricia.[16]

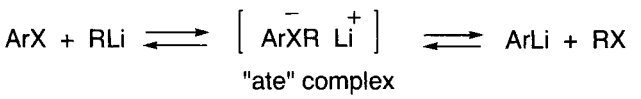
Four-Center Transition State:



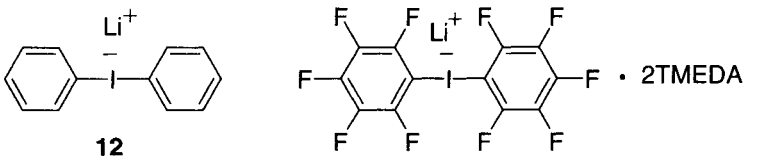
SET Mechanism (abbreviated):



Nucleophilic Mechanism:

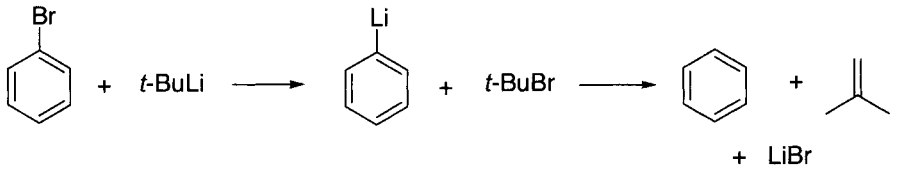


The equilibria implied in the nucleophilic mechanism are firmly grounded in experiment.[17,18] The ate complex **12** formed in the reaction of phenyllithium with iodobenzene has been characterized at low temperature,[23] and that from (pentafluorophenyl)lithium and iodopentafluorobenzene, **13**, has been isolated and characterized by X-ray crystallography.[19]



12 **13**

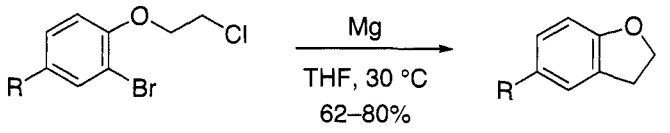
Although halogen-lithium exchange can occur at very low temperatures (< –100 °C), it is often necessary to employ two equivalents of alkyllithium for each equivalent of aryl halide so as to "neutralize" the alkyl halide, lest it destroy the aryllithium. This is illustrated below for the reaction between bromobenzene and *tert*-butyllithium.



3.4.4 Variations and Improvements

The main variation of the Parham cyclization might be considered the generation of the requisite aryllithium or hetaryllithium species by "directed-lithiation", rather than via halogen-lithium exchange.[2,8,27–31] However, this protocol does not fall under the rubric of the classic Parham cyclization and is not covered herein.

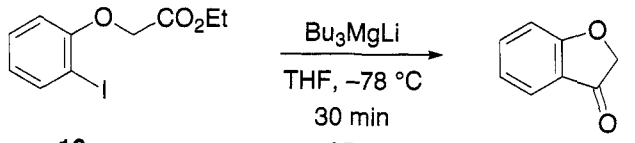
One alternative to the halogen–lithium exchange that has been employed in a Parham cyclization is halogen-magnesium exchange, as exemplified by the synthesis of 5-substituted 2,3-dihydrobenzofurans (**15**).[32] The use of *n*-butyllithium is less successful and leads to butylated by products. Lithium tributylmagnesate has also been employed, e.g., **16**→**17**.[33]



14

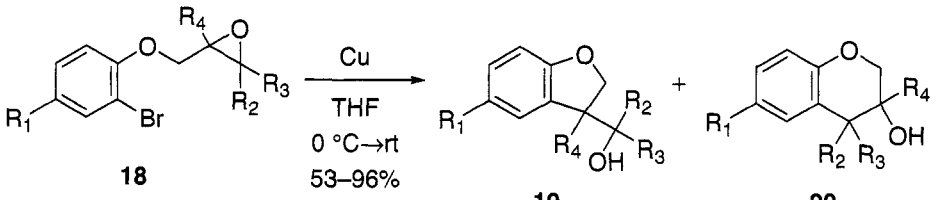
R = H, OMe, OBn, Cl, Ph

15



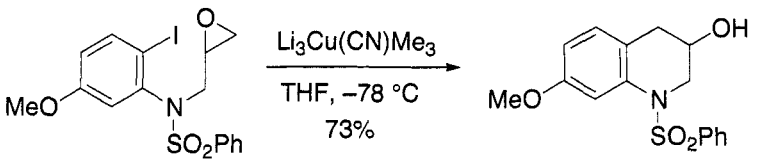
16 **17**

Copper has also been explored as an alternative to lithium. For example, CuI•PR_3 complexes effect intramolecular expoxide ring opening of **18** to afford either 5-exo (**19**) or 6-endo (**20**) cyclization, with 5-exo product normally favored except when R_4 = Me.[34] The cuprate $Li_3Cu(CN)Me_3$ was employed to cyclize **21** to the 6-endo product **22** exclusively.[35] To the contrary, $Li_3ZnMe_3(SCN)_2$ gives mainly the corresponding 5-exo product.



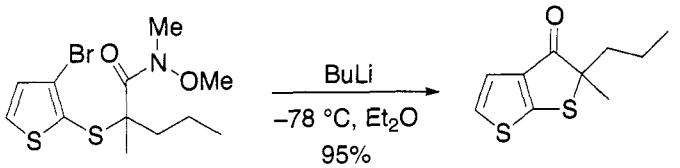
18 **19** **20**

R_1 = H, CO_2Et, Cl, Me
R_2 = H, Me, Ph
R_3 = H, Me
R_4 = H, Me

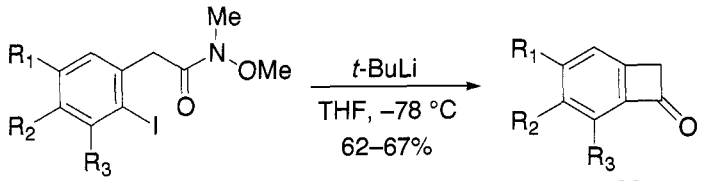


21 **22**

An important innovation in the Parham cyclization leading to cyclic ketones is the use of Weinreb amides as the electrophile, rather than carboxylic acids or esters. For example, compound **23** is converted to **24** in excellent yield,[36] and benzocyclobutenones **26** are readily available from Weinreb amides **25**.[37] Lower yields of **26** are obtained using *n*-butyllithium.



23 **24**

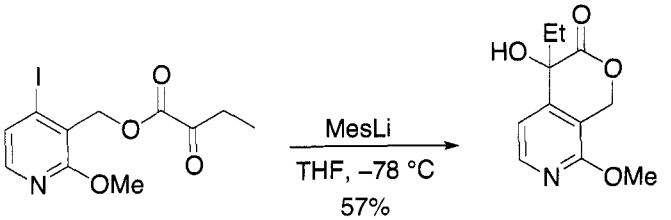


25 **26**

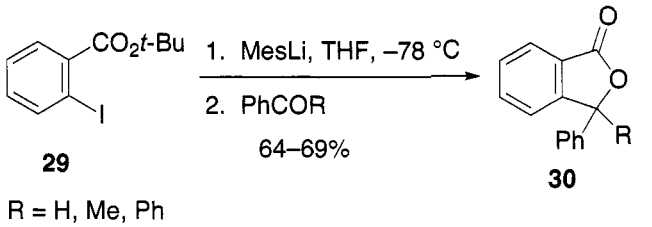
$R_1 = R_2 = R_3 = H$
$R_1 = R_2 = OMe, R_3 = H$
$R_1 = R_2 = R_3 = OMe$
$R_1,R_2 = -OCH_2-, R_3 = H$

3.4.5 Synthetic Utility

In view of three excellent recent reviews on the Parham cyclization,[3–5] this section focuses mainly on the more recent literature. While *n*-butyllithium and *tert*-butyllithium are commonly used to effect halogen–lithium exchange, these reagents do present problems as delineated earlier. Mesityllithium does not pose such problems since the resulting mesityl halides are not susceptible to the side reactions inherent with *n*-butyl and *tert*-butyl halides. Mesityllithium has been used to prepare the camptothecin precursor **28**.[38] This base can also be used with added electrophiles, as for the conversion of **29** to phthalides **30**.[38] A more conventional Parham synthesis of phthalides, i.e., **31**→**32**, has been applied to the synthesis of the aristocularine alkaloids.[39]



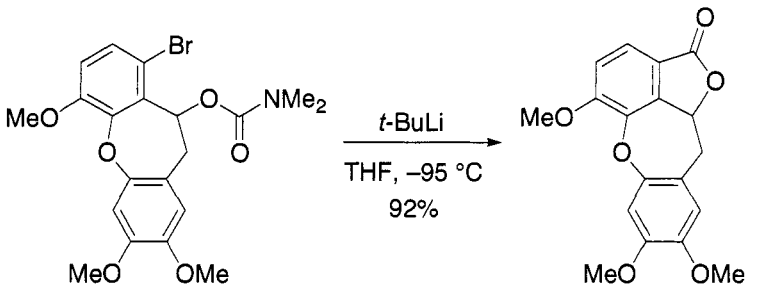
27 **28**



29

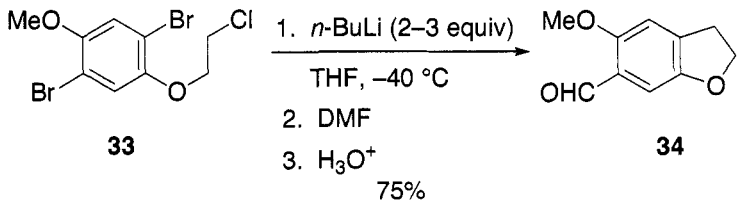
R = H, Me, Ph

30

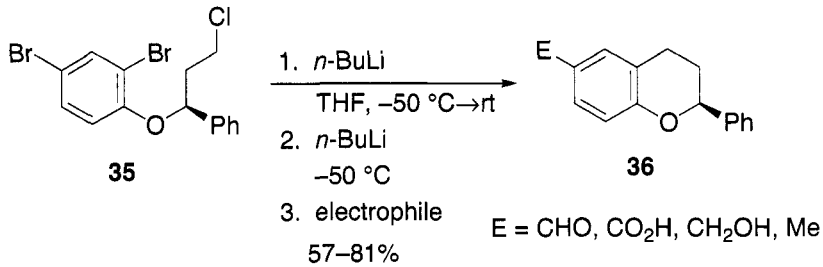


31 **32**

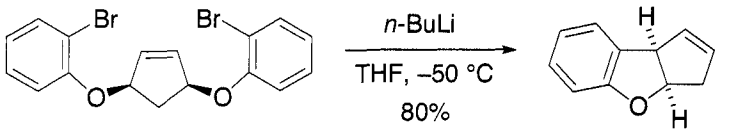
A Parham cyclization can be followed in the same pot by a second, "remote" halogen–lithium exchange and intermolecular reaction. Such a case is **33**→**34**.[40] A related one-pot sequential lithiation process has furnished substituted chromans **36**,[41] and a novel S_N2' displacement is involved in the Parham cyclization of **37** giving **38**.[42]



33 **34**

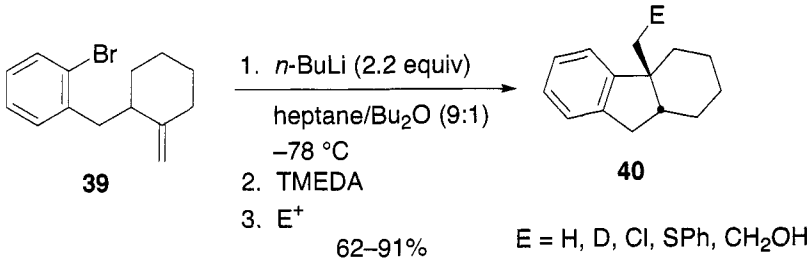


35 **36**

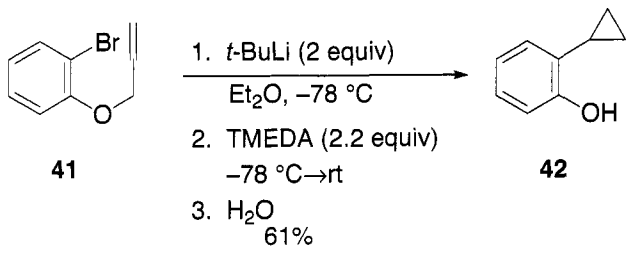


37 **38**

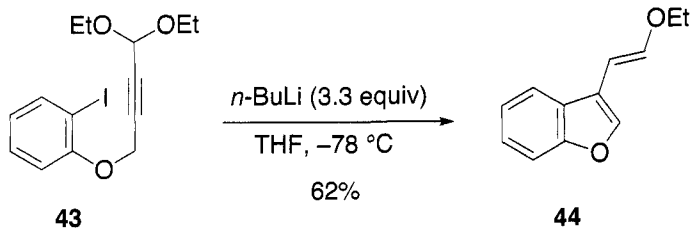
Frequently seen are Parham cyclizations onto alkene side chains. For example, bromoalkene **39** undergoes cyclization and electrophilic trapping to afford **40**.[43] A series of allyl 2-lithioaryl ethers undergo a tandem Parham cyclization-γ-elimination to afford 2-cyclopropylphenols, e.g., **41**→**42**.[44] Intramolecular carbolithiation reactions of alkenes have led to 2-azabenzonorbornanes and tetrahydroisoquinolines.[45] Similarly, carbolithiations of alkyne and allene side chains have been reported.[46] Thus, both **43** and **45** undergo iodine-lithium exchange and cyclization to provide benzofuran **44** and furopyridine **46**, respectively.



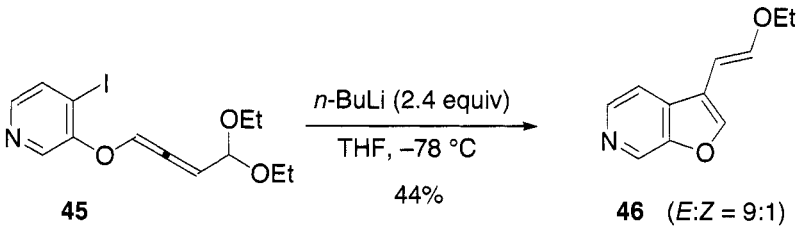
39 **40**



41 **42**

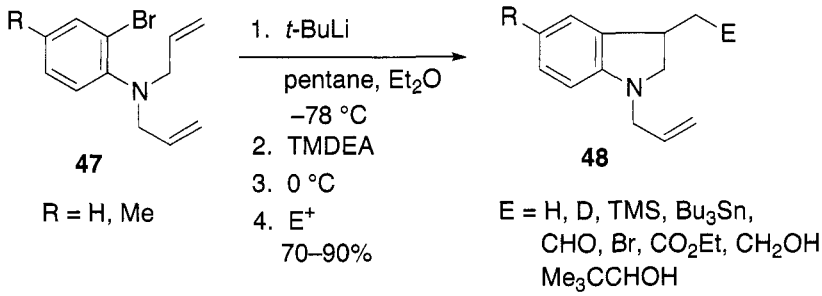


43 **44**



45 **46** (*E*:*Z* = 9:1)

A simple indoline (and hence indole) synthesis features a Parham cyclization, e.g., **47**→**48**,[47,48] and this has been extended to an enantioselective 3-substituted indoline synthesis, i.e., **49**→**50**.[49] Oxidation of indolines **48** with *o*-chloranil affords the corresponding indoles in good yield.[47,48] Related enantioselective indane construction has been described from 2-bromo-1-(3-butenyl)benzene.[49b] In the case of bromo ketenedithioacetal **51**, indane **52** is obtained after alkylation of the resulting lithiated dithiane with *n*-butyl bromide.[50]

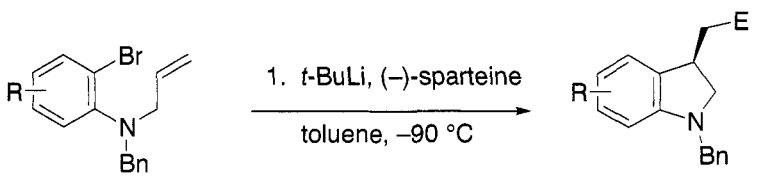


47

R = H, Me

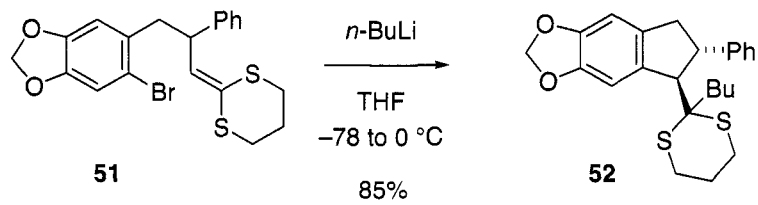
48

E = H, D, TMS, Bu_3Sn, CHO, Br, CO_2Et, CH_2OH, Me_3CCHOH



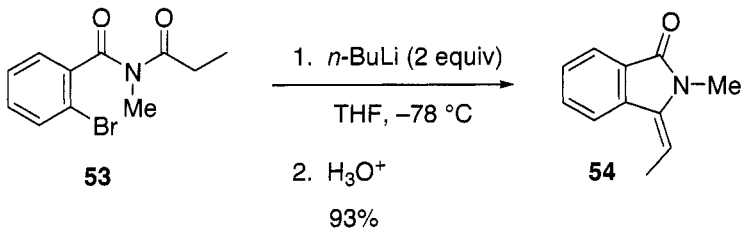
49 **50** (82–90% *ee*)

