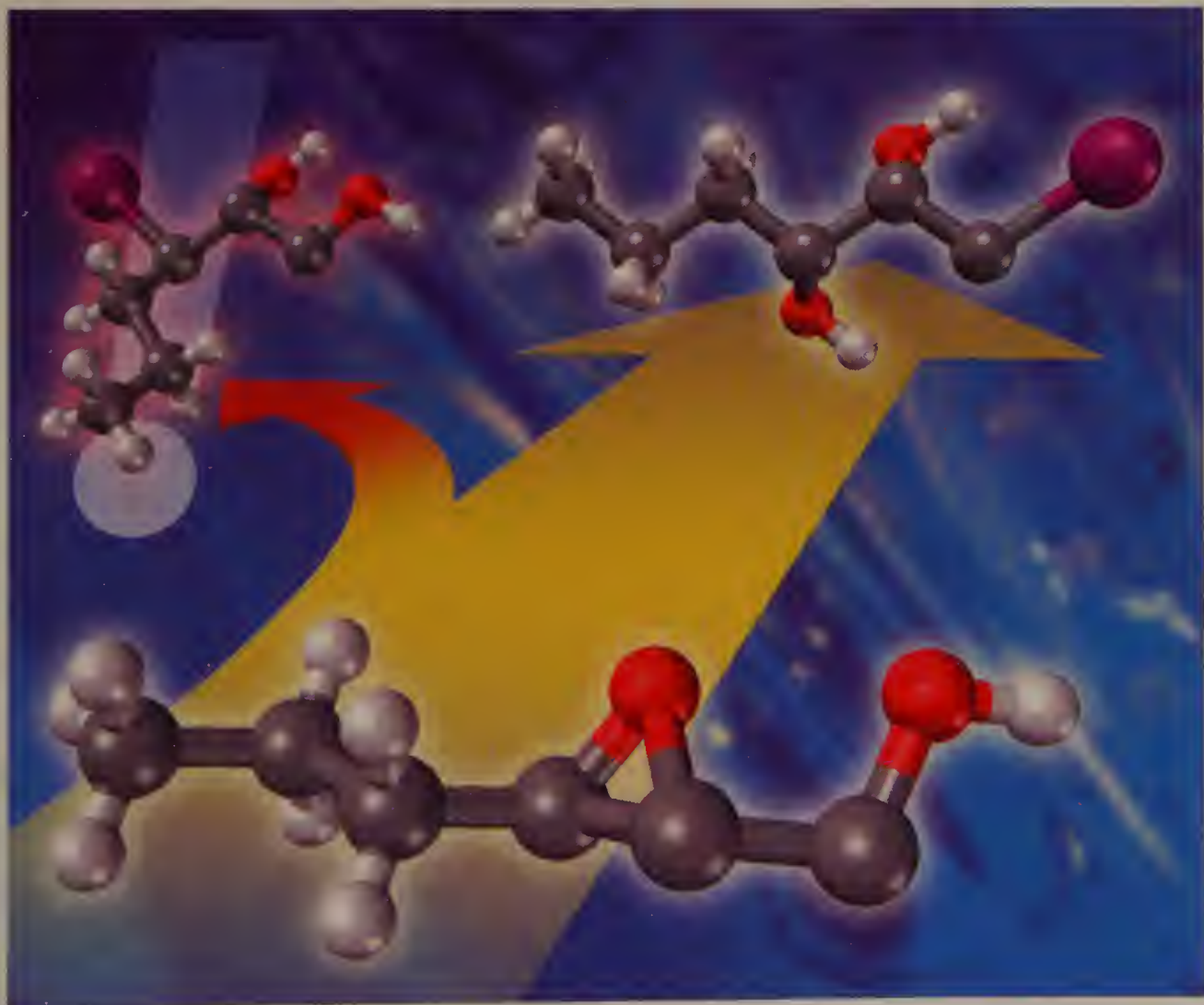


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A Guide to Successful Synthesis Design



Florencio Zaragoza Dörwald
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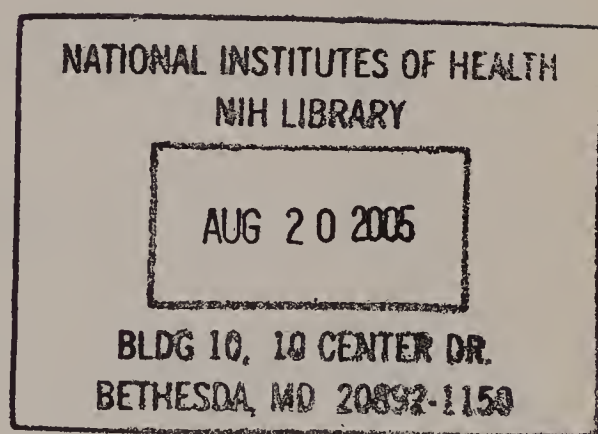
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Florencio Zaragoza Dörwald

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Preface

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

This book attempts to highlight the competing processes and limitations of some of the most common and important reactions used in organic synthesis. Awareness of these limitations and problem areas is important for the design of syntheses, and might also aid elucidation of the structure of unexpected products. Two chapters of this book cover the structure–reactivity relationship of organic compounds, and should also aid the design of better syntheses.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious). Nevertheless, I have ventured to describe some reactions as difficult or impossible. A talented chemist might, however, succeed in performing such reactions anyway, for what I congratulate him in advance. The aim of this book is not to stop the reader from doing bold experiments, but to help him recognize his experiment as bold, to draw his attention to potential problems, and to inspire, challenge, and motivate.

I wish to express my thanks to Ullrich Sensfuss, Bernd Peschke, and Kilian W. Conde-Frieboes for the many helpful discussions and for proofreading parts of the manuscript, and to Jesper Lau (my boss) for his support.

Smørum, Denmark
May 2004

Florencio Zaragoza Dörwald

Glossary and Abbreviations

Ac	acetyl, MeCO
acac	pentane-2,4-dione
AIBN	azobis(isobutyronitrile)
All	allyl
Alloc	allyloxycarbonyl
Amberlyst 15	strongly acidic, macroporous ion exchange resin
aq	aqueous
Ar	undefined aryl group
9-BBN	9-borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
bimim	<i>N</i> -butyl- <i>N'</i> -methylimidazolium
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
Bom	benzyloxymethyl
Bs	4-bromobenzenesulfonyl
BSA	<i>N,O</i> -bis(trimethylsilyl)acetimidate
Bt	1-benzotriazolyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate, (NH ₄) ₂ Ce(NO ₃) ₆
cat	catalyst or catalytic amount
Cbz	Z, benzyloxycarbonyl, PhCH ₂ OCO
CDI	carbonyldiimidazole
celite	silica-based filter agent
COD	1,5-cyclooctadiene
coll	collidine, 2,4,6-trimethylpyridine
conc	concentrated
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid

Cy	cyclohexyl
<i>D</i>	bond dissociation enthalpy
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	1,5-diphenyl-1,4-pentadien-3-one
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-5-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCP	1,2-dichloropropane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate, EtO ₂ C–N=N–CO ₂ Et
Dec	decyl
DIAD	diisopropyl azodicarboxylate, iPrO ₂ C–N=N–CO ₂ iPr
DIBAH	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
diglyme	bis(2-methoxyethyl) ether
dipamp	1,2-bis[phenyl(2-methoxyphenyl)phosphino]ethane
DIPEA	diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate, MeO ₂ C–C≡C–CO ₂ Me
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane, glyme
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one
DMPU	1,3-dimethyltetrahydropyrimidin-2-one
DMSO	dimethyl sulfoxide
DMT	4,4'-dimethoxytrityl
DNA	deoxyribonucleic acid
Dnp	2,4-dinitrophenyl
DPPA	diphenylphosphoryl azide, (PhO) ₂ P(O)N ₃
dppb	1,2-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E	undefined electrophile
EDC	<i>N</i> -ethyl- <i>N'</i> -[3-(dimethylamino)propyl]carbodiimide hydrochloride
EDT	1,2-ethanedithiol
ee	enantiomeric excess
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
eq	equivalent
er	enantiomeric ratio
Et	ethyl

Fmoc	9-fluorenylmethyloxycarbonyl
FVP	flash vacuum pyrolysis
Hal	undefined halogen
Hep	heptyl
Hex	hexyl
HMPA	hexamethylphosphoric triamide, (Me ₂ N) ₃ PO
hν	light
HOAt	3-hydroxy-3 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridine, 4-aza-3-hydroxybenzotriazole
HOBT	1-hydroxybenzotriazole
HOSu	<i>N</i> -hydroxysuccinimide
HPLC	high pressure liquid chromatography
HSAB	hard and soft acids and bases
<i>i</i> Pr	isopropyl
IR	infrared
L	undefined ligand
LDA	lithium diisopropylamide
M	molar, mol/l; undefined metal
MCPBA	3-chloroperbenzoic acid
Me	methyl
MEK	2-butanone
MES	2-(4-morpholino)ethanesulfonic acid
MMT	monomethoxytrityl
MOM	methoxymethyl
Mos	4-methoxybenzenesulfonyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
nbd	norbornadiene
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMM	<i>N</i> -methylmorpholine
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nos	nosyl, 4-nitrobenzenesulfonyl
Nu	undefined nucleophile
Oct	octyl
oxone [™]	2 KHSO ₅ · KHSO ₄ · K ₂ SO ₄ , potassium peroxymonosulfate
PEG	poly(ethylene glycol)
Pent	pentyl
PG	protective group
Ph	phenyl
Pht	phthaloyl

Piv	pivaloyl, 2,2-dimethylpropanoyl
PMDTA	<i>N,N,N',N'',N'''</i> -pentamethyldiethylenetriamine
PNB	4-nitrobenzoyl
Pol	undefined polymeric support
PPTS	pyridinium tosylate
Pr	propyl
PTC	phase transfer catalysis
PTFE	poly(tetrafluoroethylene)
R	undefined alkyl group
Red-Al TM	sodium bis(2-methoxyethoxy)aluminum hydride
satd	saturated
<i>sec</i>	secondary
L-Selectride TM	lithium tri(2-butyl)borohydride
SET	single electron transfer
S _N 1	monomolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
S _N R1	monomolecular radical nucleophilic substitution
st. mat.	starting material
Su	<i>N</i> -succinimidyl
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> Bu	<i>tert</i> -butyl
Tentagel TM	PEG-grafted cross-linked polystyrene
<i>tert</i>	tertiary
Teoc	2-(trimethylsilyl)ethoxycarbonyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	triflic acid, trifluoromethanesulfonic acid
thd	2,2,6,6-tetramethyl-3,5-heptanedione
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMAD	<i>N,N,N',N'</i> -tetramethyl azodicarboxamide
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG	<i>N,N,N',N'</i> -tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidin-1-yl
TMPP	tris(2,4,6-trimethoxyphenyl)phosphine
TMS	trimethylsilyl, Me ₃ Si
Tol	4-tolyl, 4-methylphenyl
Tr	trityl
Triton TM X-100	polyoxyethylene isooctylcyclohexyl ether
Ts	tosyl, <i>p</i> -toluenesulfonyl
Tyr	tyrosine
UV	ultraviolet

Wang resin	cross-linked polystyrene with 4-benzyloxybenzyl alcohol linker
X	undefined leaving group for nucleophilic displacement
X, Y	undefined heteroatoms with unshared electron pair
Z	Cbz, benzyloxycarbonyl; undefined electron-withdrawing group

1

Organic Synthesis: General Remarks

1.1

Introduction

Organic reactions almost never yield exclusively the desired product. Students learn this when they perform their first synthesis in the laboratory, for example the synthesis of anisole from phenol. Although the starting materials, the intermediates, and the product are all colorless, the reaction mixture will turn uncannily dark. This darkening shows that in reality much more is going on in addition to the expected process, and that obviously quite complex chemistry must be occurring, giving rise to extended conjugated polyenes from simple starting materials. Fortunately these dyes are usually formed in minute amounts only and the student will hopefully also learn not to be scared by color effects, and that even from pitch-black reaction mixtures colorless crystals may be isolated in high yield.

Because most reactions yield by-products and because isolation and purification of the desired product are usually the most difficult parts of a preparation, the work-up of each reaction and the separation of the product from by-products and reagents must be carefully considered while planning a synthesis. If product isolation seems to be an issue, the work-up of closely related examples from the literature (ideally two or three from different authors) should be studied. Many small, hydrophilic organic compounds which should be easy to prepare are still unknown, not because nobody has attempted to make them, but because isolation and purification of such compounds can be very difficult. Therefore the solubility of the target compound in water and in organic solvents, and its boiling or melting point, should be looked up or estimated, because these will aid choice of the right work-up procedure.

The chemical stability of the target compound must also be taken into account while planning its isolation. Before starting a synthesis one should also have a clear idea about which analytical tools will be most appropriate for following the progress of the reaction and ascertaining the identity and purity of the final product. Last, but not least, the toxicity and mutagenicity of all reagents, catalysts, solvents, products, and potential by-products should be looked up or estimated, and appropriate precautionary measures should be taken.