R = H, 4-OBn, 5-OBn, 4-Me, 4-F 65–90% E = H, Br

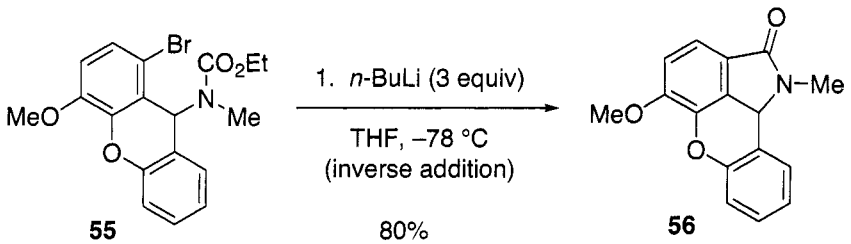


51 85% **52**

Parham cyclizations have been employed extensively to construct isoindolin-1-ones, which are embodied in a large number of natural products, and 3-alkylidenephthalimidines. An example of the latter is **53**→**54**.[51] Imides unsubstituted on nitrogen were initially treated with sodium hydride prior to exposure with *n*-butyllithium. The synthesis of chromeno[4,3,2-*cd*]isoindolin-2-one **56** was achieved via a Parham ring closure, as were the related chromeno[4,3,2-*de*]isoquinolin-3-ones.[52]

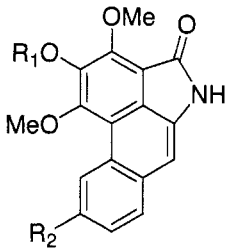


53 **54**

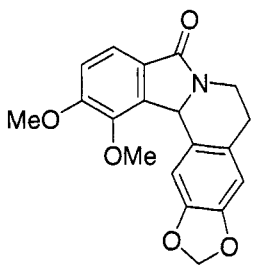


55 **56**

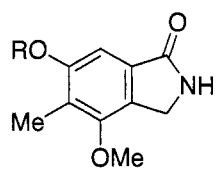
Alkaloids that have been synthesized via a key Parham cyclization similar to **55**→**56** include piperolactam C (**57**),[53] goniopedaline (**58**),[53] stigmalactam (**59**),[53] nuevamine (**60**),[54] cichorine (**61**),[55] zinnimidine (**62**),[55] fumaramidine (**63**),[56] porritoxin (**64**),[57] and vitedoamine A (**65**).[58]



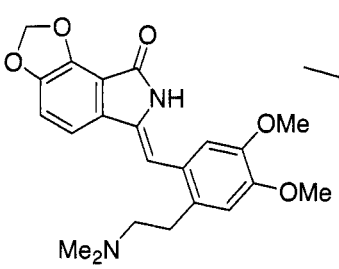
57, R_1 = Me, R_2 = H
58, R_1 = R_2 = H
59, R_1 = Me, R_2 = OH



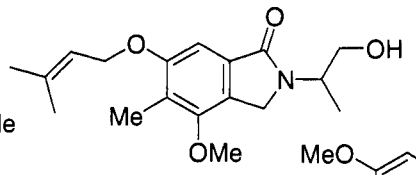
60 (nuevamine)



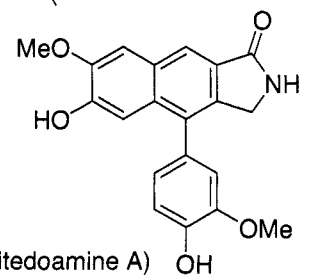
61, R = H (cichorine)
62, R = $CH_2CH{=}CMe_2$ (zinnimidine)



63 (fumaramidine)

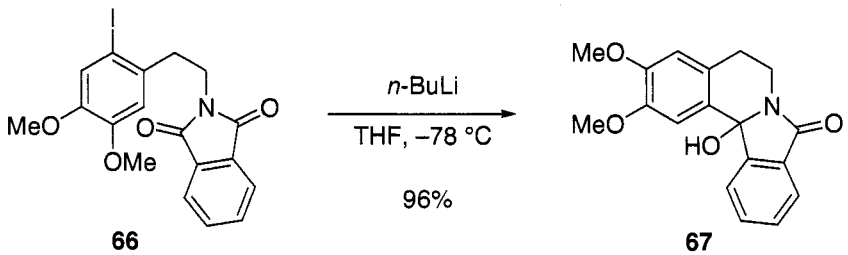


64 (porritoxin)

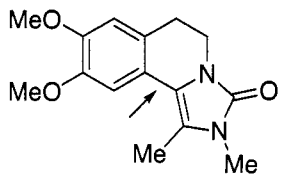


65 (vitedoamine A)

A Parham cyclization strategy has been used to synthesize a wide variety of isoquinolines. For example, iodide **66** is smoothly converted to **67**, which can be reduced (sodium borohydride/trifluoroacetic acid, 99%) or treated with nucleophiles and a Lewis acid to effect α-amidoalkylation.[59] Likewise, imidazo[4,3-*a*]isoquinolinones (**68**),[60] thiazolo[4,3-*a*]isoquinolinones (**69**),[60] pyrrolo[2,1-*a*]isoquinolines (**70**),[61] pyrrolo[1,2-*b*]isoquinolines (**71**),[62] pyrrolo[1,2-*b*]acridinones (**72**),[63] pyrrolo[1,2-*g*]quinolones (**73**),[63] thieno[3,2-*f*]indolizinones (**74**),[63] and furo[3,2-*f*]indolizinones (**75**).[63] It should be noted that the latter ring system **63** was prepared by deprotonation (LDA) rather than halogen–lithium exchange.[63]



66 **67**



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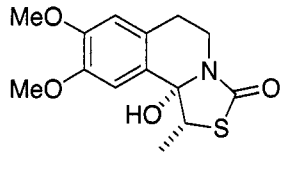

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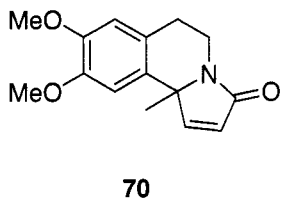

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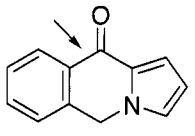

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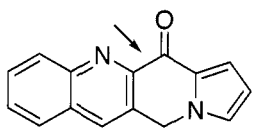

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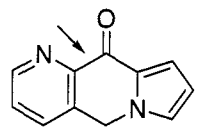
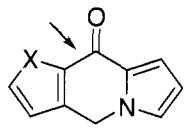
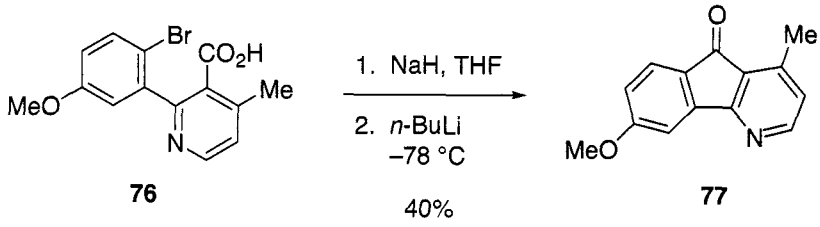


73

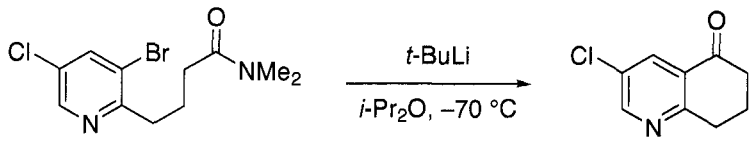


74, X = S
75, X = O

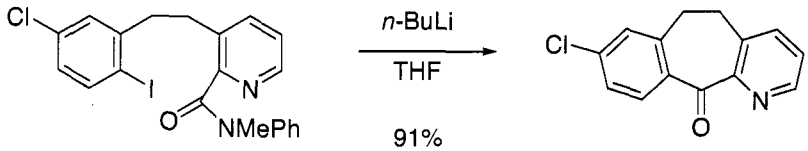
The Parham cyclization has been featured in the synthesis of a multitude of different ring systems. Thus, azafluorenone **77** is formed from nicotinic acid **76** in modest yield,[64] and azatetralone **79** is obtained from dimethyl amide **78**.[65] Other amides and the carboxylic acid corresponding to **78** are poor cyclization substrates. Azadibenzosuberone **81** is the product from **80** with *n*-butyllithium.[66] A Grignard-based reaction with mesitylmagnesium bromide is much less efficient. The key step in the synthesis of indolizidines is the Michael addition of **82**→**83**.[67]



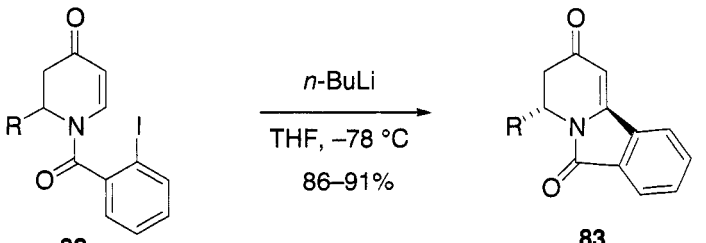
76 **77**



78 **79**



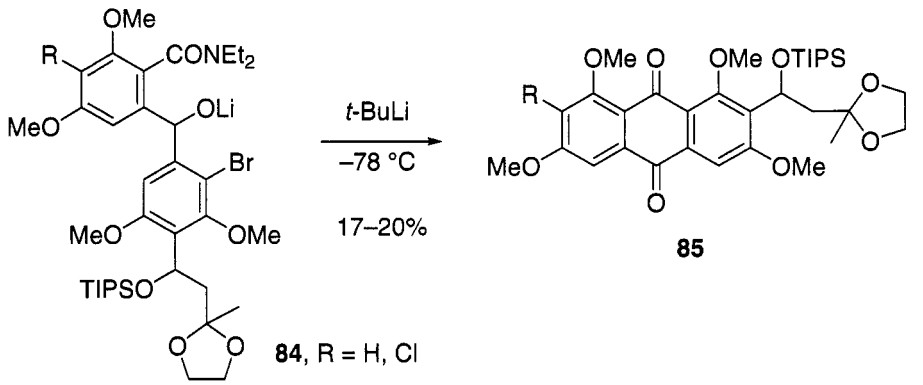
80 **81**



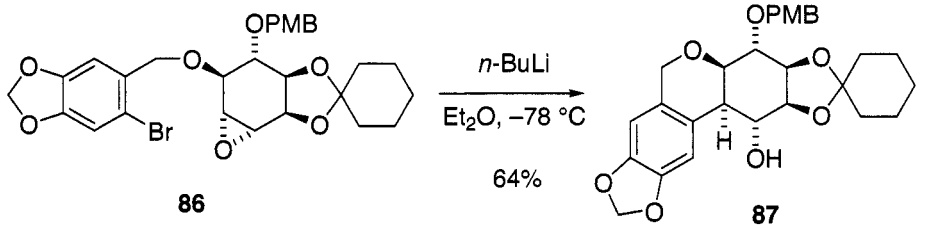
82 **83**

R = Ph, *c*-C_6H_{13}, vinyl, HCC, BuCC

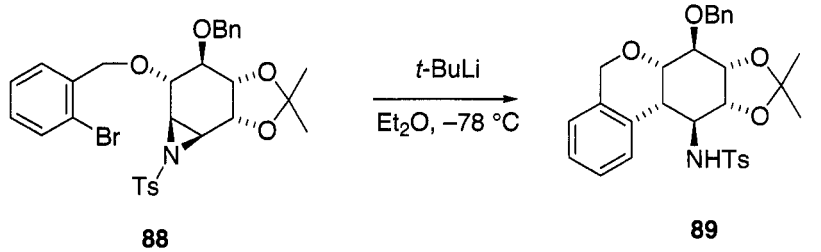
The first syntheses of topoisomerase I inhibitors topopyrones B and C feature the cyclization of **84** to **85** albeit in low yield.[68] Parham cyclizations onto both epoxides (e.g., **86**→**87**) and aziridines (e.g., **88**→**89**) are aspects of two approaches to pancratistatin and related alkaloids.[69,70]



84, R = H, Cl **85**

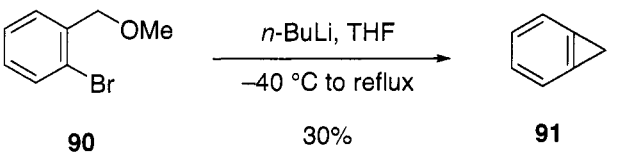


86 **87**

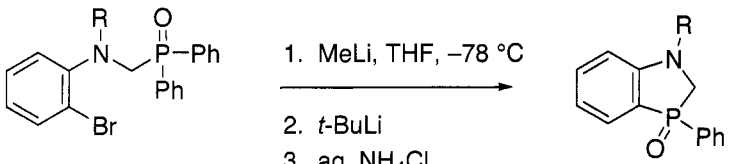


88 **89**

In contrast to applications in complex natural product synthesis (*vide supra*), a Parham cyclization affords the simplest known route to benzocyclopropene (**91**),[71] and a convenient synthesis of benzazaphospholines **93**.[72] The function of methyllithium pretreatment is to deprotonate the methylene group. An approach to iminoglycitol mimics involves the synthesis of thiazolo[4,5-*c*]pyridinones **95** and oxazolo[4,5-*c*]pyridinones.[73]

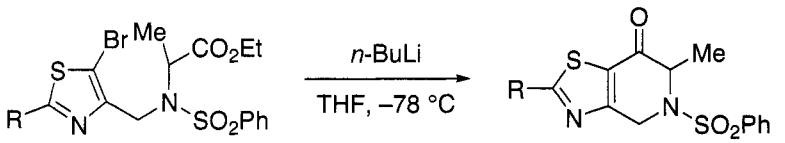


90 **91**



92 **93**

R = Bn, *i*-Pr, Me, 4-MeOBn, 3,4-(OCH_2O)Bn



94 **95**

R = Ph, morpholino

3.4.6 Experimental

Dihydrothieno[2,3-*b*]thiophene 24:[36]

To a solution of bromothiophene **23** (10.28 g, 0.0292 mol) in anhydrous diethyl ether (200 mL) at –78 °C was added over 20 min *n*-BuLi (16.0 mL, 0.040 mol, 2.5 M solution in hexane). The solution was stirred for an additional 40 min at –78 °C. To the solution was added aqueous saturated $NaHCO_3$ (60 mL) and H_2O (50 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL) and dried over $MgSO_4/NaHCO_3$ and concentrated. The product was purified by flash chromatography on silica

gel (3% ethyl acetate/hexane) to give 5.90 g (95%) of **24** as a low melting solid.

Pyridine Lactone 28:[38]
Under an argon atmosphere, *t*-BuLi (1.44 M in pentane, 2.8 mL, 4.0 mmol) was added to a solution of mesityl bromide (398 mg, 2.0 mmol) in dry THF (7 mL) at –78 °C and stirred at –20 °C for 1 h. The mixture was then cooled to –78 °C and a solution of ketoester **27** (349 mg, 1.0 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred at the same temperature for 5 h and an aqueous solution saturated with NH_4Cl was added. The resulting mixture was extracted with diethyl ether (3 × 20 mL) and washed with brine (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give a residue, which was purified by silica gel column chromatography using hexane/EtOAc (5:1) as eluent to give **28** as a viscous oil (127 mg, 57%).

(*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-carboxaldehyde 36 (E = CHO):[41]
To a stirred solution of *n*-butyllithium in hexane (2.5 M, 0.24 mL, 0.6 mmol) in THF (3 mL) at –50 °C was added dropwise a solution of (*S*)-2,4-dibromo-1-(3-chloro-1-phenylpropoxy)benzene (202 mg, 0.5 mmol) in THF (2 mL). After 1 h at –50 °C, the cooling bath was removed and the solution was stirred at room temprature for 1 h. The solution was re-cooled to -50 °C and *n*-butyllithium in hexane (2.5 M, 0.3 mL, 0.75 mmol) was added dropwise. After 30 min, DMF (365 mg, 5 mmol) was added and, following stirring for 30 min, the solution was allowed to return to room temperature. The reaction was quenched by pouring into saturated aqueous ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography over silica gel of the residue, eluting with hexane, gave the title compound (1.6 g, 81%) as a white solid.

3a,8b-*cis*-Dihydro-3*H*-cyclopenta[*b*]benzofuran 38:[42a]
To a stirred solution of 3,5-*cis*-bis(2-bromophenoxy)-2-cyclopentene (**37**) (6.0 g, 14.6 mmol) in THF (80 mL) at –50 °C was slowly added *n*-BuLi (2.0 N solution in hexane, 11 mL, 22 mmol). After 1 h, the solution was warmed to –10 °C and stirred for 3 h. Then brine (5 mL) was added. The mixture was concentrated and the residue was dissolved in Et_2O (300 mL). The solution was washed with 1 N aqueous NaOH (20 mL) and brine (30 mL) and then was dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (cyclohexane/EtOAc, 95:5) to give **38** as a colorless oil (1.84 g, 80%).

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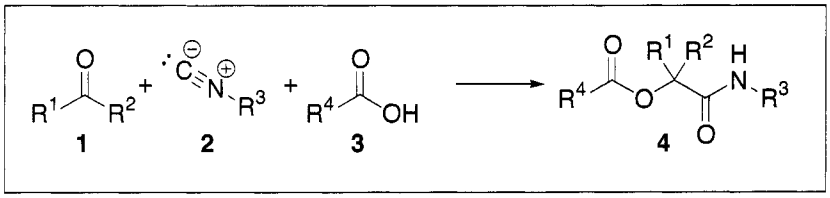
3.5 Passerini Reaction

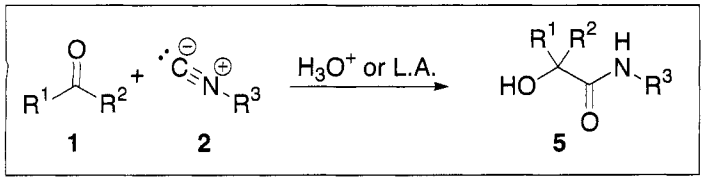
J. Cullen Klein and David R. Williams

3.5.1 Description

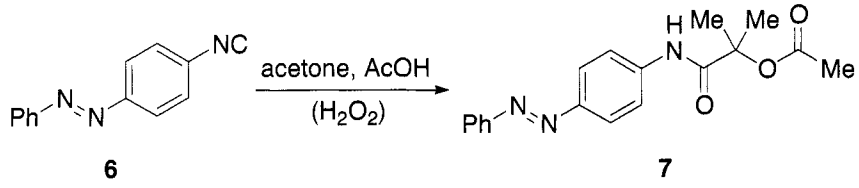
The Passerini reaction[1] describes the coupling of three components, an aldehyde or ketone **1**, an isonitrile **2**, and a carboxylic acid **3**, to form an α-acyloxyamide **4**. The reaction is typically performed at high concentration, in organic solvents of low polarity (as permitted by the solubilities of the starting materials) at or below room temperature. In many cases, the α-acyloxyamides precipitate from solution as the reactions proceed and a simple filtration of the crude reaction provides the desired product.



As a further development, the substitution of Lewis acids or mineral acids for carboxylic acids in the Passerini reaction has allowed for the direct generation of α-hydroxyamides **5**.



3.5.2 Historical Perspective

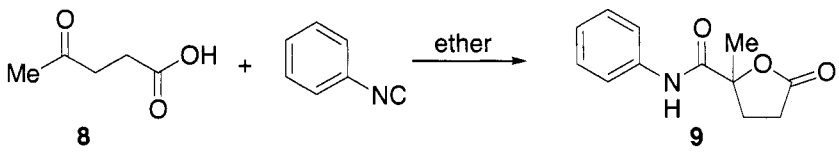


In studies summarized over two reports in 1920 and 1921, Mario Passerini described that the treatment of *p*-isonitrileazobenzene (**6**) with an acetone

solution of acetic acid and aqueous hydrogen peroxide lead to isolation of a solid[2] which was later established to be the α-acetoxyamide **7**.[3]

In the second communication, Passerini also determined that the addition of hydrogen peroxide was unnecessary and, to an extent, deleterious as it mediated the decomposition of *p*-isonitrileazobenzene. The formation of α-acyloxyamides from isonitriles, carboxylic acids and ketones or aldehydes subsequently became known as the Passerini reaction or the Passerini multicomponent reaction. The process is sometimes denoted as P-3CR according to Ugi's classification of multicomponent reactions (MCR).[4]

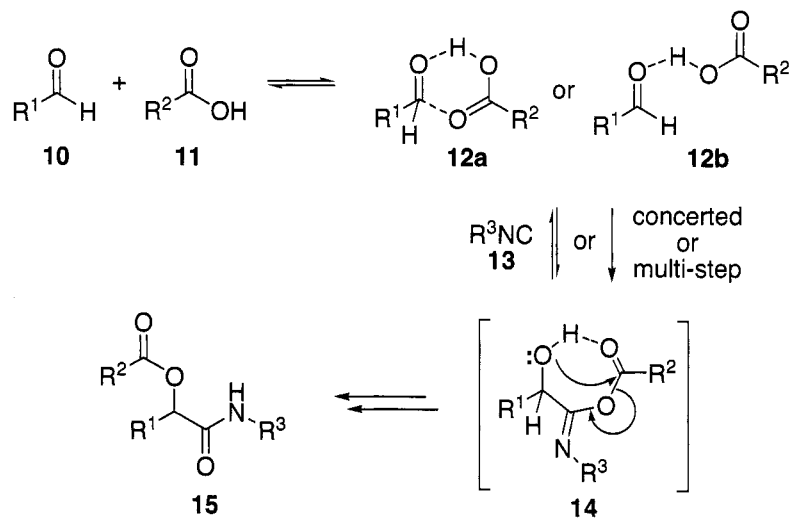
Through further followup studies,[5] Passerini expanded the scope of substrates to include a number of aldehydes and ketones as the carbonyl component and a variety of isonitriles including saturated alkyl isocyanides. Passerini also examined reactions where two components were combined into a single bifunctional substrate such as levulinic acid (**8**), where the carboxylic acid is proximally connected to a ketone. The reaction of levulinic acid with phenyl isocyanide gave amide **9** with the acyloxy moiety of the generic product now a γ-lactone.[5b]



8 **9**

3.5.3 Mechanism

Mechanism of the Classic Passerini Reaction



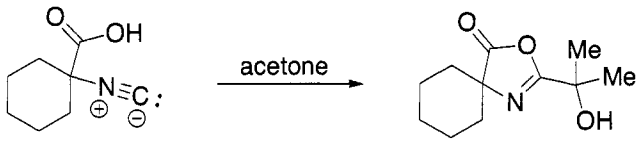
The generally accepted mechanism[1b] for the Passerini reaction is illustrated by aldehyde **10** (or ketone) being activated for nucleophilic addition by complexation with carboxylic acid **11**. The precise nature of this complex is has not been established, however, Ugi has favored the internally hydrogen bonded, six-membered arrangement of **12a**[1b] over that of **12b**. The subsequent α-addition to isonitrile **13** leads to an iso-imide species **14**. It is not known concretely whether the α-addition is a concerted[6] or stepwise[7,1a] process. The iso-imide then undergoes an *O*→*O* internal acyl transfer and tautomerization to give the product α-acyloxyamide **15**.

The mechanistic hypothesis is supported by several lines of evidence. First, the reaction rate for a simple three component system was found to be first order in each of the three components.[8] Since reactions that proceed by a rate-limiting step in which three components simultaneously collide are rare, an intervening pre-equilibrium step is proposed.

Secondly, the reaction rate is inversely correlated to the polarity of the solvent,[9] indicating that the product of the rate limiting step has little charge or presents dipole-minimized characteristics. This observation also suggests that the addition of isonitrile **13** to **12** is a concerted process which avoids ionic or zwitterionic species.

Thirdly, the rates of Passerini reactions in methanol are slow, implying that the strong hydrogen-bonding ability of the solvent may disrupt the formation of the hypothesized transient **12**.[10]

Fourthly, no intermediates have been isolated from Passerini reactions that used conventional substrates. However, the reaction of 1-isocyanocyclohexane carboxylic acid (**15**) and acetone resulted in the isolation of oxazolin-5-one **16**. Due to geometrical constraints **16** cannot easily undergo the *O*→*O* acyl migration[11] supporting the likelihood of an iso-imide intermediate for the three-component Passerini reaction.



15 **16**

Finally, the rates of the reaction do not increase upon the addition of benzoate salts[8] and suggests that attack by benzoate is not involved in the rate limiting step.

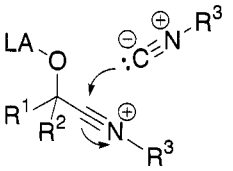
Some additional recent findings have had implications for the contemporary understanding of the Passerini mechanism. The application of high pressure to these reactions has demonstrated a dramatic accelerating effect,[12] as does performing the reactions "on water".[10,13] Both of these accelerating effects are thought to be explained by a large negative volume of

activation. Furthermore, a study has suggested that nucleophilic catalysis may also enhance the rates of these reactions.[14]

Mechanism of Lewis Acid-Promoted Passerini-type Reactions

The mechanism of Passerini reactions promoted by a Lewis acid has not been as extensively studied as the mechanism of the "classic" reaction. However, two precepts in regard to the component substitution should be noted. First, metal and metalloid-based Lewis acids are typically much more powerful acids than common carboxylic acids and second, as a consequence, nucleophiles (i.e., Lewis bases) will be both lower in strength and concentration under these conditions. Most of the differences in mechanism are inferred from indirect evidence, relying upon insight about the origins of observed products and side reactions,[1a] all of which logically proceed from a nitrilium intermediate.

A survey of the many examples of Lewis acid-promoted Passerini-type reactions, finds that most are characterized by one of four distinct processes: a) nucleophilic attack of an additional equivalent(s) of isonitrile to form oligomeric products[15–18] (**17**); b) nitrogen dealkylation to give cyanohydrin-type products[19,20] (**18**); c) intramolecular capture of tethered-nucleophiles to form cyclic products[21–25] (**19**); and d) intermolecular capture of other weakly-basic nucleophiles such as dissociable counterions of the Lewis acid[20,26] (**20**) such as the chloride ion for $TiCl_4$.



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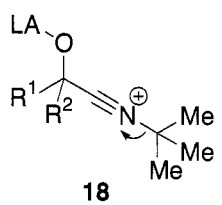
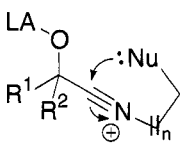
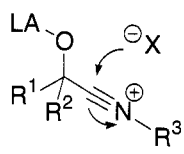


18



19



20

For a brief period of time it was thought that the $TiCl_4$-promoted Passerini reaction occurred via a mechanism where a nitrilium adduct did not play any significant role.[27] This thinking was based on some initial evidence that isonitriles inserted into Ti–Cl bonds and formed titanium imidochlorides[28] and that these species were incorporated into the mechanism as intermediates.[19,27,29] However, subsequent FT-IR and X-ray crystal structure data[30,31] strongly suggested that isonitriles do not insert into

Ti–Cl bonds. The investigations clearly demonstrated that, in the absence of secondary reactive species (e.g., nucleophiles), isonitriles can form Lewis acid–Lewis base adducts with $TiCl_4$ without undergoing α-addition.[31] The early IR evidence for the supposed titanium imidochloride species was reassigned to the corresponding formamide which resulted from the hydration of the isonitrile in the presence of acid and adventitious water.[30]

The high yields of $TiCl_4$-promoted reactions can be explained by free chloride ion attacking the generated nitrilium at carbon to give an iminochloride. The iminochloride is resistant to nucleophilic attack by additional equivalents of isonitrile thereby preventing oligomerization.[26] The iminochloride is hydrolyzed to the corresponding amide upon termination of the reaction by an aqueous quench.

3.5.4 Substrate Compatibility Trends

The Passerini reaction is normally a sluggish reaction, often performed over several days.[5,32] Therefore, an important consideration is the relatively low reactivity of the component substrates. Electronic or steric elements that might further retard the reaction rate will predictably give lower yields and substantially more side products. Conversely, more reactive carbonyl compounds such as chloral can be attacked by isonitriles and form α-hydroxyamides even in the absence of an acid component.

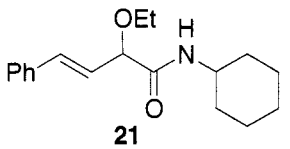
Because of the inherently low reactivity of most components, a very large number of other functional groups are tolerated in the reaction.[33] Functionalities that are not compatible within the Passerini reaction include those that are reactive toward activated or unhindered aldehydes or ketones under the mildly acidic conditions, lest such reactivity be competitive with the slow Passerini reaction. As a direct consequence, unprotected primary or secondary amines are not compatible because of the facility by which they form imines and iminiums by acid-catalyzed condensation. Iminiums, themselves are susceptible to nucleophilic attack by isonitriles and the formation of α-acylamino amides by this process is called the Ugi reaction[9] (see chapter 3.6). In reactions where the Ugi and Passerini reactions are possible competitive processes the Ugi products are generally favored to the detriment of any Passerini products.[34]

With regard to the carbonyl component, the low nucleophilicity of isonitriles means that only the more active carbonyl substrates give Passerini products in good yields. Formaldehyde, aldehydes, and unhindered or activated ketones all have participated in successful Passerini reactions.[33] On the contrary, α,β-unsaturated aldehydes and ketones fail to give good yields of Passerini products under classical conditions,[32] but the more strongly acidic mineral acid-based or Lewis acid-based protocols can result in good yields of the desired products.[19,21,33]

The carboxylic acid component is limited by similar sensitivity to steric factors for difficult couplings as with the other two components of the P-3CR. These steric problems can be overcome somewhat by perfoming the reaction at high pressure.[12]

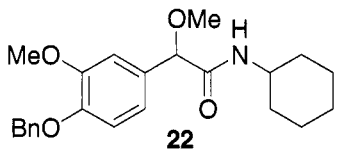
Carbonyl Surrogates in the Passerini Reaction

In many instances, ketals can serve as masked carbonyls in the Passerini reaction. The product α-alkoxyamides, exemplified here by **21**[35] and **22**,[36] can be obtained in high yield from the appropriate ethyl or methyl ketals mediated by either Bronsted or Lewis acids. Both cyclic and acyclic acetals can function as suitable substrates.



21

$TiCl_4$, CH_2Cl_2, –35 °C, 85% yield



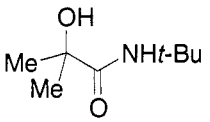
22

TFA, PhH, rt, 1 d, 76% yield

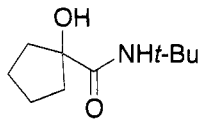
Alternatively, cyclic enol ethers can serve as the electrophile in Passerini-type reactions[37] as they undergo protonation by strong Bronsted acids to produce oxocarbeniums as the reactive partner. More recently, acyl cyanides have been demonstrated to participate as the carbonyl component in Passerini reactions, giving α-acyloxy-α-cyano amides in good yields.[38]

Acids Components Other Than Carboxylic Acids

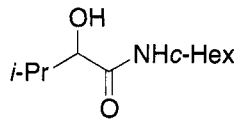
Aqueous mineral acids[17,39,40] have been shown to be capable of promoting Passerini-type reactions, producing α-hydroxyamides in good yields. Both aldehydes and unencumbered ketones function well as appropriate substrates.



HCl, H_2O
0 °C, 72% yield



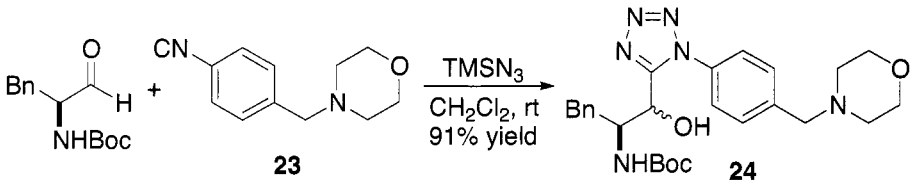
H_2SO_4, H_2O
0 °C, 70% yield



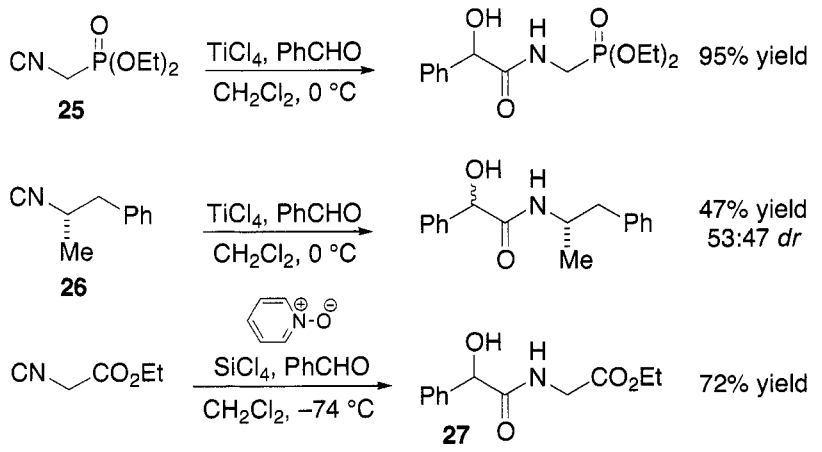
HCl, acetone
88% yield

Other acids that have been used in Passerini-type reactions include hydrazoic acid[40] and its Lewis acid congenitors,[41,42] such as $Al(N_3)_3$ and $TMSN_3$. In these presence of azide salts the intermediate nitrilium is instead intercepted by azide in a stepwise [3 + 2]-cycloaddition to give the 1,5-

disubstituted tetrazole. The reaction of Boc-protected phenylalanal, $TMSN_3$ and phenylisocyanide derivative **23** gave tetrazole **24** in high yield.[42]

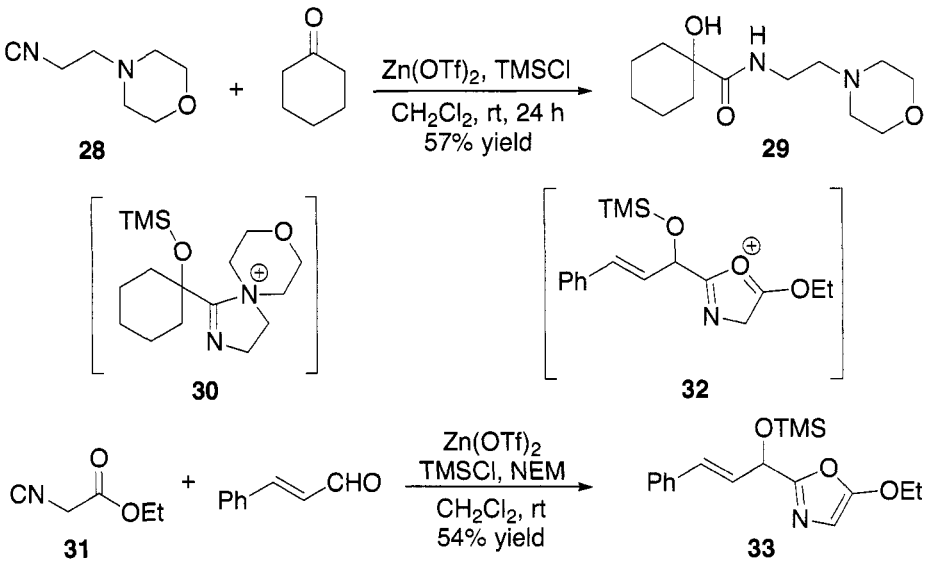


There are many examples of Passerini-type reactions mediated by Lewis acids with $TiCl_4$ having the most widespread use. Passerini-type reactions using $TiCl_4$ are compatible with a variety of functional groups as can be seen in the nearly quantitative reaction of α-isocyano phosphonate ester **25** with benzaldehyde.[28] An examination of $TiCl_4$-mediated diastereoselective Passerini reaction failed to show any clear stereoselection with chiral isocyanide **26** among many other cases. Weaker Lewis acids such as $SiCl_4$ can also mediate Passerini-type reactions, but effectively do so only in the presence of a Lewis base.[26] Denmark demonstrated that α-hydroxyamides, such as **27,** could be formed in good yields, by using Lewis bases such as pyridine-*N*-oxide to activate the $SiCl_4$.