1.2

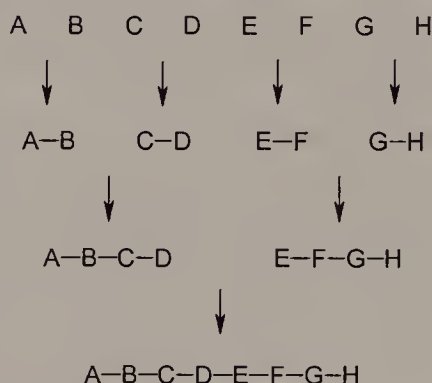
Synthesis Design

The synthesis of a structurally complex compound requires careful retrosynthetic analysis to identify the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity. It is critical to keep the synthesis as short as possible, because, as discussed throughout this book, each reaction can cause unexpected problems, especially when working with structurally complex intermediates. Also for synthesis of “simple-looking” structures several different approaches should be considered, because even structurally simple compounds often turn out not to be so easy to make as initially thought.

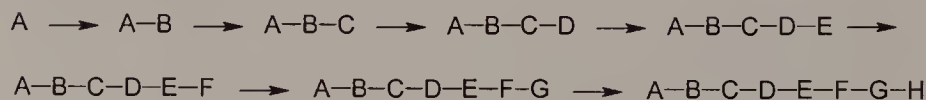
1.2.1

Convergent vs Linear Syntheses

If a target compound can be assembled from a given number of smaller fragments, the highest overall yields will usually be obtained if a convergent rather than linear strategy is chosen (Scheme 1.1). In a convergent assembly strategy the total number of reactions and purifications for all atoms or fragments of the target are kept to a

convergent strategy:

7 reactions, total yield with respect to monomer A: 51%
(for 80% yield per coupling step)

linear strategy:

7 reactions, total yield with respect to monomer A: 21%
(for 80% yield per coupling step)

Scheme 1.1. Convergent and linear assembly strategies.

minimum. If a linear strategy is chosen the first fragment (A in Scheme 1.1) will be subjected to a large number of reactions and purifications, and the total yield with regard to this first fragment will be rather low. Syntheses should be organized in such a way that expensive and/or structurally complex fragments are subjected to the fewest possible number of transformations.

1.2.2

Retrosynthetic Analysis

1.2.2.1 Introduction

When planning a synthesis, the most suitable starting materials should be chosen. These should be structurally and/or stereochemically as closely related to the target as possible, to keep the synthesis brief. The first steps of a good synthesis may even be low-yielding (if the products are easy to purify), because at these early stages little work and reagents have been invested and the intermediates are still cheap. Poor yields at later stages of a multistep synthesis, however, strongly reduce its usefulness, because most steps of the synthesis will have to be run on a large scale, using large amounts of solvents and reagents, to obtain a small amount only of the final product, which will, accordingly, be rather expensive.

In a retrosynthesis the easiest bonds to make are often cleaved first (i.e. these bonds will be made at the end of the synthesis), yielding several fragments which can be joined together at late stages of the synthesis, using straightforward and high-yielding chemistry. Such reactions would usually be condensations, for example acetal, amide, or ester formation, or the formation of carbon–heteroatom bonds, but might also be high-yielding C–C bond-forming reactions if the required reaction conditions are compatible with all the structural elements of the final product.

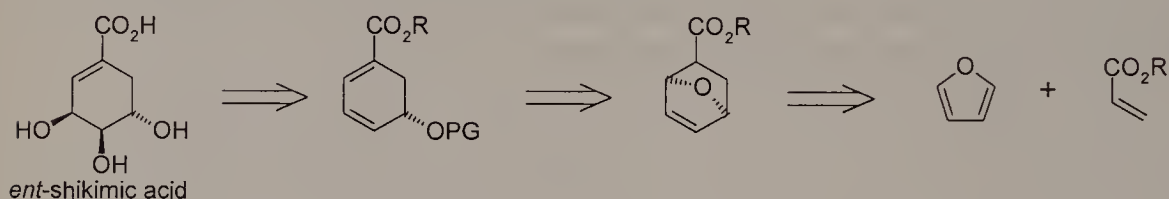
If the target contains synthetically readily accessible substructures (e.g. cyclic elements accessible by well established cycloaddition or cyclization reactions), these might be chosen as starting point of a disconnection [1]. If such substructures are not present, their generation by introduction of removable functional groups (e.g. by converting single bonds into double bonds or by formal oxidation of methylene groups to carbonyl groups, Scheme 1.5) should be attempted. If this approach fails to reveal readily accessible substructures, the functional groups present in the target structure which might assist the stepwise construction of the carbon framework must be identified, and the bonds on the shortest bond paths between these groups should be considered as potential sites of disconnection (Scheme 1.3). Retro-aldol or Mannich reactions, optionally combined with the “Umpolung” of functional groups, have been the most common and successful tools for disconnection of intricate carbon frameworks, but any other, high-yielding C–C bond-forming reaction can also be considered. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures.

1.2.2.2 Shikimic Acid

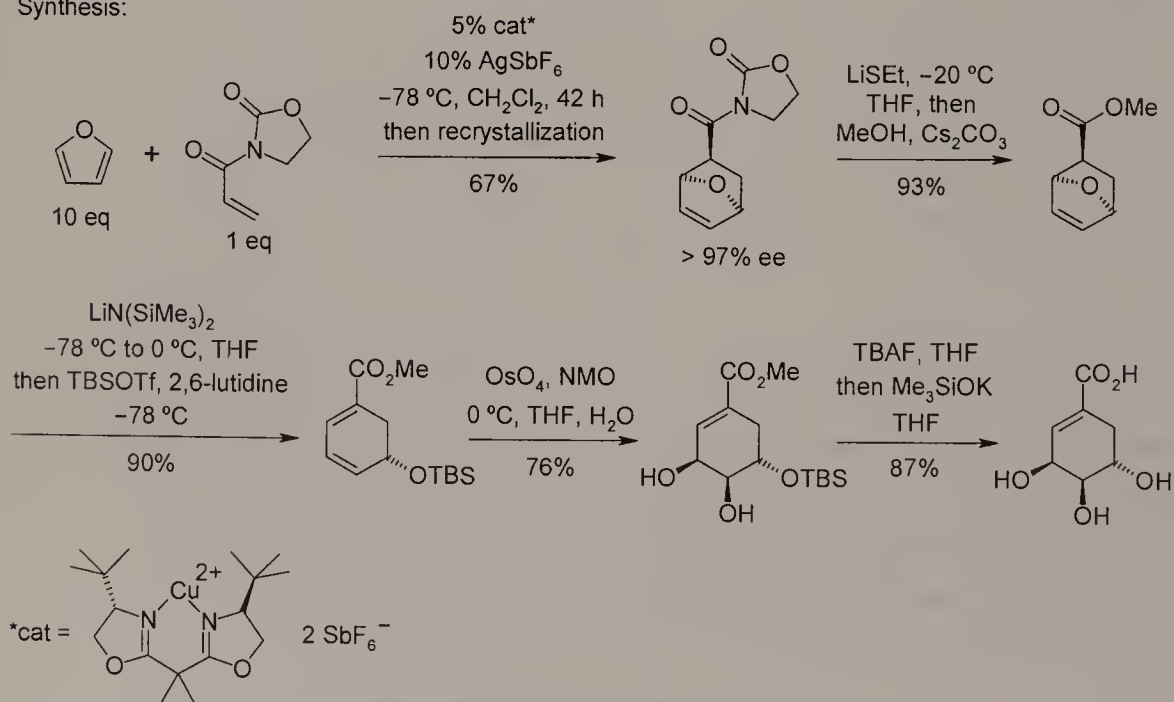
In Scheme 1.2 one possible retrosynthetic analysis of the unnatural enantiomer of shikimic acid, a major biosynthetic precursor of aromatic α -amino acids, is sketched. Because *cis* dihydroxylations can be performed with high diastereoselectivity and yield, this step might be placed at the end of a synthesis, what leads to a cyclohexadienoic acid derivative as an intermediate. Chemoselective dihydroxylation of this compound should be possible, because the double bond to be oxidized is less strongly deactivated than the double bond directly bound to the (electron-withdrawing) carboxyl group.

Despite being forbidden by the Baldwin rules (5-*endo*-trig ring opening; see Section 9.2), cyclohexadienoic acid derivatives such as that required for this synthesis can be prepared by base-induced ring scission of 7-oxanorbornene derivatives, presumably because of the high strain-energy of norbornenes. The required 7-oxanorbornene, in turn, should be readily accessible from furan and an acrylate via the

Retrosynthesis:



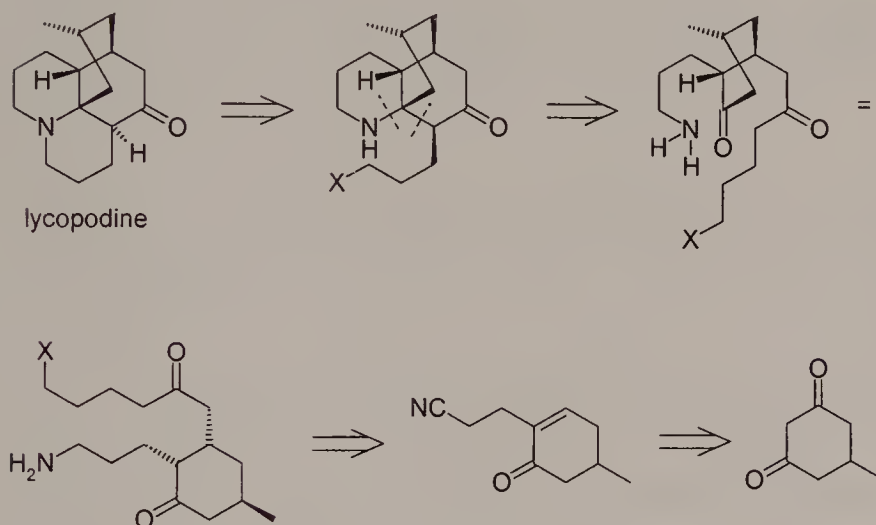
Synthesis:

Scheme 1.2. Retrosynthetic analysis and synthesis of *ent*-shikimic acid [2].

Diels–Alder reaction. With the aid of an enantiomerically pure Lewis acid this Diels–Alder reaction yields a highly enantiomerically enriched 7-oxanorbornene, so that the remaining steps of this elegant synthesis only need to proceed diastereoselectively and without racemization.

1.2.2.3 Lycopodine

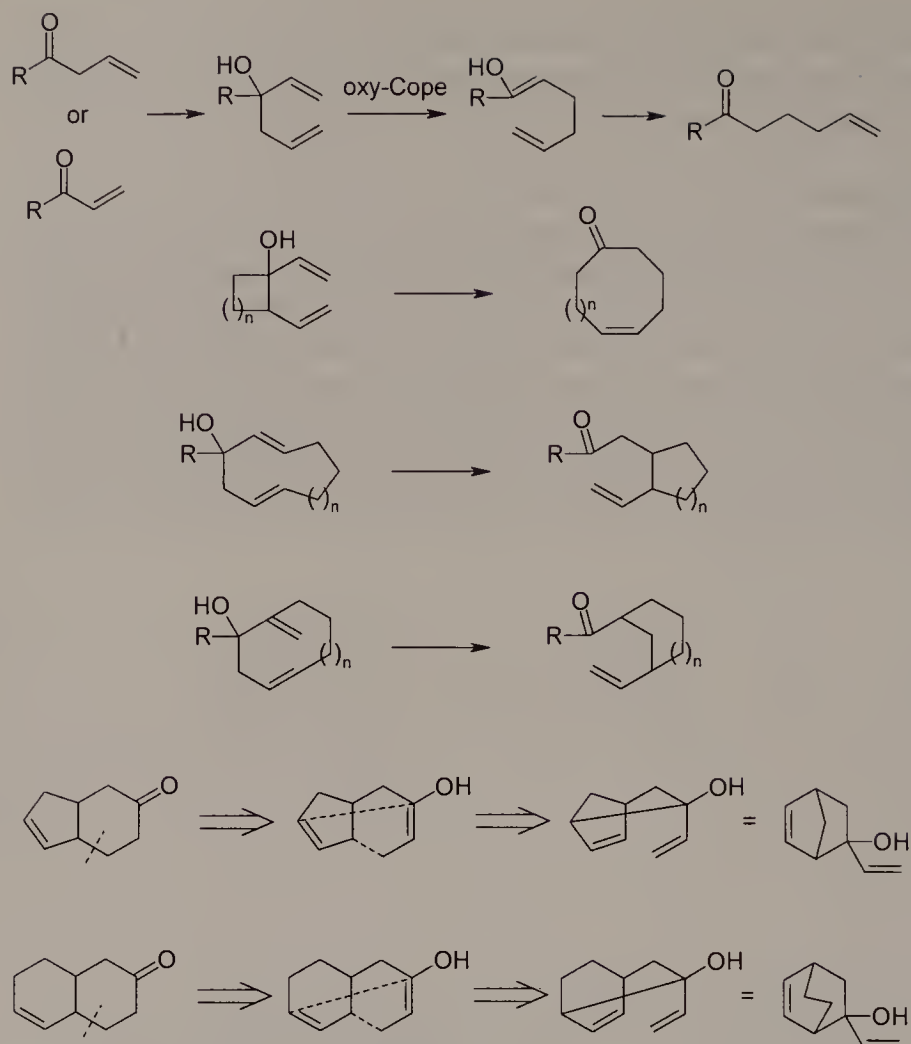
A further target which contains a readily accessible and easily recognizable substructure is the alkaloid lycopodine. Being a β -amino ketone, a possible retrosynthesis could be based on an intramolecular Mannich reaction, as outlined in Scheme 1.3. In this case two of the targets four rings would be generated in one step by a Mannich condensation; this significantly reduces the total number of steps required. A robust, intramolecular *N*-alkylation was chosen as last step. Realization of this synthetic plan led to a synthesis of racemic lycopodine in only eight steps with a total yield of 13 % [3]. Fortunately the Mannich reaction yielded an intermediate with the correct relative configuration.