Ganem and co-workers have developed the use of a $Zn(OTf)_2$/TMSCl system to promote a variety of Passerini-type processes.[21] The combination is active even for α,β-unsaturated aldehydes and usually problematic ketones. The promoter system was developed around a strategy of tethering nucleophilic functional groups to the isonitrile component to intercept the transient nitrilium species internally. Depending on the attached functionality either the α-hydroxy amide or a substituted oxazole could be obtained in high yield. For 1-isocyano-(2-morphilino)ethane (**28**), the reaction with

cyclohexanone and aqueous work-up gave the α-hydroxyamide **29** in good yield via the interceding intermediate **30**. In the case of α-isocyano ester **31** (or similarly *N,N*-dialkylamides) and with added *N*-ethylmorpholine base, elimination of a proton from intermediate **32** gave the 2,5-disubstituted oxazole **33** in good yield.[43]



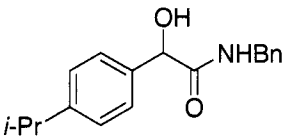
3.5.5 Stereoselective Passerini Reactions

Diastereoselective Passerini Reactions

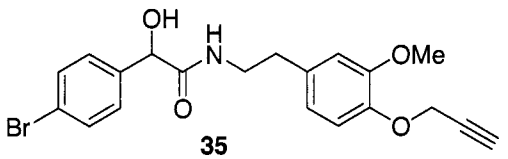
Most attempts to construct diastereoselective variants of the Passerini reaction have met with a certain degree of failure. Undoubtedly, the numerous uncertainties of the reaction mechanism have contributed to these difficulties. The usual low levels of control for the Passerini reaction have also impeded efforts to establish empirical trends in the diastereofacial selectivity. This is exemplified in the construction of peptidomimetics, a class of molecules which has stimulated numerous applications of the Passerini reaction, where the diastereoselectivity is typically in the range of 1:1 to 4:1. A survey of results of the diastereofacial selectivity of carbonyl addition does not consistently follow a clear trend of either the Felkin–Anh or chelation-controlled models of carbonyl addition.[33]

For the classic P-3CR there are only a few examples of auxiliary-controlled highly diastereoselective reactions. Ugi developed a camphor-based nonracemic isonitrile[48] which gave good yields of Passerini products with high diastereoselection (92–93% *de*). However, this methodology was demonstrated for only a very limited number of simple alkyl aldehydes.

Lamberth and co-workers[49] examined the use of several optically active carboxylic acids as potential auxiliaries in the P-3CR and found that the use of 1,2,3,4-tetra-*O*-acetyl-α-*D*-galacturonic acid resulted in excellent diastereoselectivity for the formation of a variety of *p*-substituted mandelamides (e.g., **34** and **35**). During the subsequent workup the acid was cleaved with aqueous base in 1,4-dioxane and recovered.



34
90:10 *er*

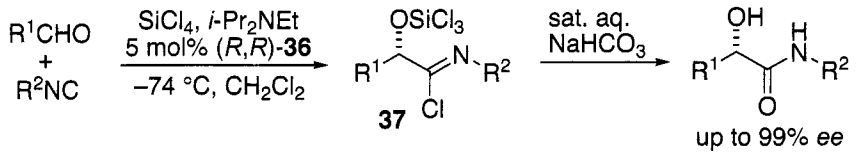


35
98:2 *er*

Asymmetric Passerini Reactions

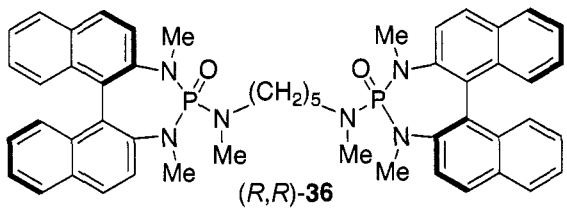
The development of Lewis acid catalysis has led to a variety of ready-made systems useful for asymmetric catalysis. A number of these chemical technologies have proven to be effective in promoting enantioselective addition of isonitriles to aldehydes.

Denmark has described several chiral bis-phosphoramides as Lewis base activators of weak Lewis acid $SiCl_4$ and demonstrated their ability to mediate an enantioselective Passerini-type reaction.[26] Catalytic bis-phosphoramide **36** and stoichiometric $SiCl_4$, in the presence of a proton scavenger (Hünig's base), promoted the formation of α-hydroxyamides with remarkably good enantioselectivity and yield. A variety of aromatic and unsaturated aldehydes and aryl, alkyl, and functionalized alkyl isocyanides proved to be useful and effective starting materials. High yields of Passerini products were attributed to the production of imidoyl chloride **37,** which reduced the prevalence of the nitrilium intermediate and prevented the addition of a second equivalent of isonitrile.



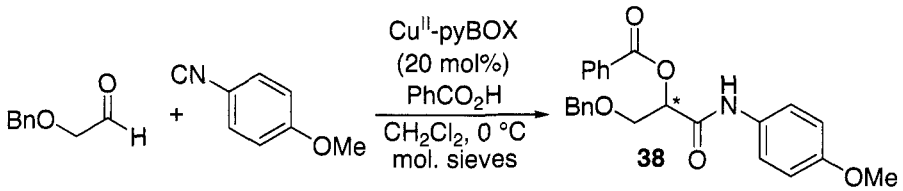
37

up to 99% *ee*



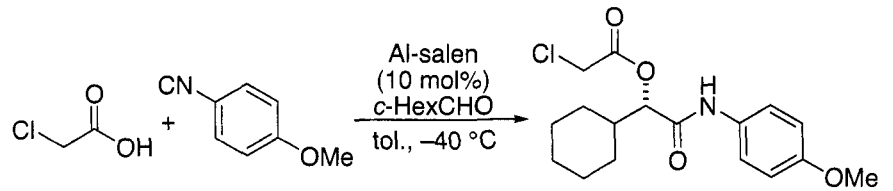
(*R*,*R*)-**36**

Schreiber and co-workers[46] have described the use of a copper(II) complex with an aminoindanol-derived pyBOX ligand for the catalytic enantioselective addition of isonitriles to bidentate aldehydes to give α-acyloxyamides such as **38**. Excellent yield and good enantioselectivity is observed in many cases and the protocol was also applied toward tandem Passerini–intramolecular Diels–Alder reactions for use in complexity-generating diversity oriented synthesis.



93% yield, 97% *ee*

Recently, Zhu and Wang[47] have collaborated to identify an Al^{III}/salen complex which catalyzed the P-3CR in modest yields, but generally with useful enantioselection as shown in the construction of amide **39**.



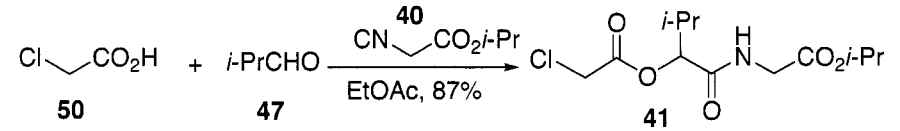
39, 59% yield, 87% *ee*

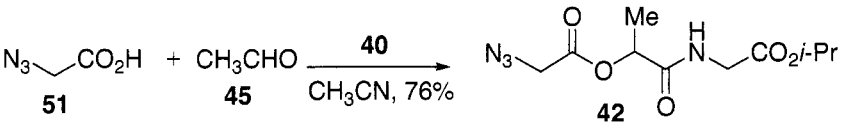
3.5.6 Use of the Passerini Reaction in Complex Synthesis

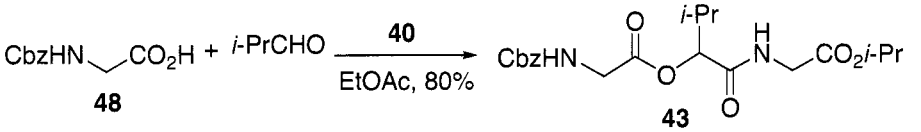
Depsipeptides, α-Ketoamides and β-Amino-α-hydroxyamides

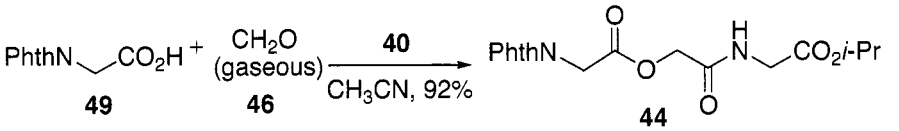
Early development of the Passerini reaction focused on the convergent synthesis of complex depsipeptide derivatives. In 1962 Ugi described the use of isopropyl α-isocyano ester **40** as a glycine precursor to prepare the simple

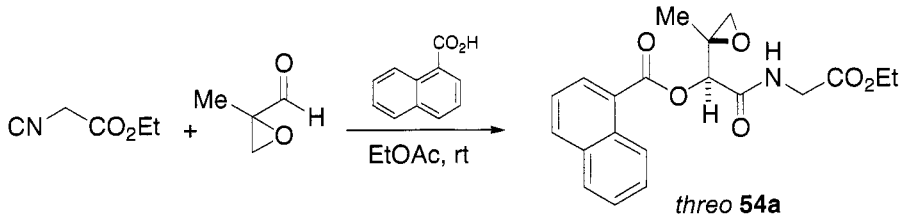
depsipeptides (**41**–**44**) in excellent yields.[48] Simple (**45** and **46**) and branched aldehydes (**47**) proved to be excellent substrates and protected glycines (**48** and **49**) or glycine surrogates (**50** and **51**) could also be utilized.





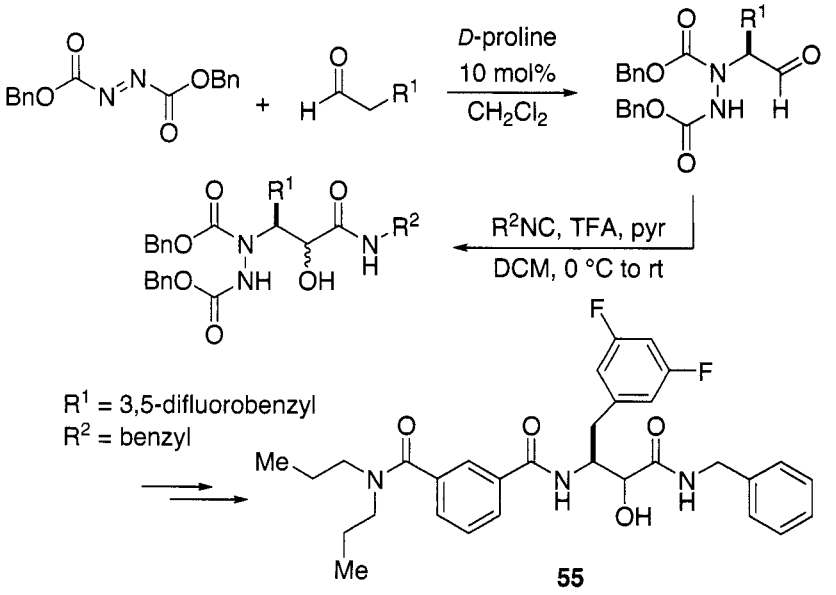






The Passerini reaction has been explored by Armstrong for use in the attempted construction of the antitumor azinomycins A (**52**) and B (**53**)[49] and a variety of analogs.[50] The reaction of ethyl isocyanoacetate, 1-naphthoic acid and 2-methylglycidal in ethyl acetate provided the α-acyloxyamides **54** in 73% overall yield (dr 3.6:1, *threo* **54a** : *erythro* **54b**). Similarly, the use of α-isocyano methylphosphonate yielded the corresponding P-3CR amide in similar fashion (75% yield, dr 3.5:1 *threo*:*erythro*).

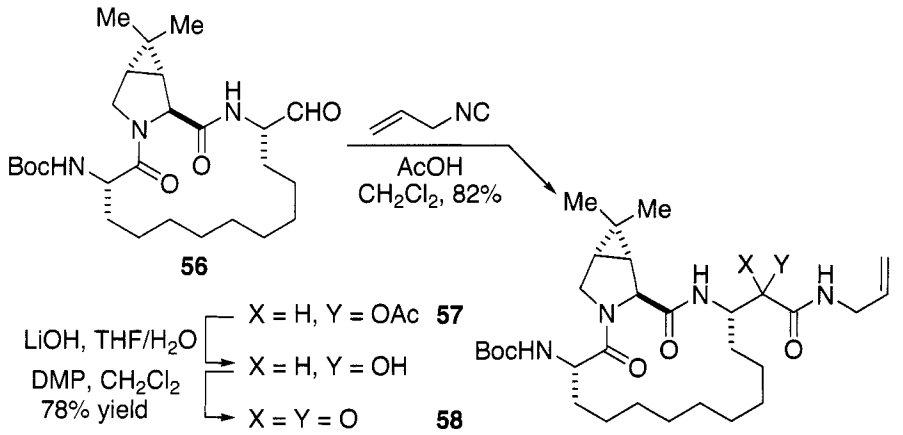
The norstatines are a class of β-secretase (BACE) inhibitors, which may have therapeutic relevance for the treatment of Alzheimer's disease. A number of norstatines were synthesized via the Passerini reaction following the catalytic α-amination of alkyl aldehydes using *D*-proline.[51] The two step protocol was accomplished in good yields (**55**, 86% yield, 80:20 dr) but with low diastereoselectivity for almost all examples. The nitrogen protecting groups were removed with HCl and the N–N bond of the resulting hydrazines cleaved with Pd/C and hydrogen. Standard amide coupling subsequently provided a library of norstatines.



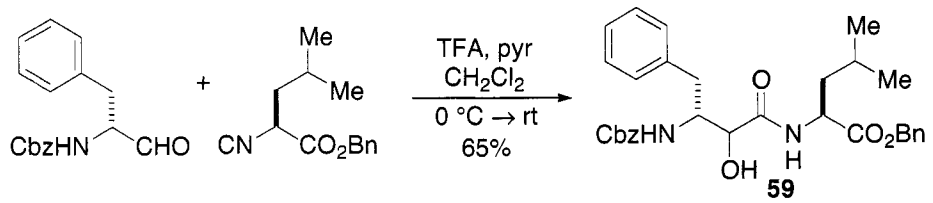
55

Many protease/peptidase inhibitor peptidomimetics include α-ketoamide moieties as key bioactive functionalities and the Passerini reaction provides a facile entry for their preparation through the oxidation of α-hydroxy amides. Researchers at Schering–Plough[58] have utilized this strategy to synthesize a variety of a macrocyclic α-ketoamides towards the development of Hepatitis C virus (HCV) NS3 protease inhibitors. Aldehyde **56** was treated with allylisocyanide and acetic acid to give α-acyloxyamide

57 in 82% yield. Subsequently, hydrolysis of the acetate ester and Dess–Martin oxidation gave the α-ketoamide **58** in 78% overall yield from aldehyde **56**.

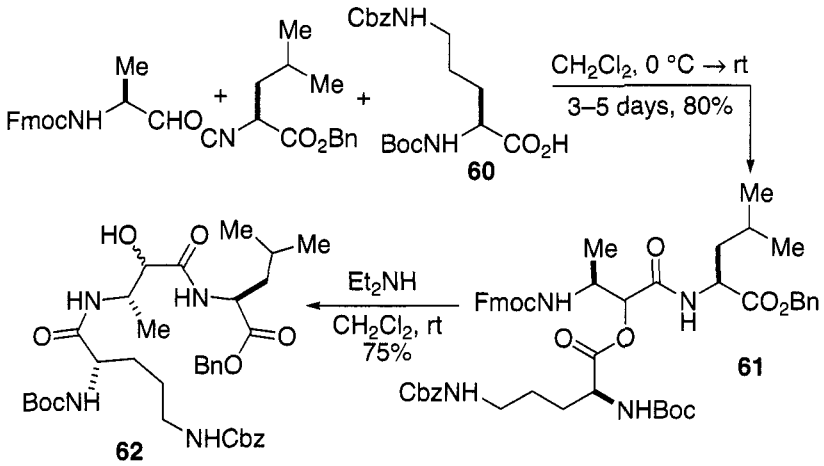


The Passerini reaction is also an efficient method to construct β-amino-α-hydroxyamide residues and to simultaneously couple two or more fragments. An effective protocol for multi-gram syntheses[53] has been the use of TFA/pyridine[54] to promote the Passerini reaction of α-amino aldehydes and the α-isocyano esters. The α-(trifluoroacetoxy)amide products are usually hydrolyzed to the corresponding α-hydroxyamides during normal reaction workup and chromatography. The TFA/pyridine conditions are compatible with many standard peptide protecting groups and have been used to synthesize several selective chimeric Factor Xa inhibitors.[55] Bestatin, a natural product demonstrating potent peptidase inhibition, was also efficiently synthesized using this method[53] in only two steps from the Passerini product **59**.

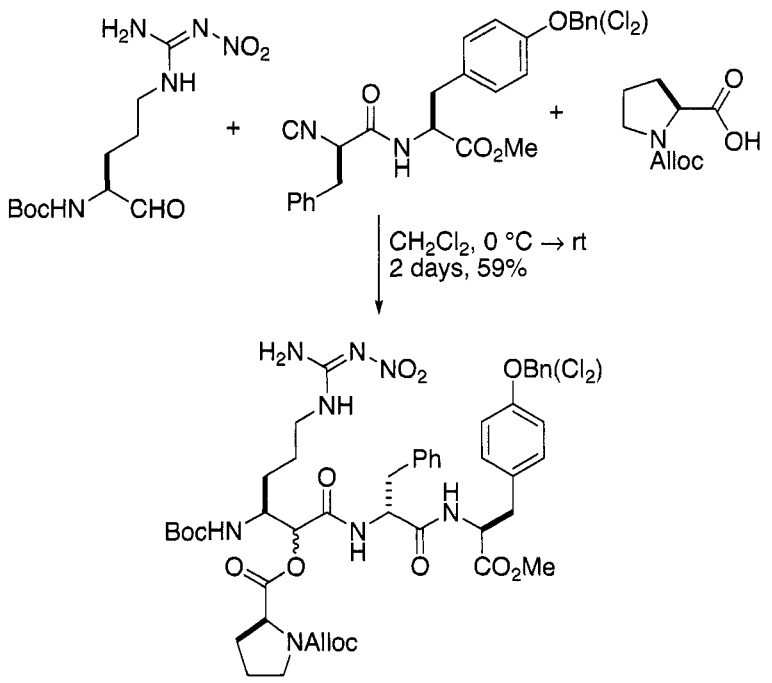


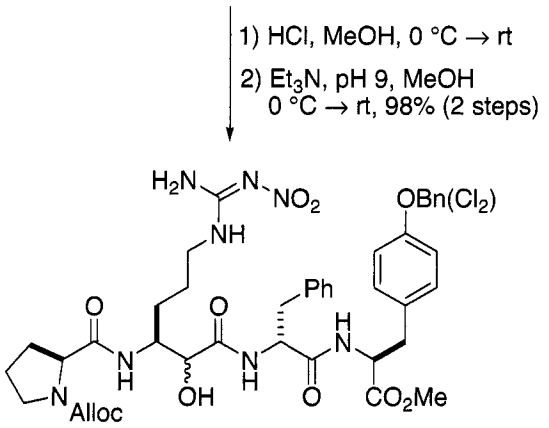
The prolyl endopeptidase (PEP) inhibitor eurystatin A has been synthesized by two distinct strategies[56,57] that incorporated the P-3CR. A particularly efficient approach used protected ornithine **60** as the carboxylic acid component and then utilized[57] a post-Passerini *O*→*N*-acyl transfer

(**61**→**62**),[58] occurring in situ upon deprotection of the N-terminus by diethylamine to construct advanced intermediate **62**.



The strategy of using a post-Passerini *O*→*N*-acyl transfer has also proven to be highly efficient for the synthesis of a cytomegalovirus protease inhibitor,[59] and the N(10)–C(17) fragment of the cyclotheonamides (**60**), a series of important inhibitors of several trypsin-like serine proteases.[60]

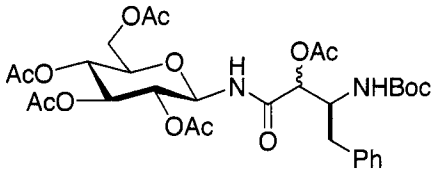




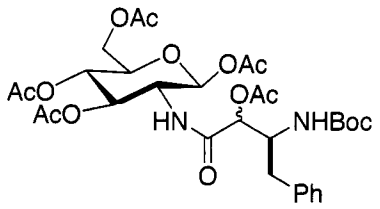
60

Glycopeptides

The use of the Passerini reaction for oligopeptide synthesis has been extended to glycopeptides by using suitably functionalized and protected sugars. Anomeric glycosyl isonitriles and 2-isocyanoglucopyranoses have been used for coupling with *N*-Boc protected phenylalanal or glycinal derivatives and a variety of carboxylic acids to give the desired glycopeptides in modest yields (14–90%).[61]



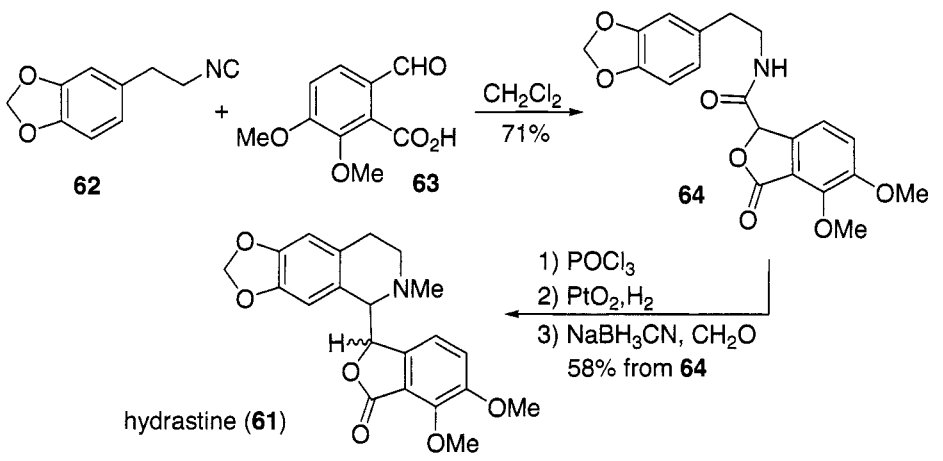
41% yield, 58:42 *dr*



57% yield, 60:40 *dr*

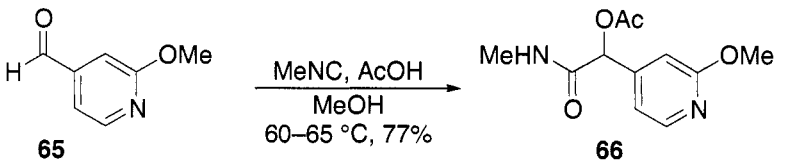
Heterocycles

The synthesis of hydrastine (**61**) by Falck and Manna[62] demonstrate that the amide product of the Passerini reaction could be used in a subsequent Bischler–Napieralski reaction as a method to produce isoquinolines. In their report, carboxybenzaldehyde derivative **62** was condensed with isonitrile **63** in 71% yield to provide amide **64**. Cyclization ($POCl_3/CH_3CN$), reduction of the dihydroisoquinoline (Adam's catalyst/H_2), and reductive alkylation with formaldehyde gave a diastereomeric mixture of α- and β-hydrastines in 58% overall yield from Passerini product **64**.

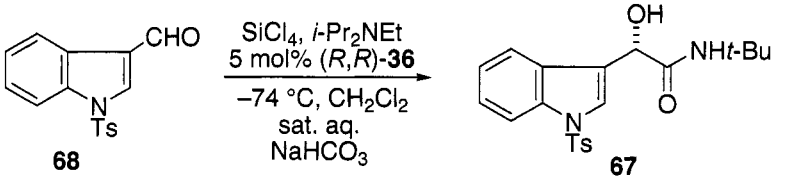


The particularly mild conditions of Passerini reactions, and the corresponding broad functional group tolerance, has meant that many reactive functionalities can remain unprotected on the component substrates and then utilized in a secondary reaction as a tandem or domino reaction sequence. Notably, this facet has led to the extensive use of the Passerini reaction for the construction of numerous functionalized furans,[63] oxazoles,[21,64] tetrazoles,[41,42] β-lactams,[65] butenolides[66] and other complex heterocycles.[67]

The Passerini reaction has also been utilized as a method for the homologation of heterocyclic carboxaldehydes.[68] Studies by Weinreb and co-workers,[69] directed toward the synthesis of amphimedine, have used a Passerini reaction for the homologation of the methoxypyridine derivative **65** with methyl isocyanide and acetic acid in methanol to give **66** in 77% yield.

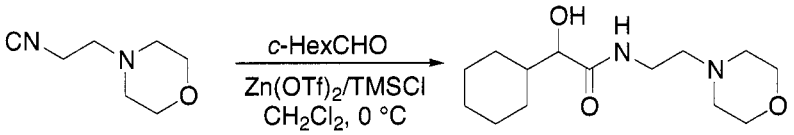


6.5.7 *Experimental Procedures*



(*S*)-(–)-*N*-*tert*-Butyl-2-hydroxy-3-(1-(4-methylphenyl)sulfonyl-1*H*-indole)acetamide (67)[51a]

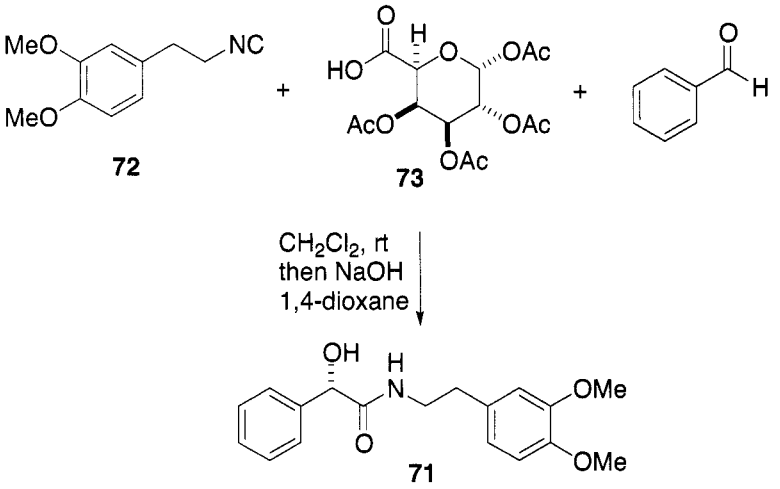
A solution of *tert*-butyl isocyanide (125 μL, d = 0.735, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via syringe pump to a cold solution of indole-3-carboxaldehyde **68** (300 mg, 1.0 mmol), catalyst (*R*,*R*)-**36** (43 mg, 0.05 mmol, 0.05 equiv), $SiCl_4$ (125 μL, d = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, d = 0.742, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at –74 °C. The reaction was then stirred for an additional 4 h and transferred dropwise to a vigorously stirred, ice-cold, saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was then stirred for 2 h at rt. The white precipitate was filtered off through Celite and the filtrate extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Subjection to silica gel chromatography (20 mm column, 60 g silica) gave 323 mg (81%) of amide **67** as a white solid.



70 **69**

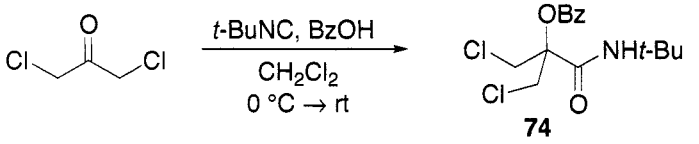
2-Cyclohexyl-2-hydroxy-*N*-(2-morpholinoethyl)acetamide (69)[21]

To a stirred suspension of $Zn(OTf)_2$ (0.3 mmol) and cyclohexanone (1 mmol) in CH_2Cl_2 (5 mL) was added TMSCl (3 mmol) at 0 °C under argon. The heterogeneous mixture was stirred for 5 min at 0 °C, then 2-morpholinoethyl isonitrile (**70**) (1.05 mmol) was added. The reaction mixture was warmed to rt and stirred for 24 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was stirred for another 20 min. The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated and the residue purified by silica gel flash column chromatography to afford **69** (57%).



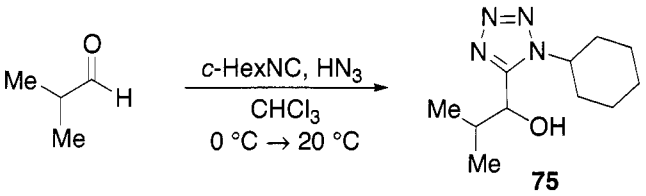
(*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-2-phenylacetamide (71)[45]

A mixture of benzaldehyde (6 mmol), 2-(3,4-dimethoxyphenyl)ethyl isocyanide (**72**) (6 mmol) and 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid (**73**) (6 mmol) in 15 mL of acetonitrile was stirred for 16 h at r.t. Subsequently, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated. The residue was taken up in a mixture of 1 N NaOH (5 mL) and dioxane (10 mL). This mixture was stirred for 1 h at r.t., acidified to pH 2 with 2 N HCl and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel flash chromatography to obtain **71** (1.2 g, 63%) as a colorless crystalline solid.



***N-tert*-butyl-2-Benzyloxy-3-chloro-2-chloromethylpropanamide (74)**[65]

To solution of 1,3-dichloroacetone (2.35 g, 50 mmol) in CH_2Cl_2 (10 mL) was added benzoic acid (50 mmol) and followed by *tert*-butylisocyanide (50 mmol) at 0 °C. The reaction mixture was maintained at 0 °C for 15 min before allowed to come to room temperature. After the reaction was complete, the solvent was evaporated and ether was added. The resulting crystalline solid was collected giving **74** (68%).



75

1-Cyclohexyl-5-(1-hydroxy-2-methyl-propyl)tetrazole (75)[41]

To a stirred solution of HN_3 in chloroform (40 mL, 7.3%, 68 mmol) at 0 °C was added freshly distilled isobutyraldehyde (4.33 g, 60 mmol). To the mixture was added dropwise cyclohexylisocyanide (5.45 g, 50 mmol) with continued ice-cooling. The mixture was then kept below 20 °C for the next three days at which point the solid was collected and then recrystallized from cyclohexane to give tetrazole **75** (9.54 g, 85%).

3.5.8 References

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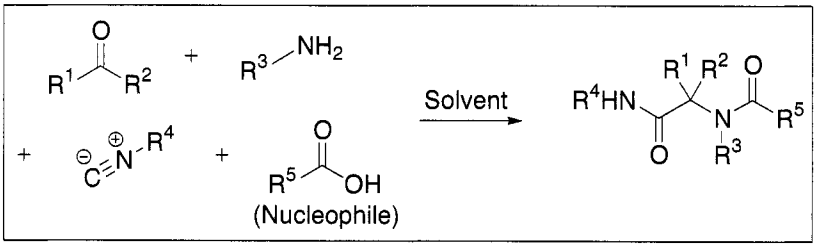
3.6 Ugi Reaction

David R. Williams and Martin J. Walsh

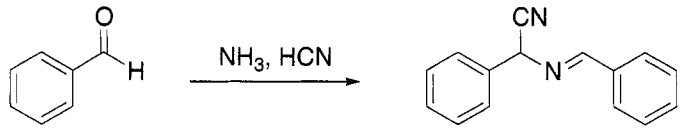
3.6.1 Description

The Ugi Reaction is the one-pot condensation of an amine, aldehyde or ketone, isocyanide, and a nucleophile to afford α-substituted carboxamide derivatives.[1] Also known as the Ugi Four-Component Reaction (U-4CR) or Ugi Four-Component Coupling (or Condensation) (U-4CC), this reaction is recognized as a reliable tool for the construction of peptide bonds and for its applications within combinatorial chemistry.[2]



3.6.2 Historical Perspective

The roots of the U-4CR lie in research reported long before its discovery in the early 1960s. The first multicomponent reaction (MCR) is credited to Laurent and Gerhardt who, in 1838, isolated an unexpected product from a reaction involving benzaldehyde, ammonia, and hydrogen cyanide.[3] The resulting "benzoyl azotide" (1) presents the Schiff base of the Strecker adduct and benzaldehyde. Ironically, Strecker described such a reaction more than a decade later.[4] In the years that followed, many variations of MCRs were reported,[5] but it wasn't until 1921 that Passerini first utilized the isocyanide functionality and its unique reactivity in a MCR.[6,7] It was this work that inspired Ugi and led to focused investigations of this reaction process.