Scheme 1.3. Retrosynthesis of lycopodine based on an intramolecular Mannich reaction [3].

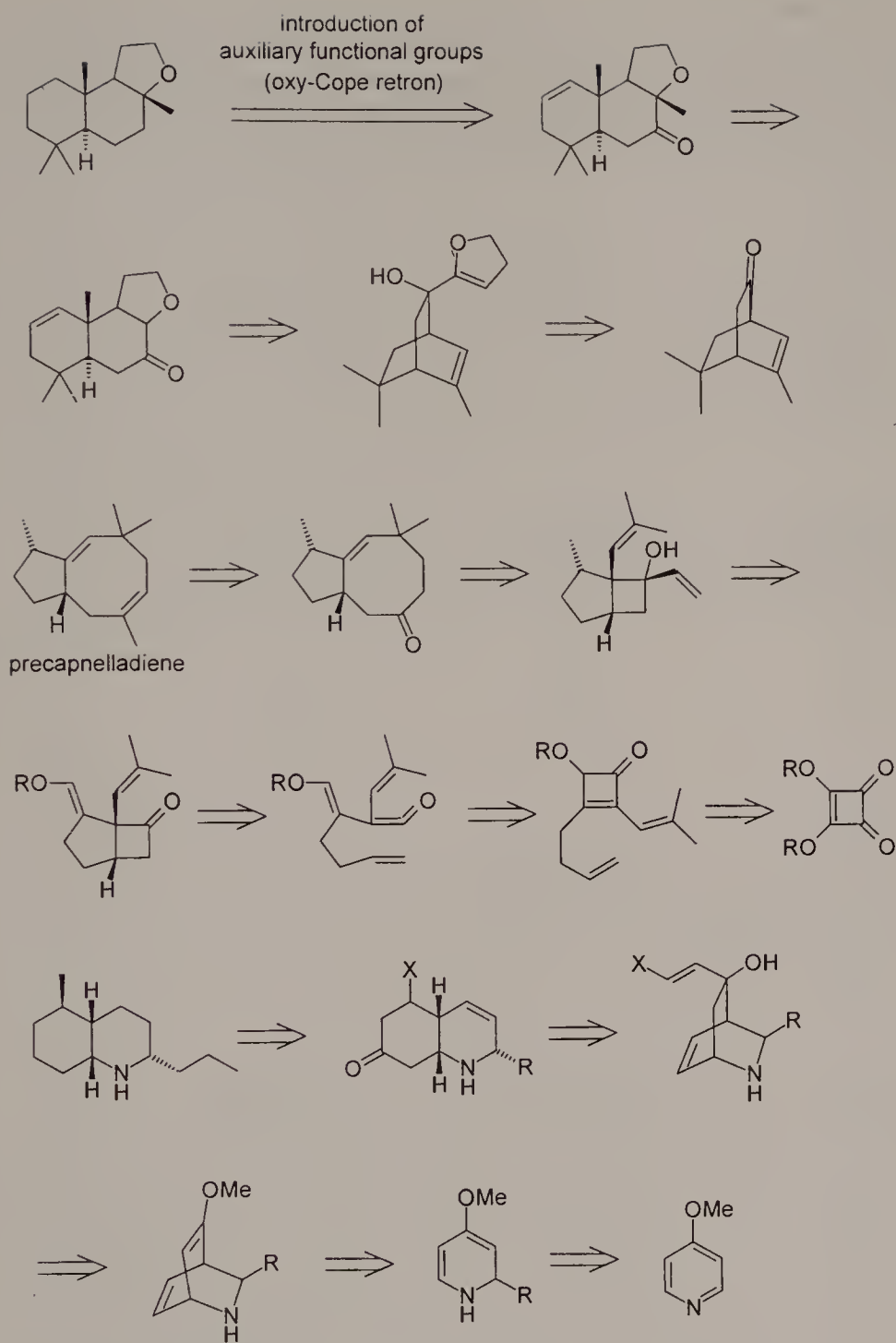
1.2.2.4 The Oxy-Cope Rearrangement

Less obvious than the retrosyntheses discussed above are those based on intramolecular rearrangements, because these often involve a major change of connectivity between atoms. For instance, exploitation of oxy-Cope rearrangements as synthetic tools requires some practice and the ability to recognize the substructures accessible via this reaction from readily available starting materials. Oxy-Cope rearrangements yield 4-penten-1-yl ketones by formal allylation of a vinyl ketone at the β position or γ -vinylation of an allyl ketone (Scheme 1.4). This rearrangement can be used to prepare decalins [4] or perhydroindenes [5, 6] from bicyclo[2.2.2]octenones or norbornenones, respectively, which can be prepared by using the Diels–Alder reaction. Moreover, oxy-Cope rearrangements may be used for ring expansions or contractions.



Scheme 1.4. The oxy-Cope rearrangement.

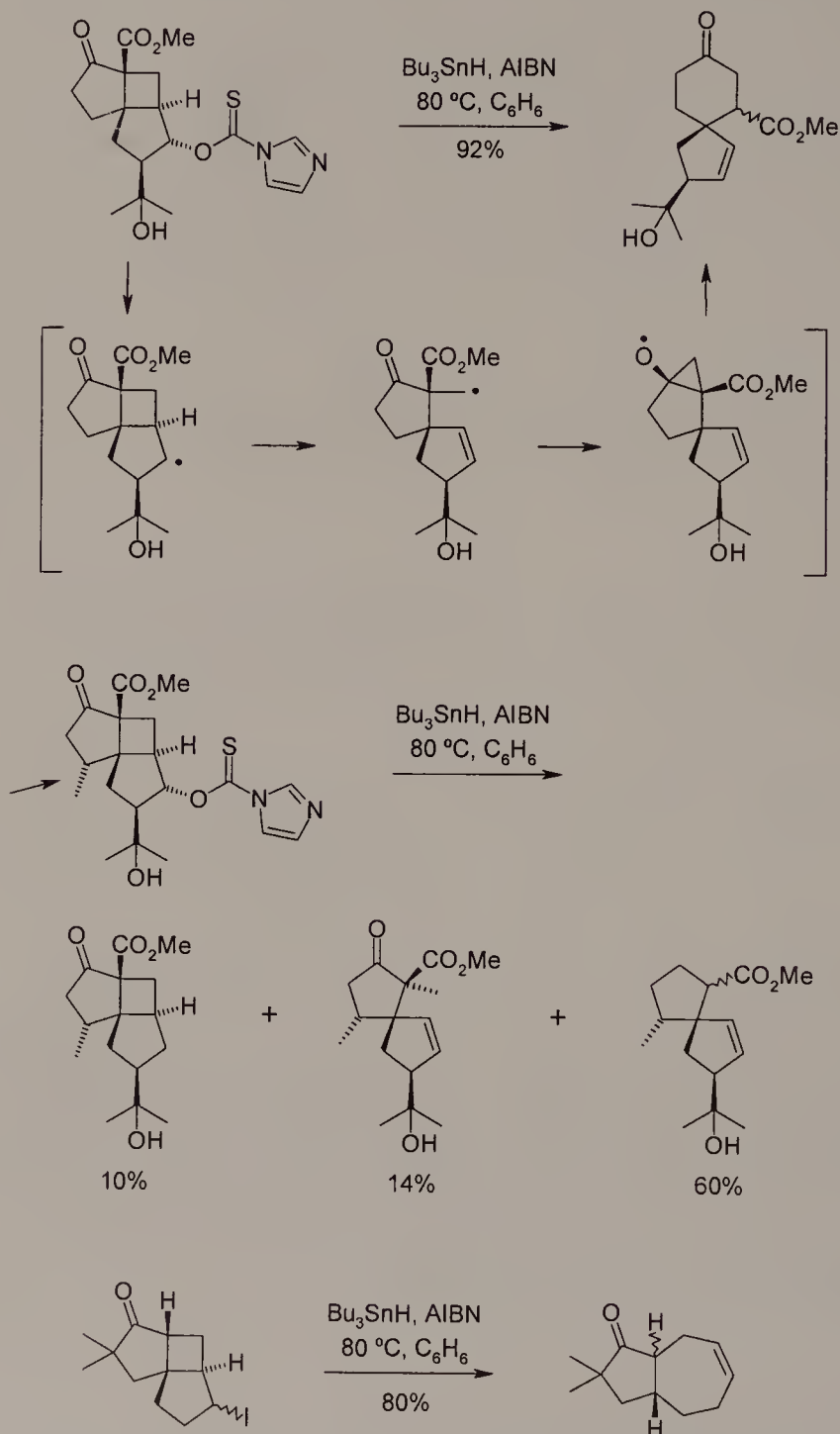
Numerous natural products have been prepared using the oxy-Cope rearrangement as the key step [5], in particular, and with high virtuosity, by the group of L.A. Paquette [4, 6, 7]. Three examples of retrosynthetic analyses of natural products or analogs thereof based on the oxy-Cope rearrangement are shown in Scheme 1.5. Because all the products are devoid of a keto group, the required 4-penten-1-yl ketone substructure (i.e. the oxy-Cope retron[1]) must be introduced during the retrosynthesis in such a way that accessible starting materials result.



Scheme 1.5. Retrosynthesis of an ambergris-type ether, of precapnelladiene, and of an alkaloid based on the oxy-Cope rearrangement [8–10].

1.2.2.5 Conclusion

As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. Therefore, while planning a multistep synthesis, it is important to keep the total number of steps as low as possible.



Scheme 1.6. Rearrangement of polycyclic cyclobutylmethyl radicals [11, 12].

Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed [11]. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity.

Examples of closely related starting materials which upon treatment with the same reagents yield completely different products are sketched in Scheme 1.6. The additional methyl group present in the second starting material slows addition to the carbonyl group of the radical formed by ring scission of the cyclobutane ring, and thus prevents ring expansion to the cyclohexanone. Removal of the methoxycarbonyl group leads to cleavage of a different bond of the cyclobutane ring and thereby again to a different type of product [12].

The understanding and prediction of such effects and the development of milder and more selective synthetic transformations, applicable to the synthesis of highly complex structures or to the selective chemical modification of proteins, DNA, or even living cells will continue to be the challenge for current and future generations of chemists.

1.3

Hard and Soft Acids and Bases

One of the most useful tools for predicting the outcome of chemical reactions is the principle of hard and soft acids and bases (HSAB), formulated by Pearson in 1963 [13–15]. This principle states that hard acids will react preferentially with hard bases, and soft acids with soft bases, “hard” and “soft” referring to sparsely or highly polarizable reactants. A selection of hard and soft Lewis acids and bases is given in Table 1.1.