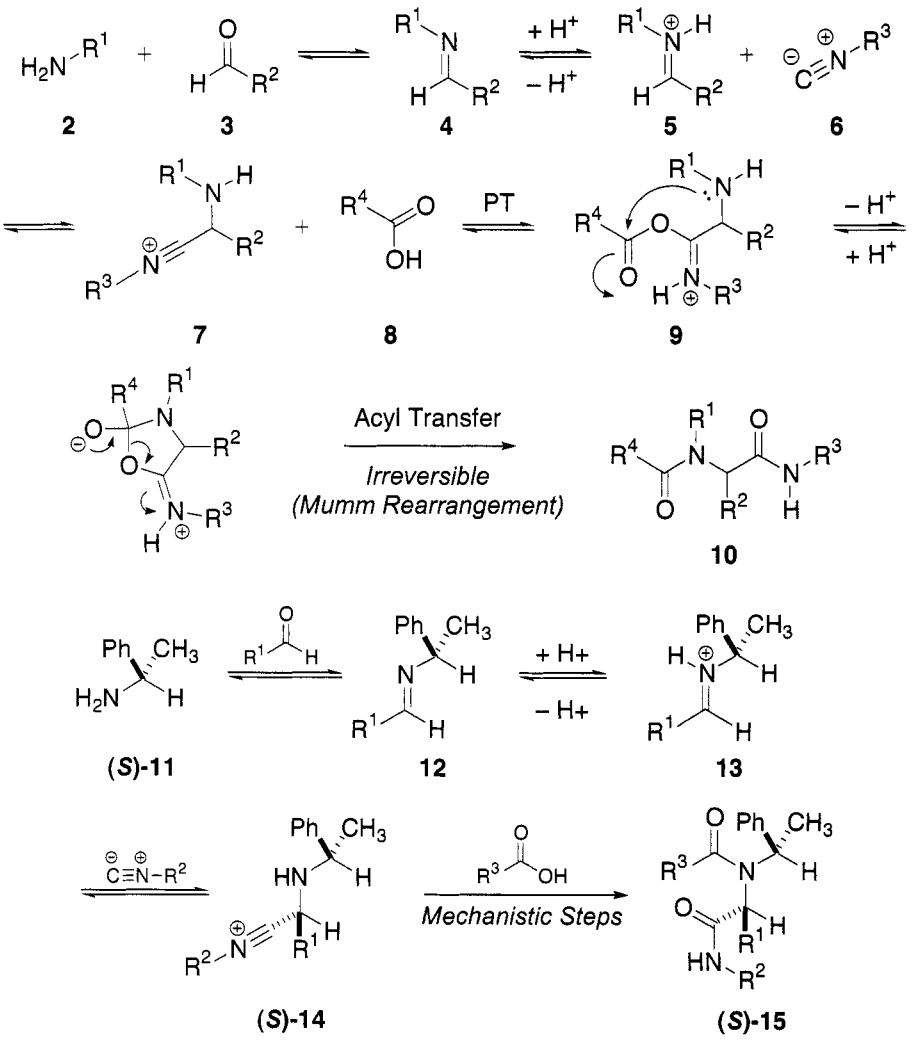
1

In a series of communications between 1959 and 1962, Ugi described the four-component condensation of an oxo-containing species, amine, isocyanide, and carboxylic acid to give α-acylamino carboxamide products.[1] This discovery introduced the multicomponent reaction to the field of peptide chemistry and, thus, dramatically increased its applicability. Ugi showed that a broad range of nucleophilic components — including hydrogen sulfide, hydrogen selenide, hydrazoic acids, cyanates, thiocyanates, carbonic acid monoesters, salts of secondary amines, and water – were viable partners in the reaction. In addition, procedures made use of either ketones or aldehydes as the oxo-containing component. Primary or secondary amines, hydroxylamines, ammonia, hydrazides and hydrazines were found to successfully participate as the amine component.

Today, the MCR is generally defined as a reaction in which more than two reactants come together to form a product that possesses some major component of each of the starting materials.[2] Ugi and Dömling have described three general types of MCRs, depending on the equilibrium characteristics associated with the reactions.[2a] A Type I MCR is one in which the starting materials, intermediates, and products are in dynamic equilibrium with one another. The Type II MCR, while possessing both reversible and irreversible preliminary steps, is characterized by an irreversible final step that drives the reaction to completion. Finally, the Type III MCR exists as a series of irreversible steps. With this in mind, an irreversible Mumm rearrangement is described as the final mechanistic step of the U-4CR as a representative of a Type II MCR.

3.6.3 Mechanism

A generalized mechanism for the U-4CR involves initial condensation of the amine component (**2**) and aldehyde component (**3**) to give an imine intermediate (**4**).[1d,8] Next, activation of **4** by either a Lewis or Brönsted acid present in the reaction mixture affords the iminium **5**. Addition of the isonitrile component (**6**) to the iminium ion gives a nitrilium species (**7**) that undergoes nucleophilic capture by the carboxylic acid component (**8**). Subsequent proton transfer generates a second iminium intermediate (**9**). Intramolecular condensation of the amine with the carbonyl and acyl transfer then gives rise to the α-acylamino carboxamide product **10**. This final acyl transfer step, or Mumm rearrangement,[9] is irreversible and, with the formation of two amide functionalities, provides a driving force in the reaction.



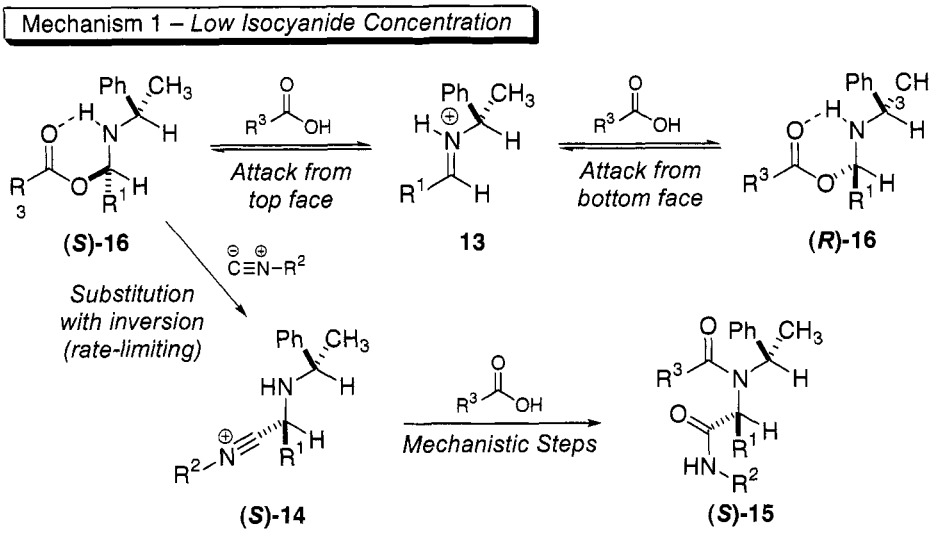
Intricate studies have shown that this mechanistic rationale may not be an accurate depiction of the U-4CR process.[2e,10] Ugi utilized chiral α-methylbenzylamines to apply an element of stereochemical control based on the described generalized mechanistic considerations. In this proposed mechanism, condensation of an aldehyde and (*S*)-α-methylbenzylamine (**(*S*)-11**) affords imine **12**. The isocyanide is then expected to approach the activated iminium ion (**13**) from the less hindered face, based on assumptions that the imine would assume an (*E*)-configuration. This is supported by a minimization of $A^{1,3}$ strain that would place the benzylic and iminium

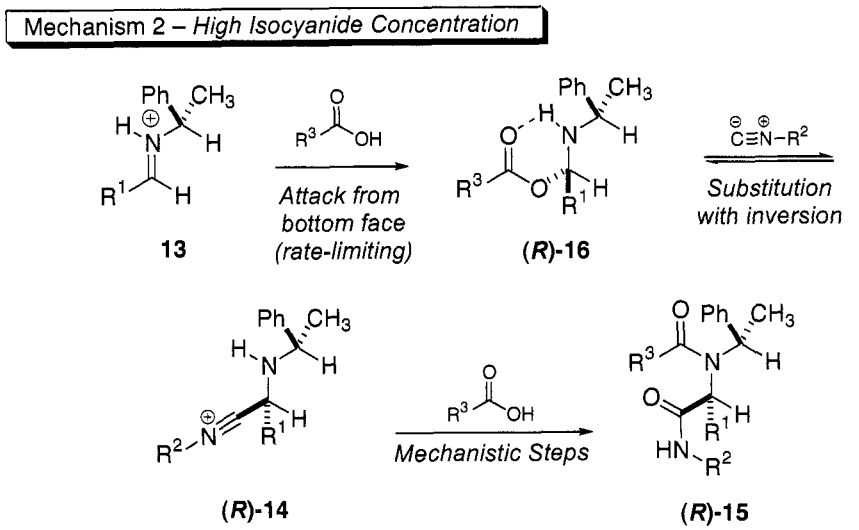
hydrogens in a coplanar conformation. The nitrilium ion **(*S*)-14** would then be captured by the nucleophilic carboxylic acid, suggesting stereoselective formation of the Ugi product **(*S*)-15**.

In the course of Ugi's experiments, the concentration of the isocyanide component was found to play a significant role in the stereochemical outcome of the reaction.[10,11] At low concentrations, **(*S*)-15** was found to be the major product, while at high concentrations, **(*R*)-15** was formed preferentially. To explain this phenomenon, Ugi proposed two competing mechanisms in which the iminium ion **13** is initially attacked by the carboxylic acid, resulting in the formation of the hydrogen-bonded aminal **16**. In mechanism 1, a low concentration of isocyanide allows for equilibration between **13** and the diastereomeric aminals **(*R*)-16** and **(*S*)-16**. It has been proposed that, kinetically, **(*R*)-16** is favored as nucleophilic capture of the iminium occurs from the less hindered face. However, destabilizing non-bonded interactions in **(*R*)-16** are suggested to thermodynamically favor **(*S*)-16**. As a result, the rate-limiting step of backside displacement of the carboxylate in **(*S*)-16** by the isonitrile yields the nitrilium intermediate **(*S*)-14**. After addition of the carboxylate to **(*S*)-14** and irreversible Mumm rearrangement, the observed Ugi product **(*S*)-15** is produced. It is not evident that this mechanistic rationalization can adequately discount the direct stereoselective addition of isocyanide to iminium **13** to give **(*S*)-14**, thus avoiding the proposed S_N2 displacement.

A significant change in stereoselectivity in the reaction occurs by increasing the concentration of isocyanide (mechanism 2). Under these conditions, Ugi argues that the addition of carboxylate to iminium **13** becomes the rate-limiting step due to the increased rate of S_N2 displacement by isocyanide. This change does not allow for the pre-equilibration described in mechanism 1 and, therefore, favors kinetic production of **(*R*)-16**. As a result, the nitrilium species **(*R*)-14** is produced and, after nucleophilic capture and Mumm rearrangement, gives rise to the Ugi adduct **(*R*)-15**.

While the mechanism of the U-4CR has not been fully explained, the reaction pathways involving hydrogen-bonded aminal intermediates are generally considered viable, especially in the polar solvents most often employed in these reactions. In non-polar solvents, the mechanism involving direct addition of the isocyanide component to the activated iminium ion cannot be discounted. Recent studies have provided spectroscopic evidence that seems to support the presence of the proposed aminal esters, such as **(*S*)-16** and **(*R*)-16**, as intermediates in the U-4CR.[12] In addition, it has been suggested that the inversion of configuration which characterizes nucleophilic isocyanide displacement may proceed through a tight ion pair.[12,13] Further studies in this area will ultimately provide information critical to the advancement of asymmetric variations of the U-4CR.





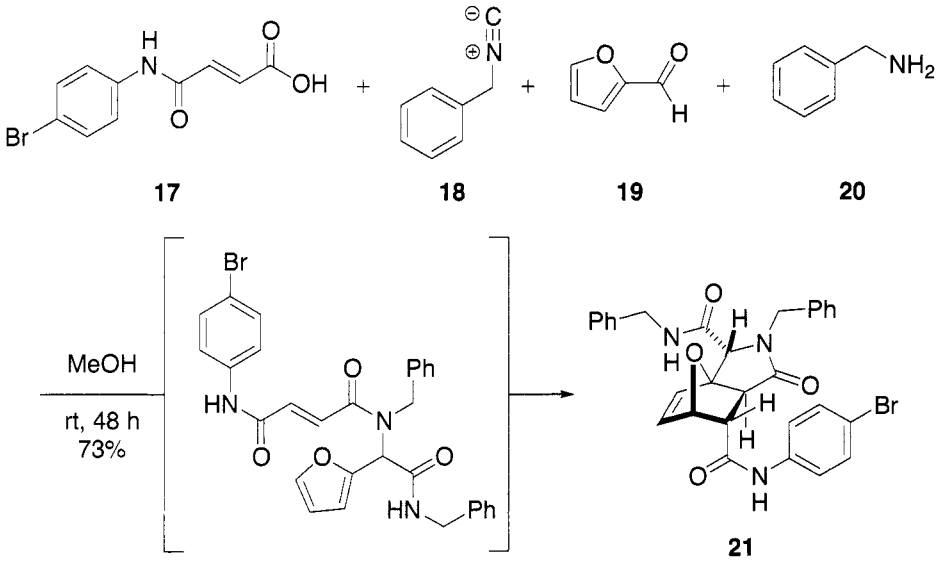
3.6.4 Synthetic Utility

Participation in Tandem Reactions

One advantage of the U-4CR lies in its ability to efficiently generate substances of significant molecular complexity from simple starting materials. As a result, the products of these reactions are often well suited for further transformations via tandem processes. Smiles rearrangements,[14] [2+2] photocycloadditions,[15] intramolecular cyclizations,[16] Horner–Wadsworth–Emmons olefinations,[17] Knoevanagel condensations,[18] ring-

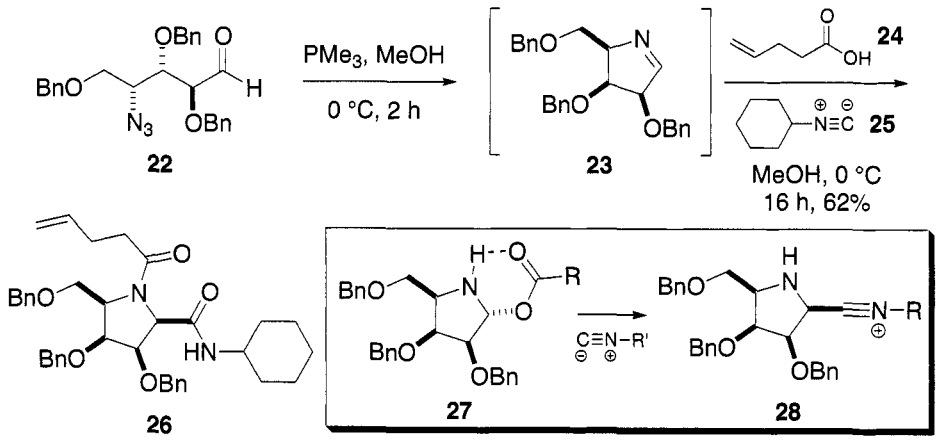
closing metatheses,[19] and Biginelli multicomponent reactions[20] are just a few of the reactions that have served as competent partners in tandem processes involving the U-4CR.[21]

Tandem U-4CR/Diels–Alder strategies have been widely employed for the synthesis of complex organic frameworks. Oikawa has shown that one-pot variants of this process can lead to good yields of products with greater than 10:1 diastereomeric ratios.[22] A solution of *N*-(4-bromophenyl) maleamic acid (**17**), benzyl isocyanide (**18**), furfural (**19**), and benzylamine (**20**) in a 1 : 1 : 1 : 1 ratio in methanol for 2 days led to the 7-oxanorbornene **21** in 73% yield.



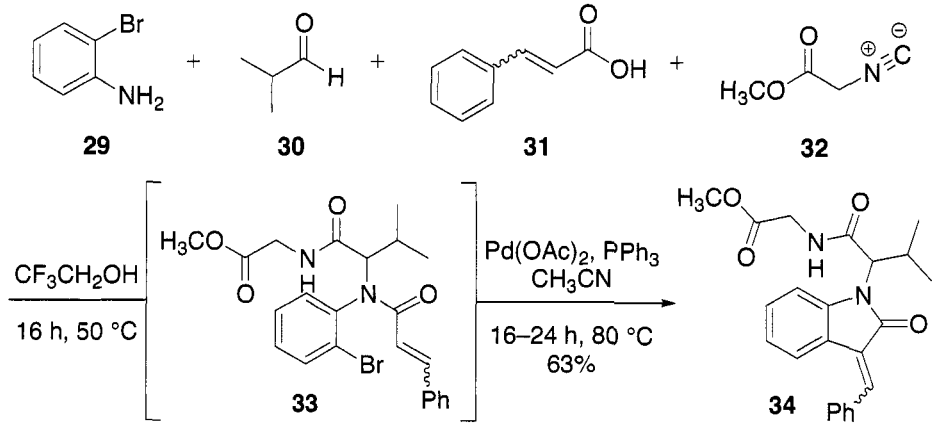
17 **18** **19** **20** **21**

The Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR) has been shown to be an effective method for the generation of polyhydroxylated proline analogues from γ-azidoaldehydes.[23] The treatment of **22** with trimethylphosphine in methanol results in the pyrroline **23**. This imine intermediate is then directly subjected to pent-4-enoic acid (**24**) and cyclohexylisocyanide (**25**) in methanol affording the all *syn* product **26** in 62% and as a single diastereomer.



The stereochemical outcome of this reaction provides further evidence supporting an aminal intermediate in the U-4CR.[12] Due to the substitution pattern of the five-membered ring, an approaching nucleophile must attack the intermediate pyrrolinium ion from the less hindered face. In the event of a carboxylate nucleophile, aminal **27** would result. Subsequent attack by the isocyanide accompanied by stereochemical inversion (S_N2) gives the nitrilium **28** and the stereochemistry as observed in the product. Overall, this process provides moderate to good yields.

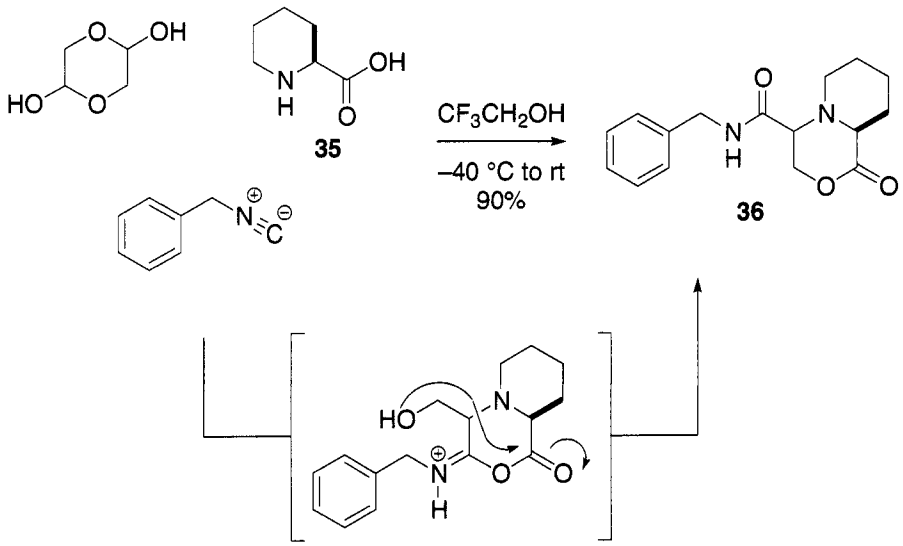
A one-pot synthesis of indol-2-ones has been reported by Umkehrer and co-workers via a tandem U-4CR/Heck coupling process.[24] In this case, optimized conditions involved the precondensation of bromoaniline **29** and aldehyde **30**. The resulting imine was then reacted with carboxylic acid **31** and isocyanide **32** to give the intermediate Ugi product **33**. The exchange of solvents from polar protic to a polar aprotic medium followed by the introduction of a palladium catalyst afforded the indol-2-one **34** in 63% yield.



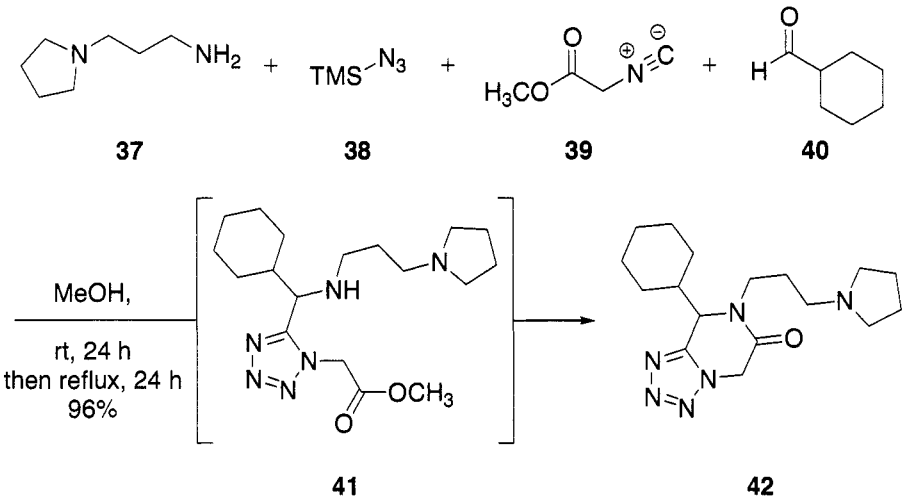
Heterocycle Formation

A major advantage of the U-4CR offers the generation of a number of hetereocyclic motifs in a single step. To date, the U-4CR has been applied for the construction of imidazolines,[25] benzothiazoles and benzoxazoles,[14] thiazoles,[26] quinolines,[27] oxazoles,[28] isoxazoles,[29] pyrrolidones and pyridones,[17] pyrroles,[30] hydantoins,[31] indoles,[32] and benzimidazoles.[33]

Kim and co-workers have recently described their efforts towards 3,5-substituted morpholin-2-one scaffolds via a three-component variant of the classic U-4CR.[34] The use of amino acids (e.g., **35**) as both the amine and carboxylic acid components in the reaction represents a particularly interesting development. By varying the length of the tether in the starting amino acid, Kim deploys this strategy to successfully prepare [2.4.0]-, [3.4.0]-, and [4.4.0]-bicycles (**36**). Overall, good to excellent yields are reported.



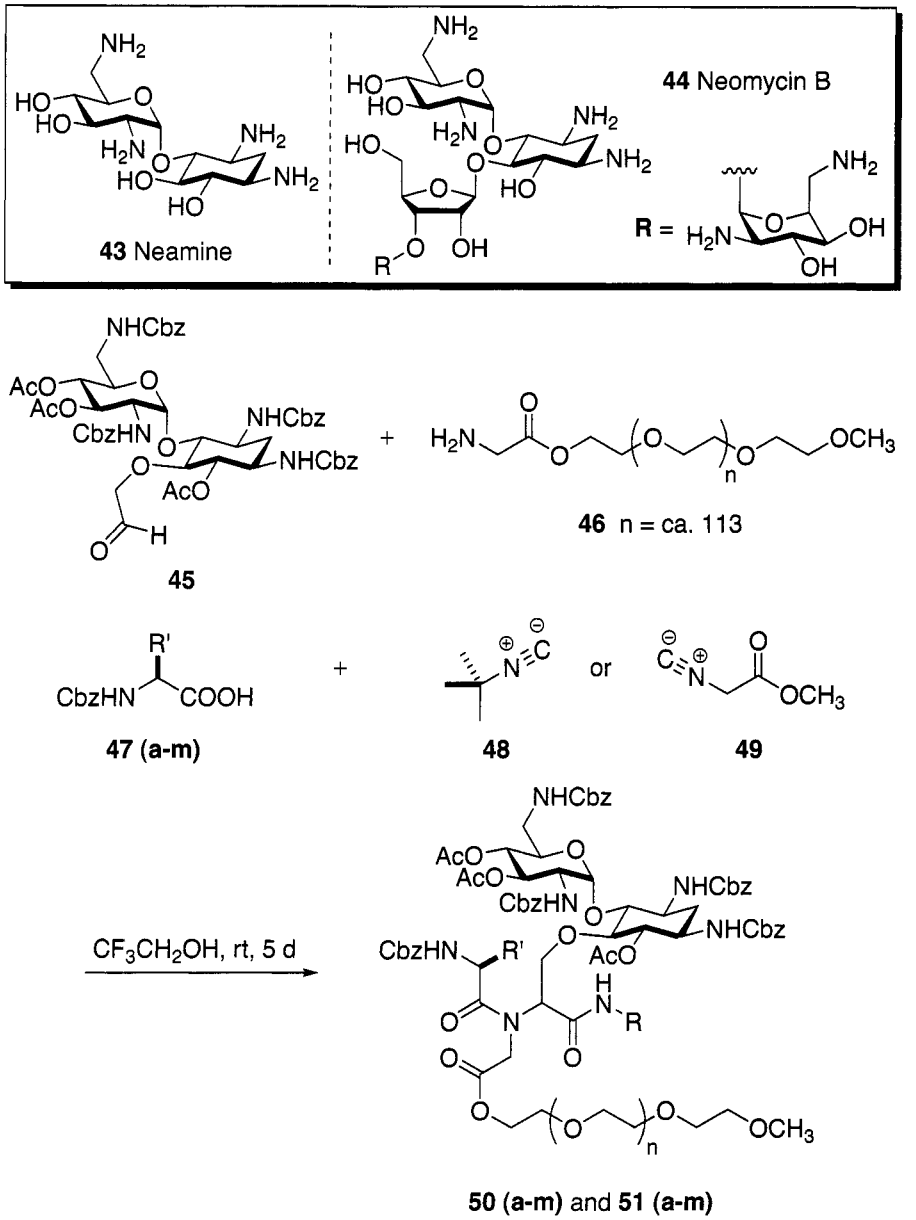
By varying the nucleophilic component in the U-4CR, a variety of heterocyclic compounds may be synthesized. Such an example is illustrated in the one-pot synthesis of fused tetrazole-ketopiperazines, as demonstrated by Hulme and co-workers.[35] The treatment of trimethylsilyl azide (**38**) with amine **37**, isonitrile **39**, and aldehyde **40** gave the intermediate tetrazole **41** that underwent spontaneous lactamization to afford **42**. In this report, the formation of [3.4.0]-bicycles proceeds in good to excellent yields for all examples. However, attempts to form [3.5.0]-bicyclic systems using methyl-β-isonitrile propionate resulted in significantly decreased yields.



Generation of Chemical Libraries

In 1961, Ugi and co-workers reported the first chemical library via the U-4CR.[36] In this work, 10,000 unique compounds were synthesized using ten different variations of each of the four starting materials (10^4). Today, the application of an efficient route to a large number of compounds has been used extensively,[37,38] including in the discovery of the HIV protease inhibitor *Crixivan*™ (MK 639), which is now marketed by Merck.[39]

An excellent application of the U-4CR effectively generates large libraries of compounds for biological evaluation as recently reported by Wong and co-workers.[40] Neamine (**43**) is the active pharmacophore substructure of neomycin B (**44**), which is an effective aminoglycoside antibiotic (inhibition of HIV (IC_{50} = 0.1 to 1.0 μM)). The instability and toxicity of neomycin B have focused attention on the development and evaluation of bioactive analogues of **44** possessing the neamine core. Wong has utilized the U-4CR to efficiently create a large library of neomycin B mimetics from the neamine-derived aldehyde **45**, amine **46**, protected amino acids **47(a-m)**, and two isocyanides (**48** and **49**). In addition, the products of these reactions (**50(a-m)** and **51(a-m)**) precipitated out of solution, minimizing the need for further purification. Finally, the stereogenicity created in the reaction provided greater than 90% diastereomeric purity in all cases. These efforts led to nine compounds that showed equal or better activity than that of neomycin B itself.

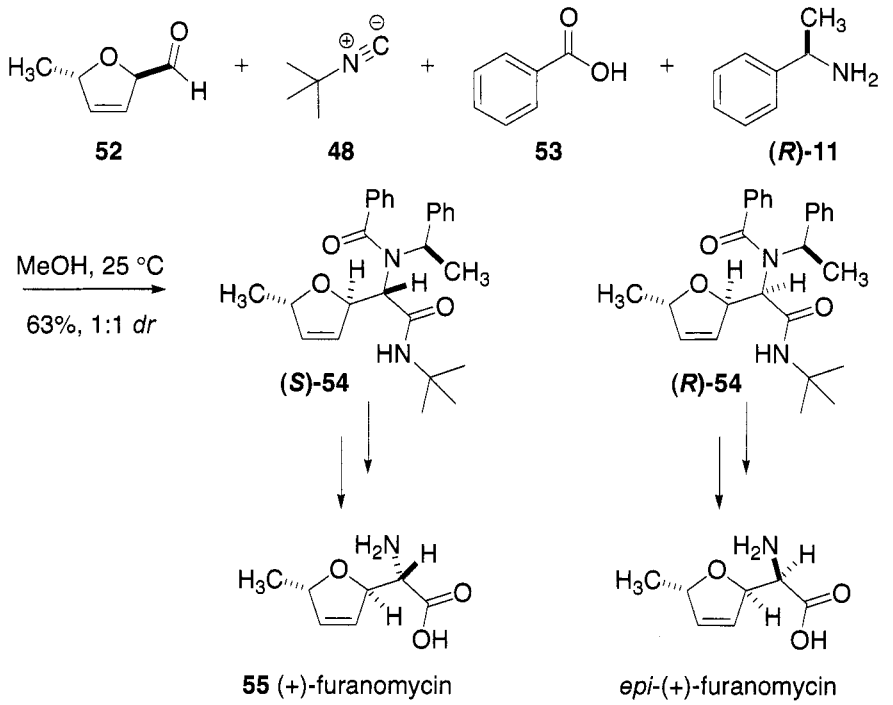


47a Gly, **47b** Ala, **47c** Val, **47d** Phe, **47e** Trp, **47f** His, **47g** Tyr, **47h** Thr, **47i** Ser, **47j** Asp, **47k** Gln, **47l** Lys, and **47m** Arg (side chains of amino acids bearing free nitrogens were also protected with Cbz). **50** R = $CH(CH_3)_3$. **51** R = $CH_2C(O)OCH_3$

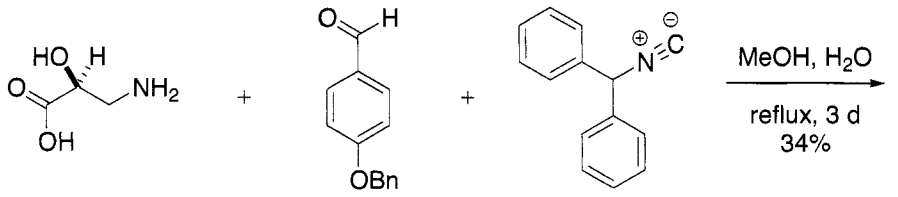
Natural Product Synthesis

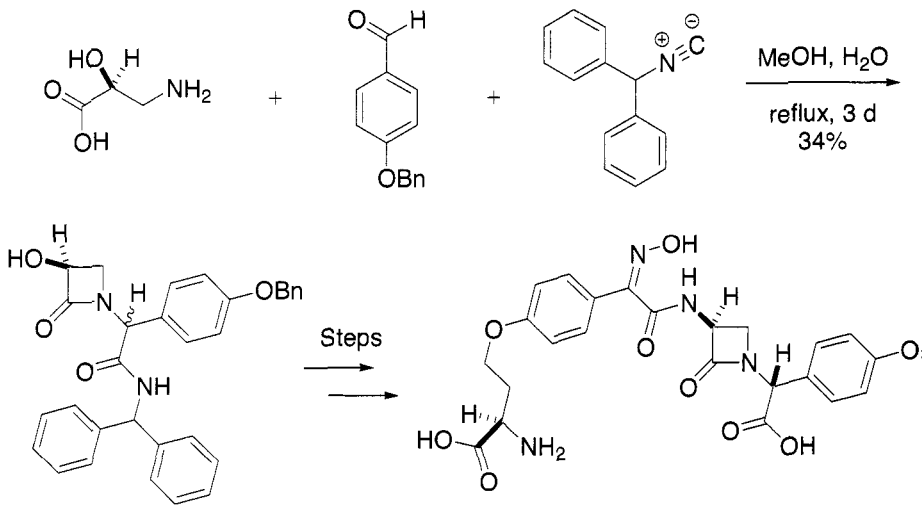
An early example of a total synthesis utilizing the U-4CR was reported by Joullié and co-workers in their efforts towards (+)-furanomycin (**55**).[41] At

the outset of these efforts, the relative and absolute stereochemistry of the natural product had not been rigorously assigned. The condensation of the D-glucose-derived aldehyde **52**, (*R*)-α-methylbenzylamine (**(*R*)-11**), benzoic acid (**53**) and *t*-butyl isocyanide (**48**) gave rise to two diastereomers **(*S*)-54** and **(*R*)-54**. These two diastereomers were separated and utilized to assign the relative stereochemistry of the natural product.



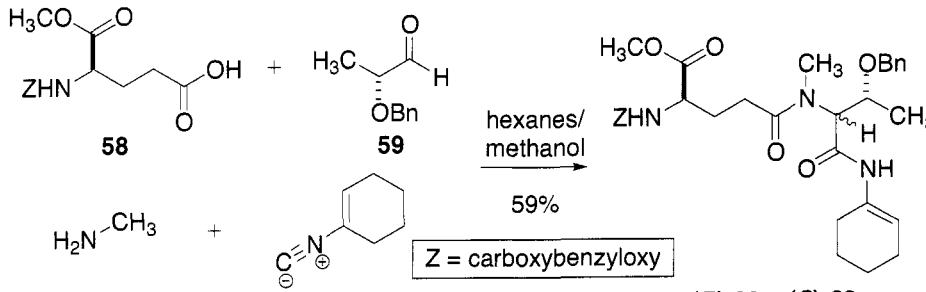
An example of heterocycle construction via the U-4CR in the context of natural product synthesis has been demonstrated by Hofheinz and Isenring.[42] Employing the U-4CR rapidly provided access to the functionalized β-lactam **56**, which was utilized in the total synthesis of the antibiotic nocardicin A (**57**). In this case, marginal yields were offset by inexpensive and readily available starting materials.