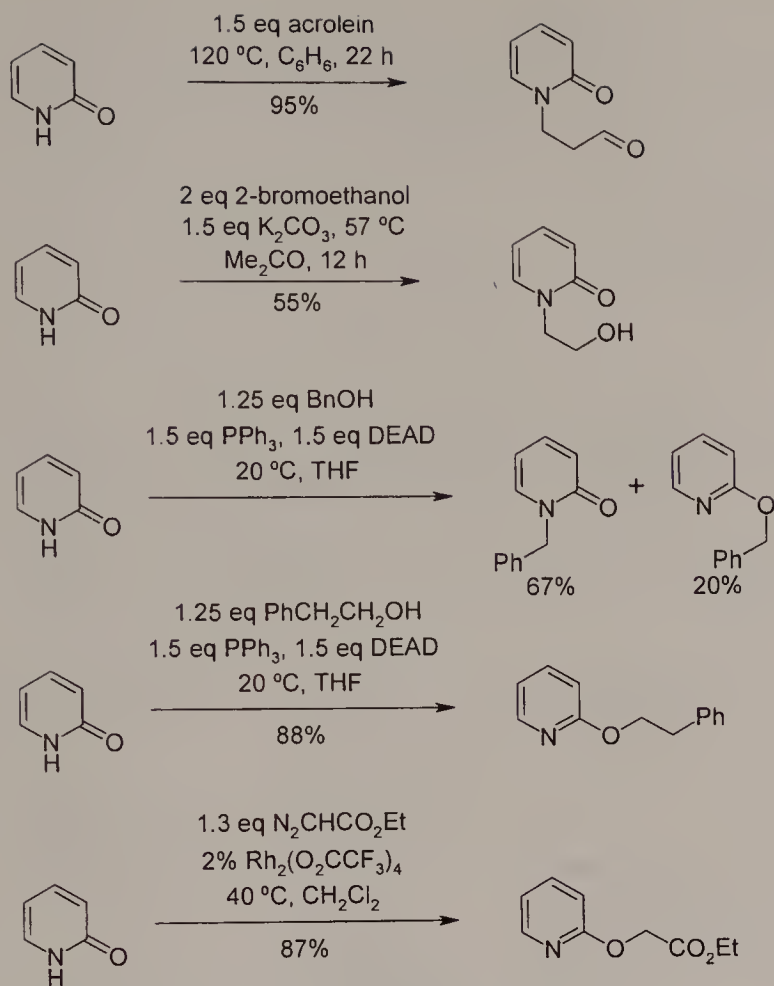
Several chemical observations can be readily explained with the aid of the HSAB principle. For instance, the fact that the early transition metals in high oxidation states, for example titanium(IV), do not usually form complexes with alkenes, carbon monoxide, or phosphines, but form stable oxides instead can be attributed to their hardness. The late transition metals, on the other hand, being highly polarizable, because of their almost completely filled *d* orbitals, readily form complexes with soft bases such as alkenes, carbanions, and phosphines, and these complexes are often unreactive towards water or oxygen. For the same reason, in alkali or early transition metal enolates the metal is usually bound to oxygen, whereas enolates of late transition metals usually contain M–C bonds [17, 18]. While alkali metal alkyls or Grignard reagents react with enones presumably by initial coordination of the metal to oxygen followed by transfer of the alkyl group to the carbonyl carbon atom [16, 19], organocuprates or organopalladium compounds preferentially coordinate and transfer their organic residue to soft C–C double bonds.

Table 1.1. Hard and soft Lewis acids and bases [13, 15, 16] (Z = electron-withdrawing group, M = metal). The acidic or basic centers in molecules are in italics.

Hard acids (non-metals)	Borderline acids (non-metals)	Soft acids (non-metals)
H^+ , $B(OR)_3$, BF_3 , BCl_3 , RCO^+ , CO_2 , NC^+ , R_3Si^+ , Si^{4+} , RPO_2^+ , $ROPO_2^+$, As^{3+} , RSO_2^+ , $ROSO_2^+$, SO_3 , Se^{3+} , Cl^{7+} , I^{7+} , I^{5+}	BR_3 , R^+ (softer $CH_3^+ > RCH_2^+ > R_2CH^+ >$ $R_3C^+ > vinyl^+ \approx C_6H_5^+ \approx$ $RC \equiv C^+$ harder), $RCHO$, R_2CO , $R_2C=NR$, NO^+ , SO_2	BH_3 , $Ar-Z$, $C=C-Z$, quinones, carbenes, HO^+ , RO^+ , RS^+ , RSe^+ , RTe^+ , Br_2 , Br^+ , I_2 , I^+
Hard acids (metals)	Borderline acids (metals)	Soft acids (metals)
Li^+ , Na^+ , K^+ , $BeMe_2$, Be^{2+} , $RMgX$, Mg^{2+} , Ca^{2+} , Sr^{2+} , $AlCl_3$, $AlMe_3$, AlH_3 , $Al(OR)_3$, Al^{3+} , $GaMe_3$, Ga^{3+} , $InMe_3$, In^{3+} , SnR_3^+ , $SnMe_2^{2+}$, Sn^{2+} , Sc^{3+} , La^{3+} , $Ti(OR)_4$, Ti^{4+} , Zr^{4+} , VO_2^+ , Cr^{3+} , Fe^{3+} , Co^{3+} , Ir^{3+} , Th^{4+} , UO_2^{2+} , Pu^{4+} , Yb^{3+}	GaH_3 , $Sn(OR)_4$, $SnCl_4$, Pb^{2+} , Sb^{3+} , Bi^{3+} , $Sc(OTf)_3$, $ScCl_3$, Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , RZn^+ , Zn^{2+} , $Yb(OTf)_3$, $YbCl_3$	Cs^+ , $TlMe_3$, Tl^+ , Tl^{3+} , $Pd(PAr_3)_2$, $Pd(PAr_3)_2^{2+}$, Pd^{2+} , Pt^{2+} , Cu^+ , Ag^+ , Au^+ , CdR^+ , Cd^{2+} , HgR^+ , Hg^+ , Hg^{2+} , M^0
Hard bases	Borderline bases	Soft bases
NH_3 , RNH_2 , R_2N^- , N_2H_4 , H_2O , OH^- , ROH , RO^- , R_2O , RCO_2^- , CO_3^{2-} , NO_3^- , PO_4^{3-} , SO_4^{2-} , ClO_4^- , F^- , Cl^-	AlH_4^- , N_2 , N_3^- , $PhNH_2$, R_3N , C_5H_5N , $R_2C=NR$, NO_2^- , SO_3^{2-} , Br^-	H^- , BH_4^- , R^- (softer $RC \equiv C^- >$ $vinyl^- > R_3C^-$ harder), C_6H_6 , $R_2C=CR_2$, $RC \equiv CR$, CN^- , RNC , CO , PR_3 , $P(OR)_3$, AsR_3 , RS^- , SCN^- , RSH , R_2S , $S_2O_3^{2-}$, RSe^- , I^-

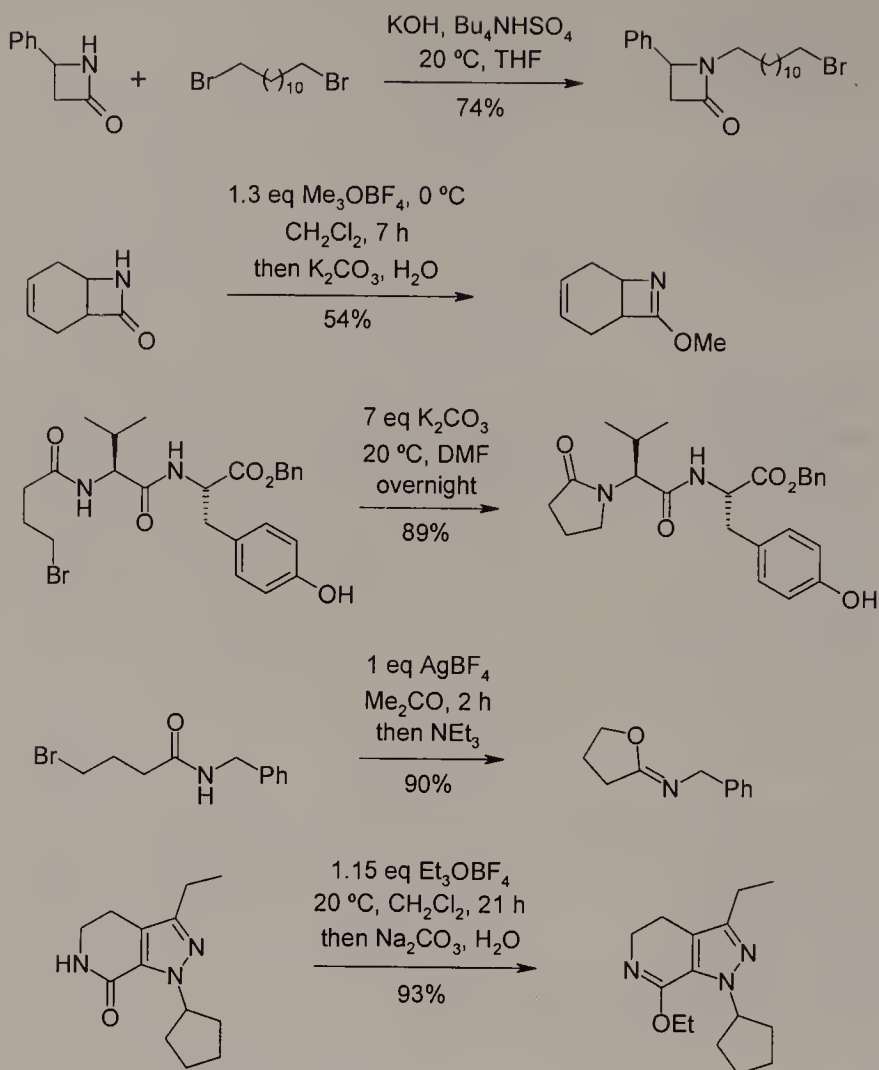
HSAB is particularly useful for assessing the reactivity of ambident nucleophiles or electrophiles, and numerous examples of chemoselective reactions given throughout this book can be explained with the HSAB principle. Hard electrophiles, for example alkyl triflates, alkyl sulfates, trialkyloxonium salts, electron-poor carbenes, or the intermediate alkoxyphosphonium salts formed from alcohols during the Mitsunobu reaction, tend to alkylate ambident nucleophiles at the hardest atom. Amides, enolates, or phenolates, for example, will often be alkylated at oxygen by hard electrophiles whereas softer electrophiles, such as alkyl iodides or electron-poor alkenes, will preferentially attack amides at nitrogen and enolates at carbon.

2-Pyridone is O-alkylated more readily than normal amides, because the resulting products are aromatic. With soft electrophiles, however, clean N-alkylations can be performed (Scheme 1.7). The Mitsunobu reaction, on the other hand, leads either to mixtures of N- and O-alkylated products or to O-alkylation exclusively, probably because of the hard, carbocation-like character of the intermediate alkoxyphosphonium cations. Electrophilic rhodium carbene complexes also preferentially alkylate the oxygen atom of 2-pyridone or other lactams [20] (Scheme 1.7).



Scheme 1.7. Regioselective alkylation of 2-pyridone [20–22].

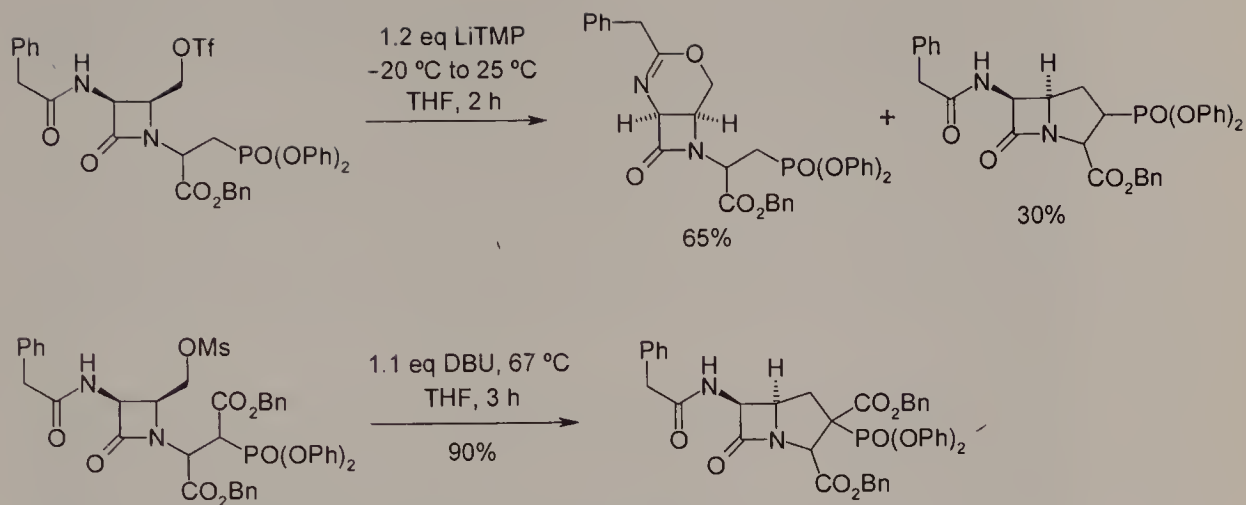
Lactams and some non-cyclic, secondary amides ($RCONHR$) can be alkylated with high regioselectivity either at nitrogen (Section 6.6) or at oxygen. *N*-Alkylations are generally conducted under basic reaction conditions whereas *O*-alkylations are often performed with trialkyloxonium salts, dialkyl sulfates, or alkyl halides/silver salts without addition of bases. Protonated imino ethers are formed; these are usually not isolated but are converted into the free imino ethers with aqueous base during the work-up. Scheme 1.8 shows examples of the selective alkylation of lactams and of the formation of 2-pyrrolidinones or 2-iminotetrahydrofurans by cyclization of 4-bromobutyramides.