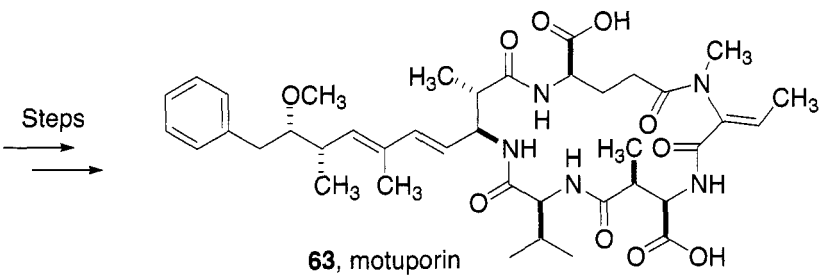


56 **57**, nocardicin A

Armstrong has recently reported the total synthesis of the protein phosphatase inhibitor motuporin (**63**), in which a U-4CR was utilized to construct the synthetically challenging tertiary amide bond found in the natural product.[43] Exploitation of the U-4CR using carboxylic acid **58**, α-benzyloxyaldehyde **59**, methylamine (**60**), and 1-isocyanocyclohexene (**61**) gave a mixture of separable diastereomers (***R*)-62** and (***S*)-62**. The isocyanide used in this reaction of particular interest as it eventually allows for the facile hydrolysis of the secondary amide generated in the reaction.[44]

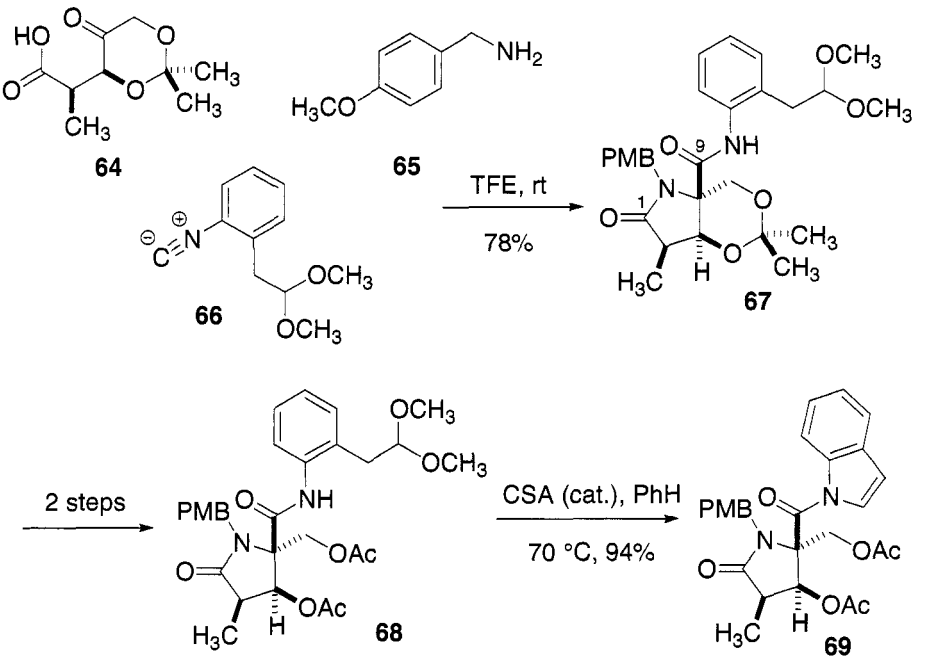


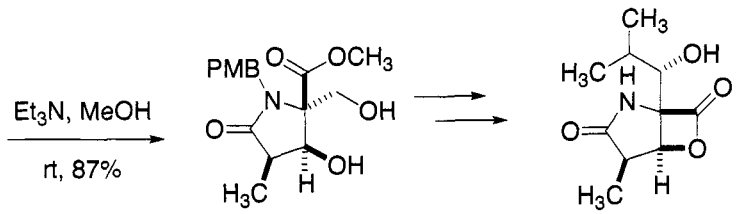
58 **59** **60** **61** **(*R*)-62 + (*S*)-62**
1.4:1 mixture of diastereomers



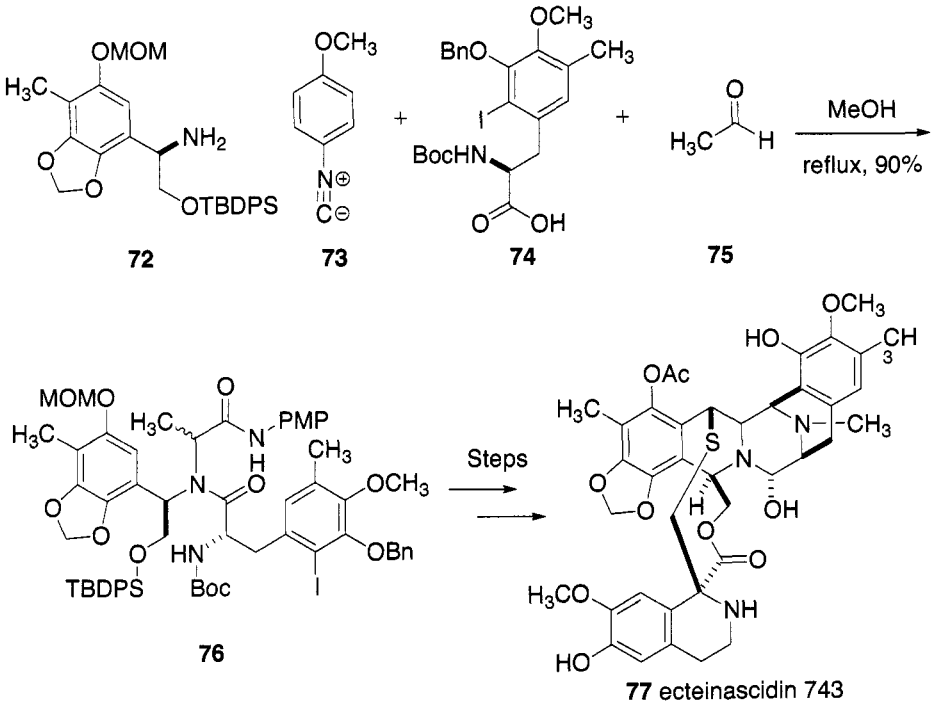
63, motuporin

A formal total synthesis of the proteasome inhibitor omuralide (**71**) has been reported by Kobayashi and co-workers involving a highly diastereoselective U-3CR.[45] The condensation of γ-ketoacid **64**, *p*-methoxybenzylamine (**65**) and isonitrile **66** resulted in the γ-lactam **67** as a single diastereomer. The source of the stereoselectivity in the reaction is rationalized by axial attack of the isonitrile with the intermediate iminium ion. In addition, the novel isonitrile **66** was developed and used in the reaction in order to avoid the difficulty associated with subsequent selective trans-esterification of the more hindered amide (C9 vs. C1) in the Ugi product. Conversion of **68** to the *N*-acylindole **69** was accomplished under mildly acidic conditions. This intermediate was then treated with methanol and triethylamine to readily afford the *neo*-pentyl methyl ester **70** without observable methanolysis of the lactam functionality.





Fukuyama and co-workers have reported the use of a highly successful U-4CR in the course of a recent total synthesis of the antitumor agent ecteinascidin 743 (**77**).[46] The coupling of amine **72**, *p*-methoxyphenyl isocyanide (**73**), carboxylic acid **74**, and acetaldehyde (**75**) afforded dipeptide **66** in high yield. This single operation installed all of the carbon atoms of the complex pentacyclic core of the natural product. Due to the potent biological activity of **77**, development and investigation of analogues is desirable, and Fukuyama's use of the U-4CR provides a route that is highly amenable to this end.



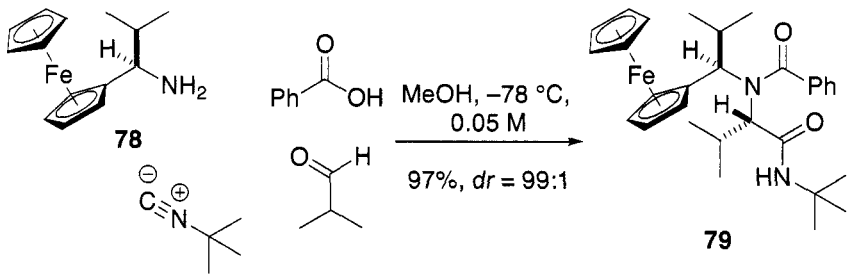
3.6.5 *Variations and Improvements*

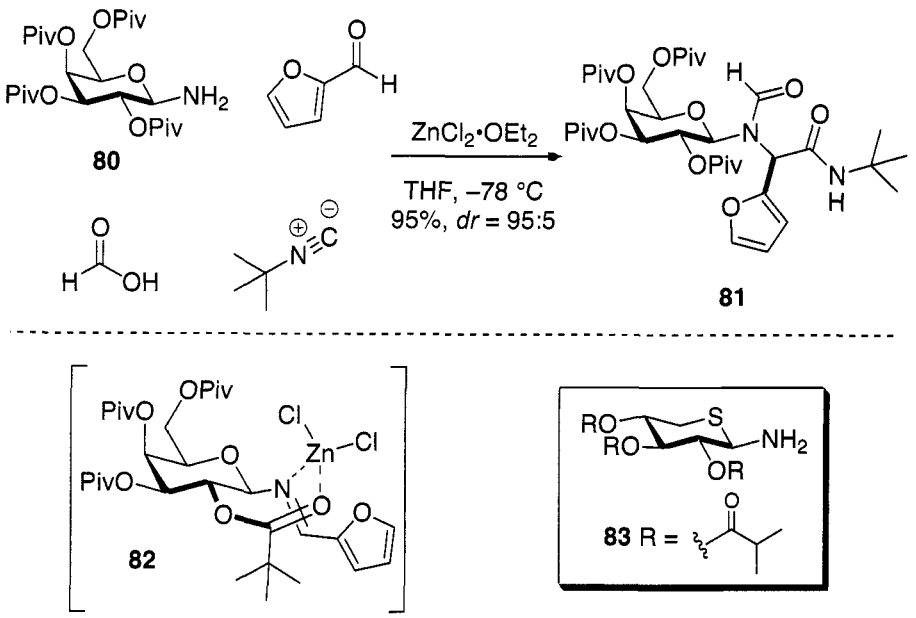
Asymmetric Variants

Despite the utility of the U-4CR and its widespread use, the stereoselectivity in these reactions remains an unsolved issue. High variability in reaction conditions (e.g., solvent, temperature, and reactants), in addition to an incomplete understanding of the reaction mechanism, have contributed to difficulties in obtaining excellent asymmetric induction. It has been suggested that an effort toward a general solution for stereocontrol in the reaction is an exercise in futility.[2b] On the other hand, a number of case-specific solutions provide the practicing scientist with multiple options when faced with problems of stereoselectivity in these reactions.

Early work by Ugi showed that chirality within the amine component was successful in generating product mixtures with high diastereomeric excess.[10,11] Intriguingly, chirality in any other coupling component of the reaction generally fails to aid diastereoselection. This is in stark contrast to the Passerini reaction, which has been shown to proceed in good to excellent stereoselectivity when chiral isocyanides[47] or chiral acids[48] are used. This aspect indicates that significantly different mechanisms may be operative in these two seemingly similar reactions.

Ugi has shown that chiral α-ferrocenylamines (**78**) provide products of moderate to excellent diastereoselectivity.[49] However, harsh conditions (trifluoroacetic acid in methanol) are necessary for the removal of the chiral auxiliary from the product **79**. This pitfall limits the applicability of this method in the presence of sensitive functionality.

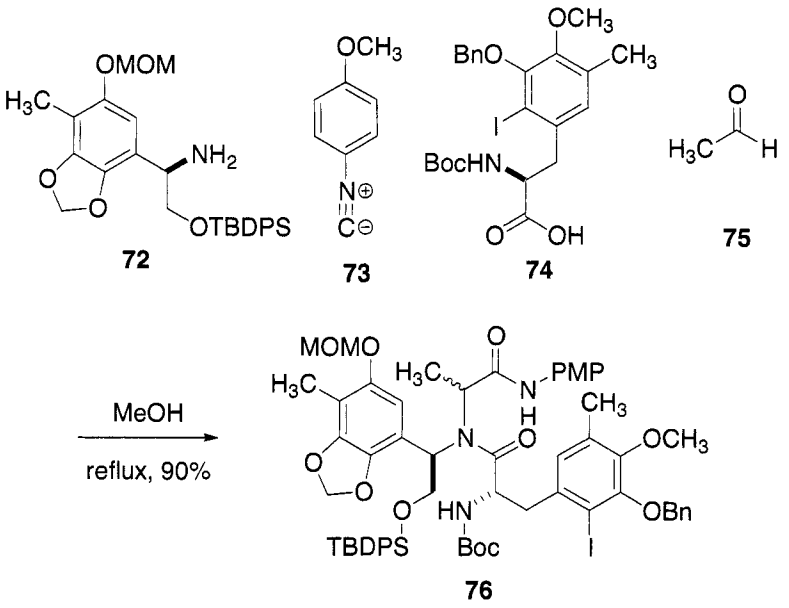




Many groups have devoted attention to the development of a chiral amine that balances the issues of high chemical yield, high diastereoselectivity, and easy cleavage in the U-4CR.[2] Kunz has developed the chiral glycosylamine **80** and has successfully utilized it as the amine component in the U-4CR.[50] Reactions have been shown to proceed with high stereoselectivity, resulting from the coordination of a Lewis acid to the imine nitrogen and the carbonyl oxygen of the adjacent pivolate (**82**), thereby exposing the *si*-face of the imine to nucleophilic attack. Unfortunately, the removal of this group requires strong acid and the formyl group in the Ugi product **81** does not survive. To address this issue, Ugi has described the xylopyranose-derived peracylated thiosugar (**83**) that gives rise to products with comparable diastereoselectivity.[51] The ability of the sulfide to react with soft electrophiles, such as mercury (II) salts, provides a mild method for the removal of the auxiliary. Unfortunately, the enantiomer of **83** is neither readily available nor easily synthesized.

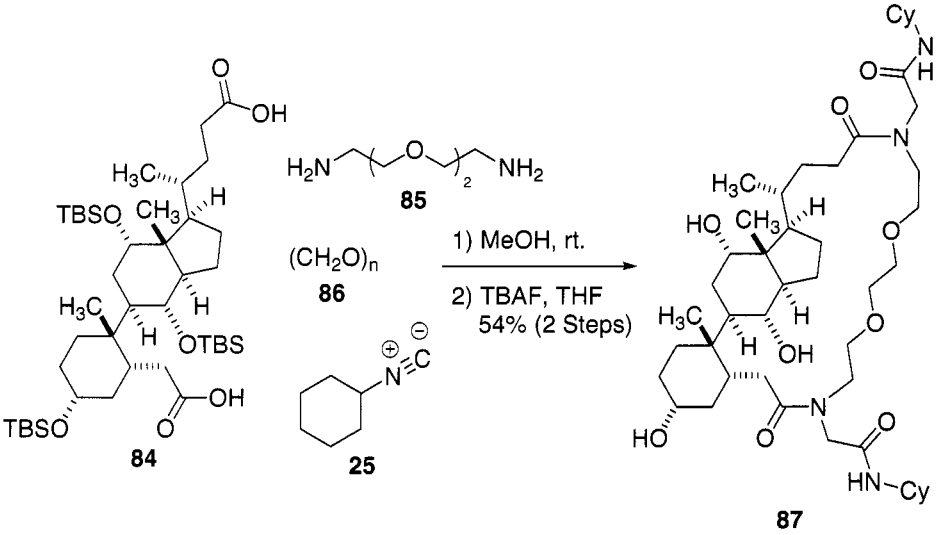
3.6.6 *Experimentals*

Classic Ugi Four-Component Reaction[46]



To a mixture of amine **72** (9.63 g, 19.5 mmol), carboxylic acid **74** (10.57 g, 19.5 mmol, 1.0 equiv), and *p*-methoxyphenyl isocyanide (PMP-NC) (**73**) (3.90 g, 29.3 mmol, 1.5 equiv) in MeOH (200 ml) at room temperature was added acetaldehyde (**75**) (22 ml, 0.39 mol, 20 equiv), and the resulting solution was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the resulting orange syrup was purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford **76** (21.02 g, 17.6 mmol, 90%) as a yellow solid.

Ugi Four-Component Reaction via Precondensation of Aldehyde and Amine[52]



A solution of the 2,6-dioxa-1,8-diaminooctane **85** (74 mg, 0.5 mmol) and paraformaldehyde **86** (1.0 mmol) in MeOH (200 mL) was stirred at room temperature for 2 h. Two solutions, one of diacid **84** (392 mg, 0.5 mmol) and another of cyclohexylisocyanide **25** (90 μL, 1.0 mmol) in 20 mL of MeOH each, were simultaneously, slowly added to the reaction mixture using syringe pumps (flow rate 0.5 mL h^{-1}). After addition was completed, the reaction mixture was stirred for 8 h and concentrated under reduced pressure to dryness. The resulting crude product was dissolved in 50 mL of THF and tetra-*n*-butylammonium fluoride trihydrate (535 mg, 1.5 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and then diluted with 150 mL of EtOAc. The solution was washed with aqueous 10% $NaHCO_3$ (2 × 30 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to dryness. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1) yielded the macrocycle **87** (224 mg, 54%) as a pale yellow oil.

3.6.7 References

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