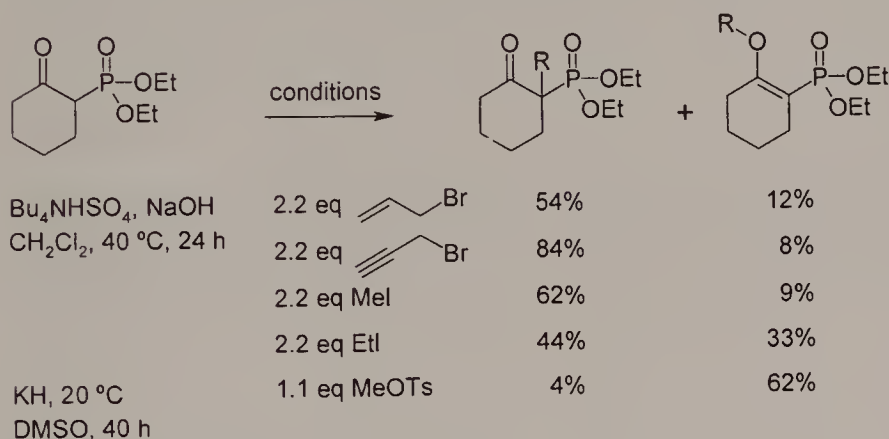
Scheme 1.8. Regioselective alkylation of amides [23–27].

The triflate sketched in Scheme 1.9 mainly alkylates the amide at oxygen, instead of alkylating the softer, lithiated phosphonate. Selective C-alkylation can be achieved in this instance by choosing a less reactive mesylate as electrophile and by enhancing the acidity of the phosphonate.

The regioselectivity of the alkylation of enolates can also be controlled by the hardness of the alkylating agent [29]. As illustrated by the examples in Scheme 1.10, allyl, propargyl, or alkyl bromides or iodides mainly yield C-alkylated products, whereas the harder sulfonates preferentially alkylate at oxygen.



Scheme 1.9. Intramolecular alkylation of amides and phosphonates [28].



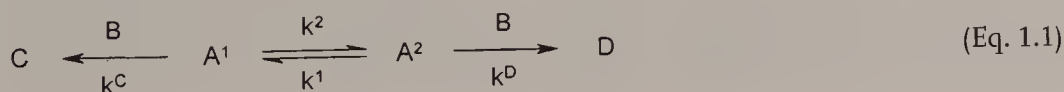
Scheme 1.10. Regioselective alkylation of enolates [30, 31].

1.4

The Curtin–Hammett Principle

In the 1940s the idea was prevalent among chemists that the conformation of a reactant could be determined from the structure of a reaction product, i.e. the major conformer would yield the major product. This assumption was shown to be incorrect by Curtin and Hammett in the 1950s [32].

For a reaction in which a starting material A is an equilibrium mixture of two conformers (or diastereomers, tautomers, rotamers, etc.) A¹ and A² (Eq. 1.1), two extreme situations can be considered – one in which equilibration of A¹ and A² is slow if compared with their reaction with B ($k^1, k^2 \ll k^C, k^D$), and one in which equilibration of A¹ and A² is much faster than their reaction with B ($k^1, k^2 \gg k^C, k^D$).

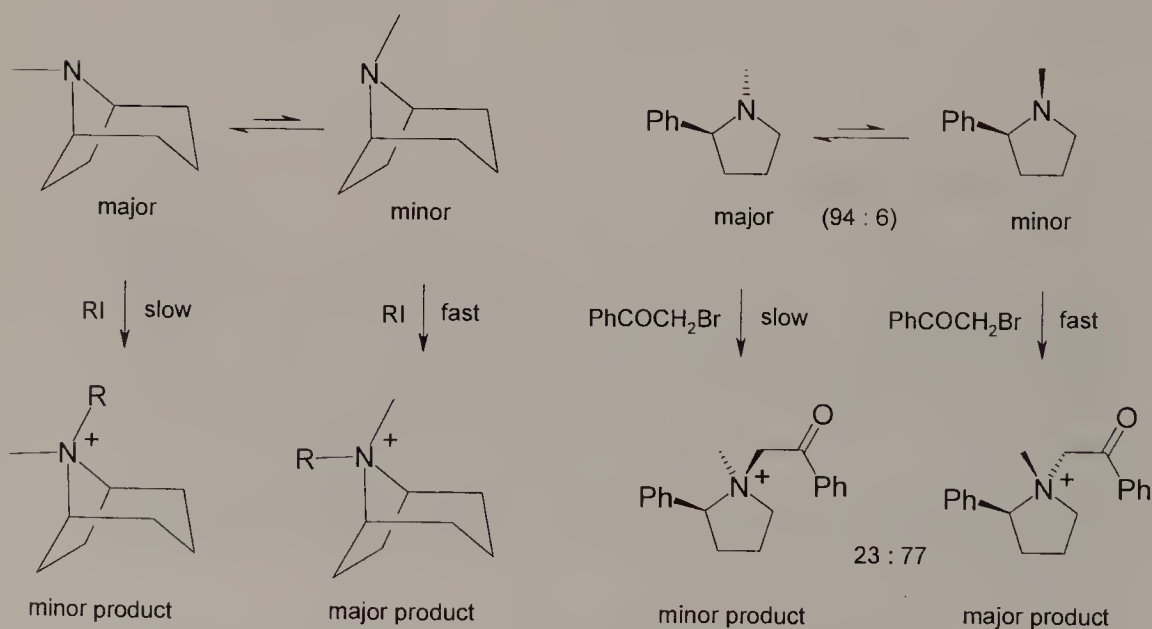


If equilibration of A^1 and A^2 is slow, the product ratio $[C]/[D]$ will be equal to the ratio of conformers of the starting material A ($[A^1]/[A^2]$) and independent of the ratio k^C/k^D . If equilibration is rapid, however, the amount of C and D formed will depend both on the ratio of starting materials ($[A^1]/[A^2]$) and on the ratio of the two reaction rate constants k^C and k^D : $[D]/[C] = [A^2]/[A^1] \times k^D/k^C$ [32].

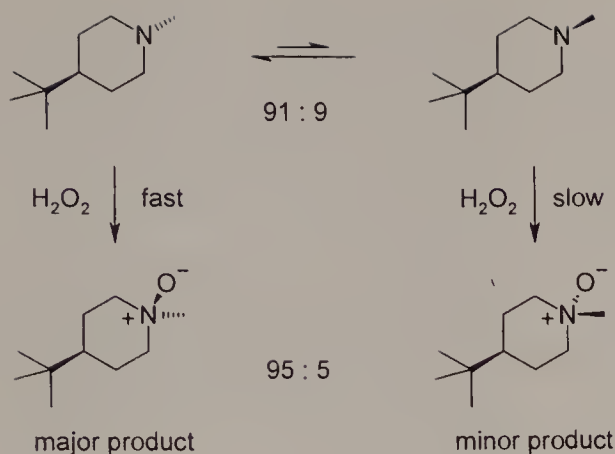
The main implication of these derivations is that if equilibration is rapid, the product ratio cannot always be intuitively predicted if the reaction rates k^C and k^D are unknown. Because energy-rich conformers, present in low concentrations only, are often more reactive than more stable conformers, it is not unusual for the main product of a reaction to result from a minor conformer which cannot even be observed.

Two examples of such situations are sketched in Scheme 1.11. Quaternization of tropane occurs mainly from the less hindered “pyrrolidine side” (equatorial attack at the piperidine ring), even though the main conformer of tropane has an equatorial methyl group. Similarly, 1-methyl-2-phenylpyrrolidine yields mainly an *anti* alkylated product via alkylation of the minor *cis* conformer when treated with phenacyl bromide [33]. In both instances the less stable conformer is more reactive to such an extent that the major product of the reaction results from this minor conformer. A further notable example of a reaction in which the main product results from a minor but more reactive intermediate is the enantioselective hydrogenation of α -acetamidocinnamates with a chiral rhodium-based catalyst [34].

This does, however, not need to be so. Oxidation of 1-methyl-4-*tert*-butylpiperidine, for example, yields mainly the amine *N*-oxide derived from the most stable conformer (Scheme 1.12). In this example the more energy-rich (less stable) conformer reacts more slowly than the major conformer.



Scheme 1.11. Diastereoselective quaternization of tertiary amines [32, 33, 35].



Scheme 1.12. Diastereoselective oxidation of 4-*tert*-butyl-1-methylpiperidine [32, 36, 37].

To conclude, the Curtin–Hammett principle states that the relative amounts of products formed from two interconverting conformers depend on the reactivity of these two conformers if the interconversion of these conformers is rapid, and cannot always be intuitively predicted.

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2

Stereoelectronic Effects and Reactivity

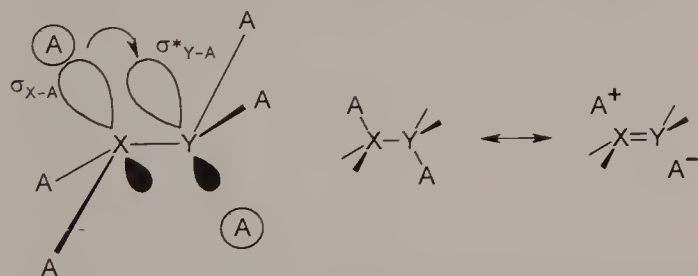
2.1

Hyperconjugation with σ Bonds

Stereoelectronic effects can be defined as effects on structure and reactivity determined by the efficiency of orbital overlap as a function of molecular conformation. Interactions involving sp^3 hybrid orbitals are usually referred to as “hyperconjugation”, whereas interactions of p orbitals of sp^2 hybridized atoms are called “conjugation”. Hyperconjugation will stabilize or destabilize certain conformations, strengthen or weaken bonds, and can increase or reduce the energy of lone electron pairs, and thereby modulate the nucleophilicity and basicity of a given compound. Those stereoelectronic effects with highest impact on the reactivity of compounds generally result from interaction of vicinal orbitals.

In Scheme 2.1 the orbital interactions between two sp^3 hybridized, tetravalent atoms X and Y are sketched in the staggered conformation. This conformation enables efficient transfer of electrons from the (bonding) σ_{X-A} orbital to the empty (antibonding) σ^*_{Y-A} orbital; this leads to longer and weaker X–A bonds and a shorter, stronger X–Y bond. The net effect is lowering of the ground state energy (i.e. stabilization) of the molecule. This form of hyperconjugation can also be illustrated by the two canonical forms sketched in Scheme 2.1.

In principle a $\sigma_{X-A} \rightarrow \sigma^*_{Y-A}$ charge-transfer interaction would also be possible when the two vicinal X–A and Y–A bonds adopt a synperiplanar conformation. However, in this latter conformation the overlap integral $\sigma_{X-A} \rightarrow \sigma^*_{Y-A}$ and thus the



Scheme 2.1. Orbital interaction and canonical forms for hyperconjugation between σ bonds.

stabilization achieved by hyperconjugation is smaller than with the antiperiplanar orientation of the two interacting bonds.

The relative abilities of $\sigma^*_{\text{C-X}}$ bonds to accept electrons from a vicinal C-H bond in ethanes have been calculated (Table 2.1), and were found not to correlate well with the electronegativity of X. Thus, within each group of the periodic table the energies of the $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-X}}$ interaction decrease with decreasing atomic weight of X, although the electronegativity increases. The reason for this is that the energy of the $\sigma^*_{\text{C-X}}$ orbitals decreases when going to the heavier elements within one group; this leads to a smaller energy gap between the bonding and antibonding orbitals, and thereby to greater stabilization [1].

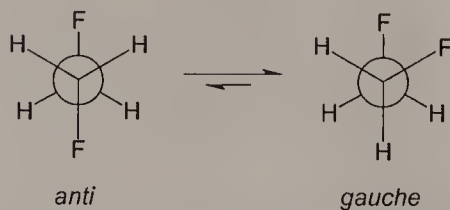
Table 2.1. Energies E_{hyp} (kcal/mol) of hyperconjugative ($\sigma_{\text{C(2)-H}} \rightarrow \sigma^*_{\text{C(1)-X}}$) interaction in $\text{CH}_3\text{-CH}_2\text{-X}$ [1].

X	I	N ₂ ⁺	Br	Cl	SH	F	OH	SeH	
E _{hyp}	7.81	7.61	6.29	6.20	5.36/4.70 ^a	5.09	4.74/4.22 ^a	4.68	
X	PH ₂	AsH ₂	NH ₂	CMe ₃	GeH ₃	SiH ₃	CF ₃	CH ₃	H
E _{hyp}	4.61/4.01 ^a	4.55	4.46/3.82 ^a	3.93	3.80	3.63	3.59	3.38	3.17

^a The two values refer to two different orientations of the lone pairs.

The energies given in Table 2.1 are valid for substituted ethanes only, and a different ranking might result with other compound classes. These values are highly sensitive to small structural variations and should, therefore, be used as a rough guideline only. The organic chemist can use these values to estimate how strongly a C,H group is acidified by a group X in compounds with the substructure H-C-C-X.

Hyperconjugation between sp^3 hybridized atoms can have important implications for the ground-state conformation of organic compounds. It has, for example, been suggested that the energy difference between the staggered and the eclipsed conformations of ethane is due to both hyperconjugation and repulsion [2–5]. The fact that 1,2-difluoroethane [6, 7] or *N*-(2-fluoroethyl)amides [8] preferentially adopt a *gauche* conformation is also thought to result from hyperconjugation between the $\sigma_{\text{C-H}}$ orbital and the $\sigma^*_{\text{C-F}}$ orbital (Scheme 2.2). The *anti* conformation is, despite the mutually repulsive C-F dipoles pointing into opposite directions, less favorable for 1,2-difluoroethane. Because the C-F bond is a poorer electron donor than the C-H bond, the *gauche* conformation, which enables two $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-F}}$ interactions, is approximately 0.7 kcal/mol more stable than the *anti* conformation.



Scheme 2.2. Conformations of 1,2-difluoroethane.

Calculations have shown that the rotational barrier of the C–O bond in methanol (1.1 kcal/mol) is significantly lower than the corresponding rotational barrier of methyl hypofluorite (MeOF, 3.7 kcal/mol) or methyl hypochlorite (MeOCl, 3.5 kcal/mol), in which a strong $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{O-Hal}}$ hyperconjugation is possible [9]. Similarly, in 1,2-dihaloethenes such as 1,2-difluoroethene, 1-chloro-2-fluoroethene, or 1,2-dichloroethene the *cis* isomers are more stable than the corresponding *trans* isomers [10, 11].

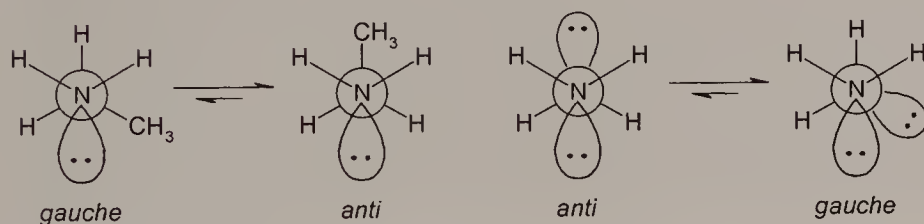
2.2

Hyperconjugation with Lone Electron Pairs

2.2.1

Effects on Conformation

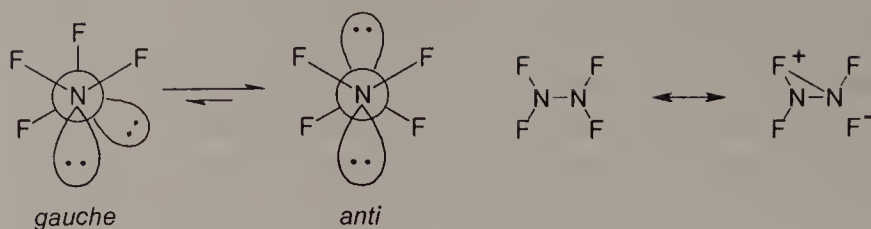
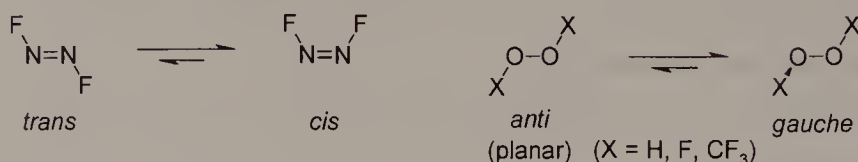
Lone electron pairs can donate electron density to the antibonding orbitals of anti-periplanar σ bonds more efficiently than most $\sigma_{\text{C-X}}$ bonds. Consequently, these interactions lead to the most conspicuous stereoelectronic effects. Examples of the interaction of lone pairs with antibonding orbitals (negative hyperconjugation) include the stabilization of the *anti* conformation of ethylamine [1] or α -fluoroamines [12], or the stabilization of the *gauche* conformation of hydrazine [13] (Scheme 2.3). In ethylamine the $\sigma^*_{\text{C-C}}$ orbital is a slightly better acceptor than the $\sigma^*_{\text{C-H}}$ orbital, whereas in hydrazine hyperconjugation between the lone pairs and vicinal antibonding orbitals is only possible in the *gauche* conformation.



Scheme 2.3. Conformations of EtNH₂ (left [1]) and H₂NNH₂ (right [13]).

Because the precise energies of charge-transfer interactions are sensitive to small structural modifications, purely intuitive predictions often turn out to be wrong. In tetrafluorohydrazine, for instance, hyperconjugation of the type $n_{\text{N}} \rightarrow \sigma^*_{\text{N-F}}$ should be even stronger than in hydrazine, and a preferred *gauche* conformation would be expected. The *anti* conformer of tetrafluorohydrazine is, though, slightly more stable than the *gauche* conformer, because of efficient hyperconjugation between the non-bonding electrons on fluorine and $\sigma^*_{\text{N-F}}$ [13] (Scheme 2.4).

Other compounds for which the most stable conformation is probably because of negative hyperconjugation include difluorodiazene [10], hydrogen peroxide, dioxygen difluoride [14], and bis(trifluoromethyl) peroxide [15] (Scheme 2.5).

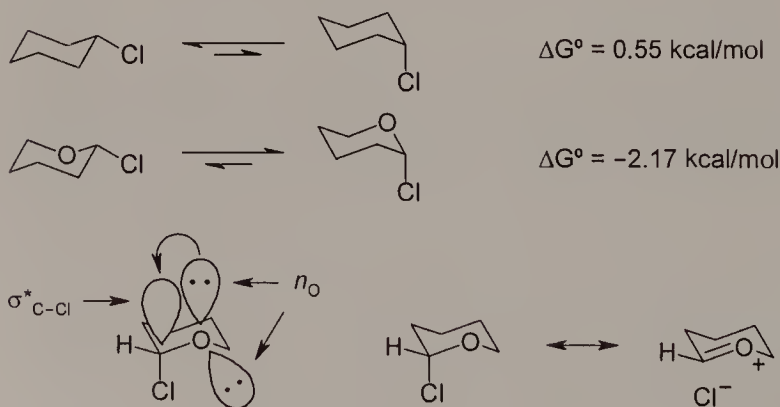
Scheme 2.4. Conformations and canonical forms of F_2NNF_2 [13].

Scheme 2.5. Conformations of diazenes and peroxides.

2.2.2

The Anomeric Effect

The anomeric effect [16], i.e. the tendency of some groups at the C-2 position of tetrahydropyrans to adopt preferentially an axial position, can also be rationalized as a consequence of negative hyperconjugation (Scheme 2.6). Efficient overlap of the antibonding C-X orbital and one lone pair at oxygen is only possible in pyrans with the substituent X positioned axially; if $\sigma_{\text{C-X}}^*$ is a good acceptor hyperconjugation may stabilize this conformation, which otherwise (i.e. in the corresponding cyclohexyl derivative) would normally be unfavorable. A further observation which points toward hyperconjugation as reason for the anomeric effect is that axially positioned substituents X have longer C-X bonds than similar compounds with X in the equatorial position [16]. The groups listed in Table 2.1 which have good ability to accept electrons from $\sigma_{\text{C-H}}$ bonds also will tend to have a strong anomeric effect when bound to C-2 of a pyran.

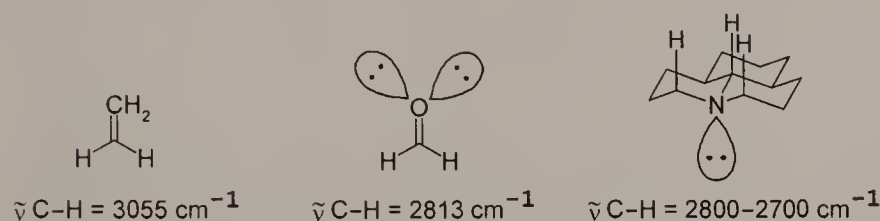


Scheme 2.6. The anomeric effect [16].

2.2.3

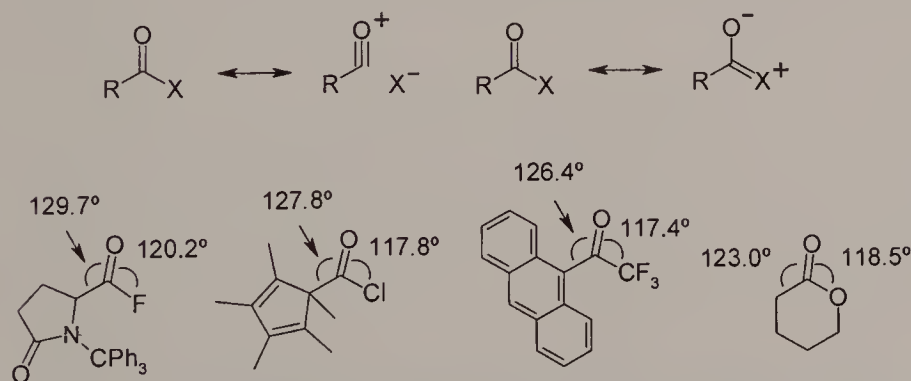
Effects on Spectra and Structure

The weakening of σ bonds by negative hyperconjugation with lone electron pairs also reveals itself in IR and NMR spectra. Thus, C–H, N–H, or O–H bonds oriented *trans* or antiperiplanar to an unshared, vicinal electron pair are weakened and have therefore a significantly reduced IR vibrational frequency [17]. The C–H vibrational frequency in aldehydes is, for example, lower than that in alkenes (Scheme 2.7). Polycyclic amines with at least two hydrogen atoms antiperiplanar to the lone pair on nitrogen have characteristic absorption bands at 2800–2700 cm^{-1} which have been used to infer the relative configuration of such amines [18].



Scheme 2.7. Antiperiplanar lone pairs weaken C–H bonds and reduce their IR wavenumber [17, 18].

Negative hyperconjugation can also be used to explain some of the structural and spectroscopic features of simple carbonyl group-containing compounds such as aldehydes, ketones, or carboxylic acid derivatives. As illustrated by the canonical forms shown in Scheme 2.8, the strength of the C=O bond in carbonyl compounds should increase with increasing electron-withdrawing capability of substituents directly attached to the carbonyl group. The hybridization of the carbonyl carbon atom should at the same time become more *sp*-like, and the angle R–C=O should become larger than 120°. This has, for instance, been observed in X-ray structural analyses of acyl halides [19, 20], trihalomethyl ketones [21], lactones, and lactams [22, 23] (Scheme 2.8).



Scheme 2.8. Hyperconjugative distortion of bond angles in carbonyl compounds [19–22].

Because the strength of the C=O bond correlates with its stretching frequency, the latter increases when the substituent X becomes more electronegative (Table 2.2). Complete abstraction of the group X (e.g. for X = BF₄⁻) leads to the formation of acylium cations with a short and strong C≡O bond, as revealed by the high vibrational IR-frequency of these compounds [24] (Table 2.2).

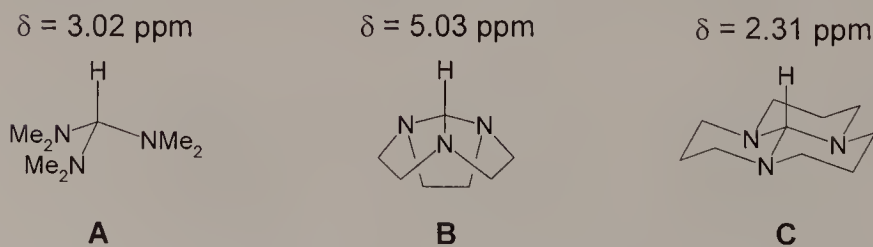
Table 2.2. C=O Wavenumbers $\tilde{\nu}(\text{C=O})$ of acetyl derivatives MeCOX.

X	CH ₃	H	CN	CCl ₃	CF ₃
$\tilde{\nu}(\text{CO})$ (cm ⁻¹)	1720	1729	1730	1765	1781
Ref.	25	26	27	28	29

X	I	Br	Cl	F	BF ₄ ⁻
$\tilde{\nu}(\text{CO})$ (cm ⁻¹)	1808	1812	1800	1848	2299
Ref.	30	31	24	24	24

If the group X has lone electron pairs, conjugation of these with the carbonyl group will not lead to a distortion of the O=C–X and R–C=O angles, but will weaken the C=O bond (Scheme 2.8). This conjugation might be the reason for the small changes in C=O stretching frequency in the series of acyl halides (Table 2.2). The decrease of electronegativity when going from fluorine to iodine (which should lead to a strong decrease of the C=O stretching frequency) is partly compensated by less efficient conjugation between the carbonyl group and the unshared electron pairs on the larger, heavier halogen atoms.

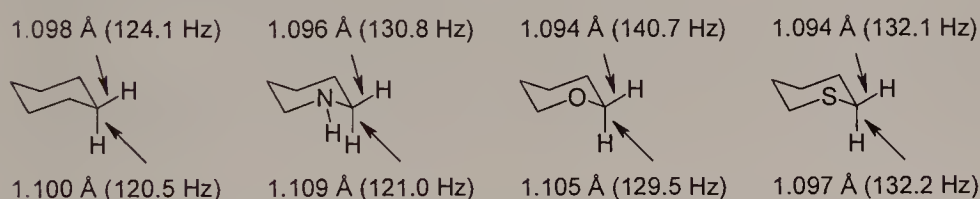
In NMR spectra, hyperconjugative electron transfer into σ^* orbitals can manifest itself as a diminished chemical shift of protons located antiperiplanar to unshared electron pairs [32, 33]. Thus, the chemical shifts of the methine proton of tris(di-alkylamino)methanes vary strongly as a function of their orientation toward the lone electron pairs at nitrogen [34] (Scheme 2.9). In compound **B** the lone pairs are syn-periplanar to the C–H bond, and efficient negative hyperconjugation is not possible. The inductive (electron-withdrawing) effect of nitrogen leads to deshielding of this proton compared with the methine proton in compound **A**, in some conformers of which hyperconjugation is possible. Strong shielding of this proton is observed in compound **C**, with three electron pairs oriented simultaneously antiperiplanar to the methine C–H bond [34].



Scheme 2.9. Magnetic shielding of protons by antiperiplanar lone electron pairs.

The weakening of C–H bonds by hyperconjugation can also lead to lower one-bond NMR coupling constants. Calculations [35] have shown that in tetrahydropyran 2-H_{ax} has a lower coupling constant to C-2 (129.5 Hz) than 2-H_{eq} (140.7 Hz). These coupling constants correlate as expected with the calculated bond lengths [35]. These C–H bond lengths have, however, relatively little dependence on the orientation of vicinal lone pairs (Scheme 2.10), because the $\sigma^*_{\text{C-H}}$ orbital is a poor electron acceptor. The similar coupling constants of the axial and equatorial C(2)–H bonds in tetrahydrothiopyran can be explained by assuming that the electron transfer $\sigma_{\text{C(6)-S}} \rightarrow \sigma^*_{\text{C(2)-H}}$ is more efficient than $n_{\text{S}} \rightarrow \sigma^*_{\text{C(2)-H}}$ [35]. This would imply that no anomeric effect should be observed in tetrahydrothiopyrans, but this is not so [16]. Certain heterocycles can, however, have an anomeric effect which is not due to negative hyperconjugation but to other factors such as steric and electrostatic effects [36, 37].

The coupling constants and calculated bond lengths for axial and equatorial C–H bonds in cyclohexane (Scheme 2.10) have been interpreted as a result of the superior electron-donating capacity of C–H bonds compared with C–C bonds (see, e.g., Ref. [38]; calculations (Table 2.1) do not support this idea). Thus, the axial C–H bonds are weaker and longer than equatorial C–H bonds because each of the former undergoes hyperconjugation with two axial C–H bonds.



Scheme 2.10. Calculated bond lengths and ^{13}C – ^1H coupling constants in cyclohexane and six-membered heterocycles [35].

2.3

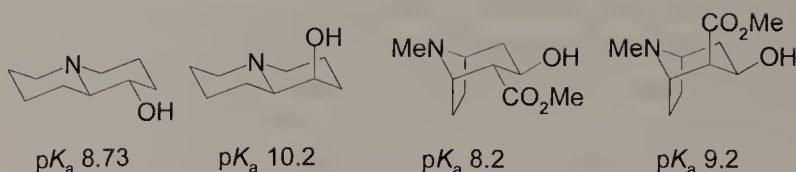
Hyperconjugation and Reactivity

2.3.1

Basicity and Nucleophilicity

The orbital interactions discussed above not only govern the energy of ground state conformations or configurations but can also modulate the energy of transition states and, therefore, the reactivity of compounds. In conformationally constrained systems it has been observed that orbital overlap can affect the nucleophilicity and basicity of unshared electron pairs. The basicity differences of the amines shown in Scheme 2.11 [39] can, for instance, be interpreted as a result of a more or less efficient overlap between vicinal $\sigma_{\text{C-N}}$ and $\sigma^*_{\text{C-X}}$ orbitals, where X represents an electron-withdrawing group.

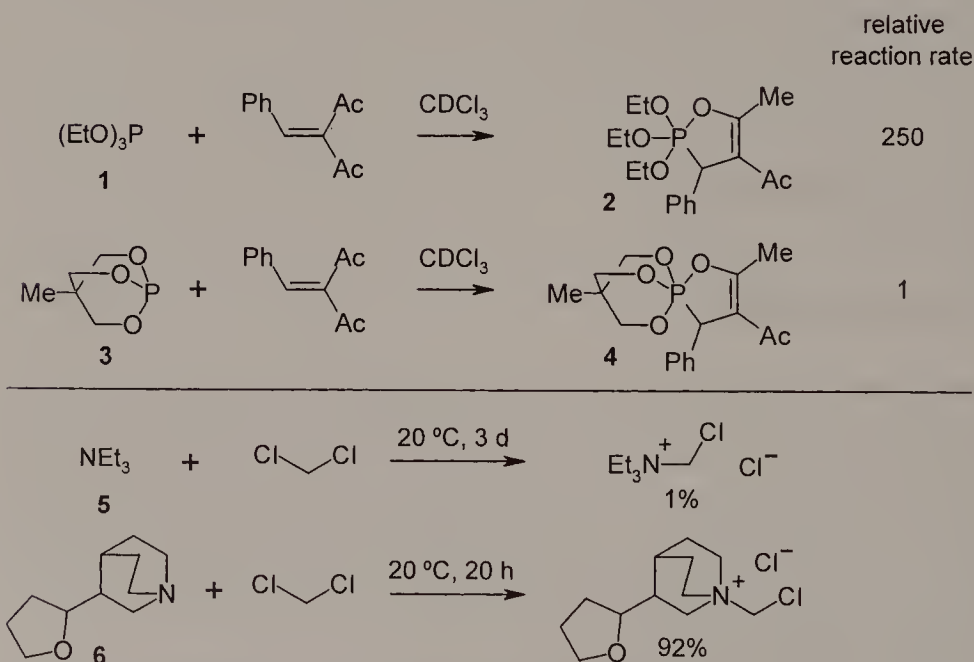
The reactivity of cyclic phosphites also depends strongly on the mutual orientation of n_{P} and n_{O} lone pairs. Triethyl phosphite (**1**) (Scheme 2.12), for instance,



Scheme 2.11. Basicity of bicyclic amines substituted with electron-withdrawing groups [39].

undergoes rapid addition to 2-benzylidenepentane-2,4-dione to yield the cyclic, pentavalent phosphorus derivative **2**. The more constrained phosphite **3**, however, reacts much more slowly, despite the easier access to its electron pair [40]. The low reactivity of phosphite **3** is even more puzzling when compared with the relative reactivity of triethylamine (**5**) [41] and quinuclidines such as **6** [42] towards electrophiles. The fixing of the lone pair (inversion of nitrogen is no longer possible) and the alkyl groups in quinuclidines enhances the rate of reactions with electrophiles (but not their basicity) to such an extent that even poor electrophiles such as dichloromethane react swiftly [43]. (The fixing of the lone pair in quinuclidines has no significant effect on their thermodynamic basicity (i.e. their pK_a), which reflects the energy difference between the protonated and the non-protonated forms. Thermodynamic basicity is not directly related to the *rate* of protonation (kinetic basicity), which should in fact be higher for quinuclidines than for acyclic tertiary amines).

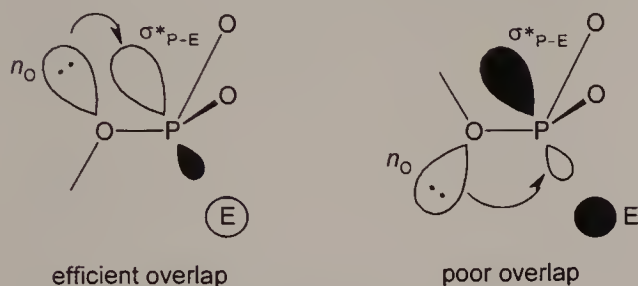
The low reactivity of phosphite **3** has been explained as follows [44]. During the reaction of phosphite **3** with an electrophile (E), efficient electron transfer from the lone pairs of oxygen to the incipient antibonding orbital of the P–E bond is not pos-



Scheme 2.12. Reactivity of phosphites and tertiary amines towards electrophiles [40–42].

sible, because their mutual orientation is *gauche*. Calculations suggest [44] that an $n_{\text{O}} \rightarrow \sigma^*_{\text{P-E}}$ interaction, where $\sigma^*_{\text{P-E}}$ is the antibonding orbital of the incipient P–E bond, which is possible during reaction of triethyl phosphite with an electrophile (left sketch, Scheme 2.13), should stabilize the transition state in a fashion similar to its stabilization of the transition state of the reverse reaction or the final product, and thereby accelerate the reaction. In other words, if a transition state is product-like, and the product is stabilized by hyperconjugation ($n_{\text{O}} \rightarrow \sigma^*_{\text{P-E}}$ in this case) the rate of formation of this product should increase [38].

The orientation of the unshared electron pairs of oxygen in compounds containing P–O bonds also modulates the gas-phase basicity [45, 46] and oxidation potentials [47] of these compounds.



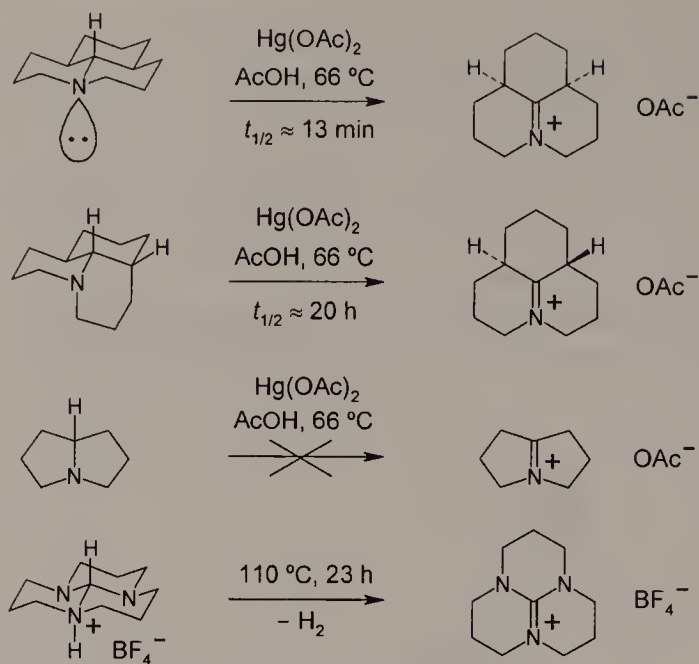
Scheme 2.13. Hyperconjugation in phosphites.

2.3.2

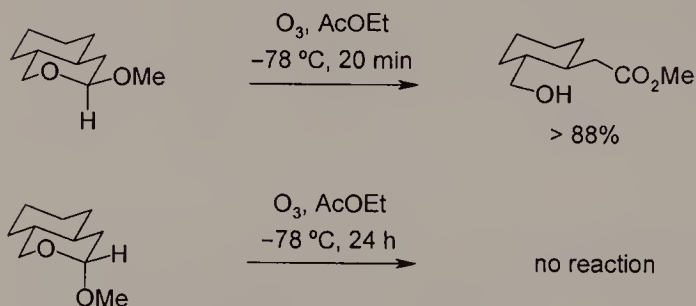
Rates of Oxidation

The rate of oxidation of organic compounds might also be influenced by stereoelectronic effects. Thus, when polycyclic amines are oxidized to iminium ions by treatment with mercury(II) acetate (Scheme 2.14), amines with a lone electron pair anti-periplanar to the reacting hydrogen atom will react most rapidly [48]. Hexahydropyrrolizine (third example of Scheme 2.14), in which the bridgehead hydrogen atom and the lone pair are synperiplanar, could not be oxidized [48]; this might, however, also be partly a result of the strained structure of the product. Similarly, compound **B** in Scheme 2.9 was resistant to oxidants. Tris(dialkylamino)methane **C** (Scheme 2.9), on the other hand, with three lone pairs antiperiplanar to the methine C–H bond, is a strong reducing agent [49], and reacts with acids to yield hydrogen and the corresponding guanidinium salt [50] (fourth reaction, Scheme 2.14).

Some 2-alkoxytetrahydropyrans show a reactivity toward oxidants which parallels the reactivity of polycyclic amines discussed above, and which is in line with the hypothesis that weakening of C–H bonds by hyperconjugation should also increase the rate of C–H bond cleavage. For instance, of the two epimeric pyrans sketched in Scheme 2.15 only that with an axial 2-H is oxidized by ozone [51]. The same selectivity has been observed in the oxidation of methyl α - and β -glucopyranoside with ozone [52], and in homolytic C–H bond cleavage in cyclic ethers [53].



Scheme 2.14. Oxidation of polycyclic amines [48, 50].

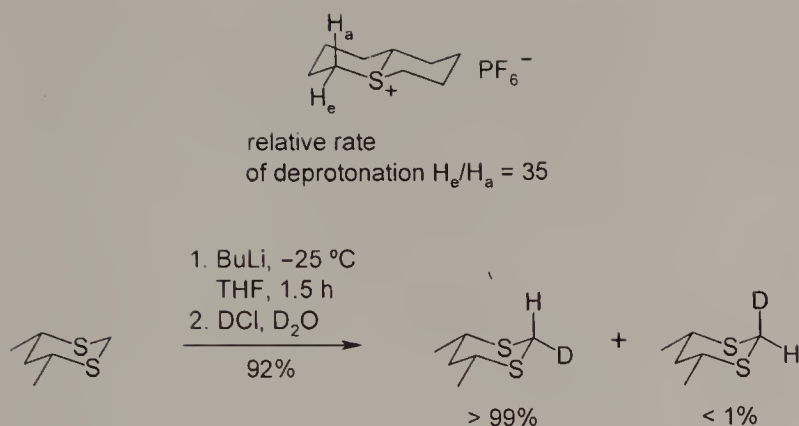


Scheme 2.15. Oxidation of tetrahydropyrans [51].

2.3.3

Rates of Deprotonation

The α -deprotonation of conformationally constrained thioethers can proceed with high diastereoselectivity (Scheme 2.16) [54]. That equatorial protons are removed much more rapidly than axial protons suggests that stabilization of carbanions $\text{C}_{\alpha}^{(-)}\text{-S-C}_{\alpha'}$ by sulfur is mainly a result of hyperconjugation between the carbanion lone pair and the antibonding $\text{S-C}_{\alpha'}$ orbital [55].

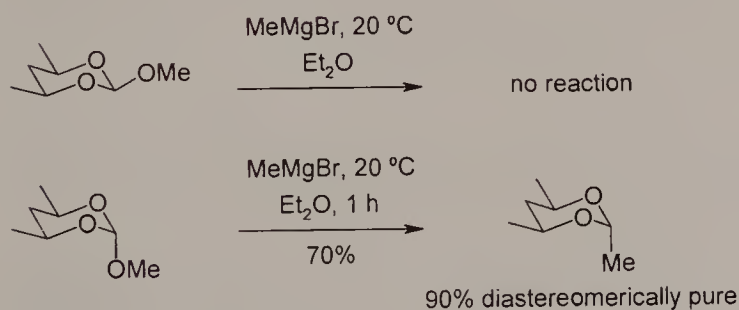


Scheme 2.16. Diastereoselective metalation of thioethers and sulfonium salts [55, 56].

2.3.4

Other Reactions

One remarkable example of nucleophilic substitution at a 1,3-dioxane in which the isomer with an axial (and thus weaker) bond to the leaving group reacts more rapidly than the equatorial epimer is shown in Scheme 2.17 [57]. Because the product is formed with retention of configuration, the reaction must proceed by an S_N1 -like mechanism.

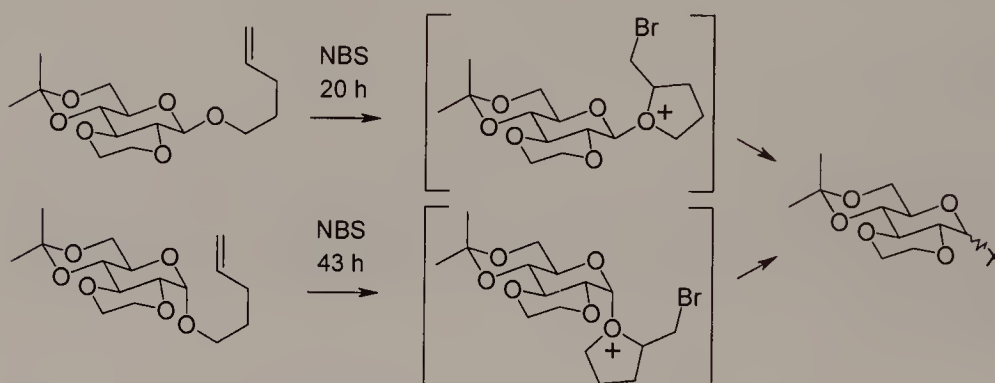


Scheme 2.17. Reactions of cyclic orthoesters with Grignard reagents [57].

Unfortunately, intuitive predictions of reactivity on the basis of stereoelectronic effects are not always possible, because these effects are subtle and can easily be overridden by steric, inductive, or field effects, or by conformational changes during the reaction [58]. It must also be kept in mind that hyperconjugation in the transition state, and not in the ground state, will have the largest effect on the reaction rate.

As discussed above, 2-halotetrahydropyrans tend to adopt a conformation in which the halogen is located axially, and which is stabilized by negative hyperconjugation of the type $n_O \rightarrow \sigma^*_{C-Hal}$. X-ray structural analyses have shown that in these

compounds the carbon–halogen bond is, as expected, longer than in similar compounds with an equatorial halogen atom [16]. Accordingly, we would expect that 2-halotetrahydropyrans with an axial halogen would react more rapidly with nucleophiles than the corresponding pyrans with an equatorial halogen atom, because $C-Hal_{ax}$ is longer and weaker than $C-Hal_{eq}$. This, however, is not observed. The rates of alcoholysis of α - and β -pyranosyl halides [59, 60] cannot be used to distinguish between the reactivity of axial and equatorial halides, because of the conformational flexibility of these substrates, which preferentially adopt the conformation with the halide axial, even if the remaining substituents are thereby also forced into the axial position [16]. But even in conformationally constrained substrates the axial leaving groups are not easier to displace [61]. For instance, α -glycosides are not always hydrolyzed more rapidly than the corresponding β -glycosides [58, 62], as is illustrated by the similarly rapid oxidative hydrolysis of the two conformationally constrained anomeric glycosides shown in Scheme 2.18 [63].

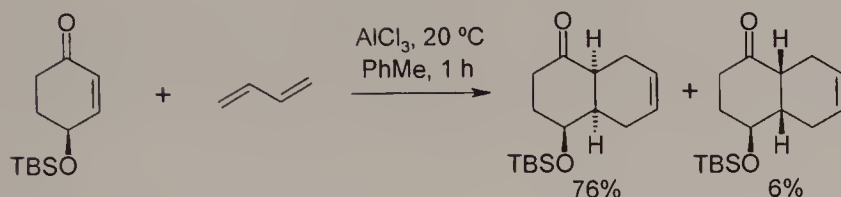
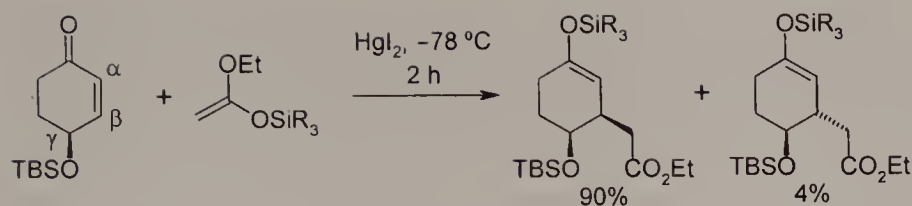


Scheme 2.18. Oxidative cleavage of anomeric pentenyl glycosides [63].

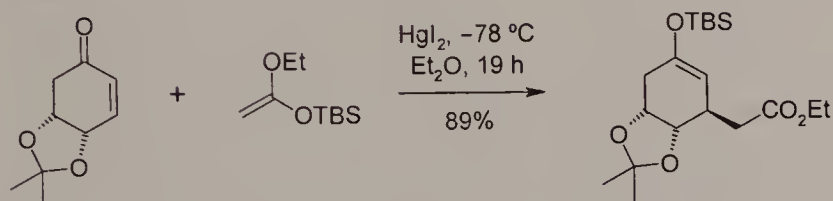
Numerous other examples have, moreover, been reported in which bonds with antiperiplanar lone electron pairs react more slowly than, or at rates similar to, comparable bonds without antiperiplanar lone pairs [52, 63–67].

The diastereoselectivity of the first two reactions shown in Scheme 2.19 [68] can also be interpreted as a result of a stereoelectronic effect. Although the diastereoselectivity of additions to enones is usually governed by steric effects, which lead to an addition of the nucleophile from the sterically less demanding side of the double bond (as in the third reaction in Scheme 2.19; for additional examples, see Refs [69, 70]), the first two reactions shown in Scheme 2.19 are, surprisingly, *syn*-selective. Cyclopentenones [68, 71] and cycloheptenones [72] can also react with the same *syn*-diastereoselectivity.

Hyperconjugation between the incipient antibonding σ^*_{Nuc-C} orbital and the binding $\sigma_{C(\gamma)-O}$ and $\sigma_{C(\gamma)-H}$ orbitals in the transition states [68] can be invoked as a possible reason for this diastereoselectivity. Because of the high electronegativity of oxygen, $C-O$ bonds have poor electron-donating properties compared with $C-H$ bonds. Accordingly, the transition state leading to the *syn* product might be stabilized by $\sigma_{C(\gamma)-H} \rightarrow \sigma^*_{C(\beta)-Nuc}$ hyperconjugation, where $\sigma^*_{C(\beta)-Nuc}$ is the incipient

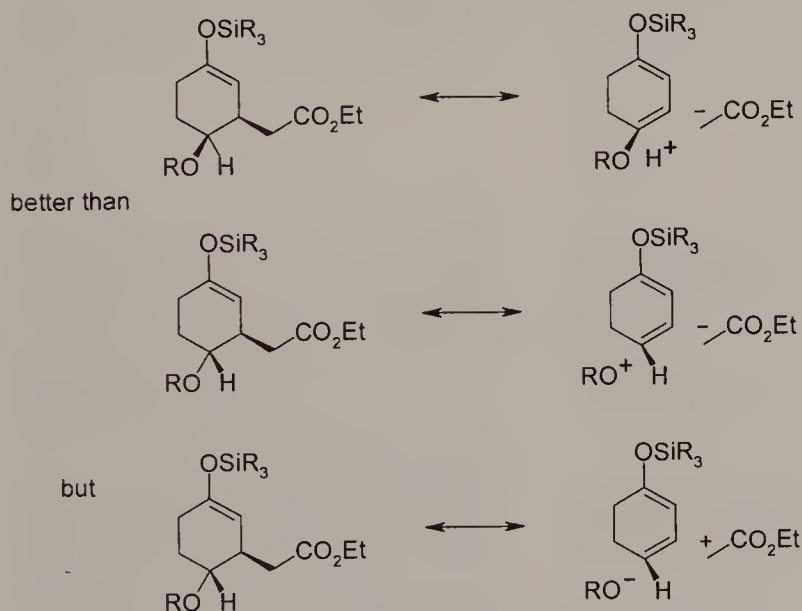


But:



Scheme 2.19. Diastereoselective addition of C-nucleophiles to enones [68, 71, 73].

antibonding orbital between $\text{C}(\beta)$ and the nucleophile. Such hyperconjugation should also stabilize the product, in the way illustrated by the first two canonical forms in Scheme 2.20. For the *anti* diastereomer, however, the third valence bond resonance structure of Scheme 2.20 can also be considered. These canonical forms, which would stabilize the *anti* product, would, however, not resemble the transition



Scheme 2.20. Valence bond resonance structures of the products as models of the transition state leading to these products.

state for addition of an electron-rich nucleophile to an electrophilic double bond, and should, therefore, not be relevant to the diastereoselectivity of this reaction.

The arguments used above to explain the diastereoselectivity of the two first reactions in Scheme 2.19 on the basis of hyperconjugation of incipient antibonding orbitals are analogous to that used to explain the reactivity of phosphites (Scheme 2.12). This form of hyperconjugation was also used by Cieplak to explain π -facial diastereoselection in the addition of nucleophiles to ketones [38, 74]. The third reaction of Scheme 2.19 clearly shows that the diastereoselectivity of these reactions is responsive to small structural changes and are, therefore, hardly predictable.

2.4

Conclusion

Stereoelectronic effects can have a profound effect on the ground-state structure of molecules, and can often help to explain counter-intuitive conformational preferences or spectroscopic features. Their effect on the energy of transition states is, however, less straightforward to predict. As stated by the Curtin–Hammett principle [75] (Section 1.4), reactions will proceed via energetically unfavorable conformers if these are more reactive (as is often the case) than better stabilized conformers. In such instances ground-state stabilization of certain conformers or the weakening of bonds by hyperconjugation will not necessarily be predictive for the outcome of a reaction.

The examples discussed above illustrate that reactivity and stereoselectivity are subject to numerous, often subtle, influences. Continuous improvements in molecular modeling have enabled clarification of many, previously unexplained observations; in the future even solvent effects might, perhaps, be taken into account. Predictive models based on such calculations should, however, always be substantiated by experimental data.

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3

The Stability of Organic Compounds

3.1

Introduction

The enormous number of known organic compounds (and the existence of life on this planet) is mainly due to the fact that hydrocarbons and many other organic compounds are kinetically stable in air over a broad range of temperatures. If an organic compound is highly strained, electron-rich, or if it contains incompatible functional groups, the activation barrier to undergo rearrangement, fragmentation, or reaction with oxygen can, however, be sufficiently reduced to make its isolation on a preparative scale a difficult if not dangerous task. Because a synthesis will only succeed if the desired product does not undergo further chemical transformations after its formation or during its isolation, the organic chemist should have a clear knowledge of the limits of stability of organic compounds.

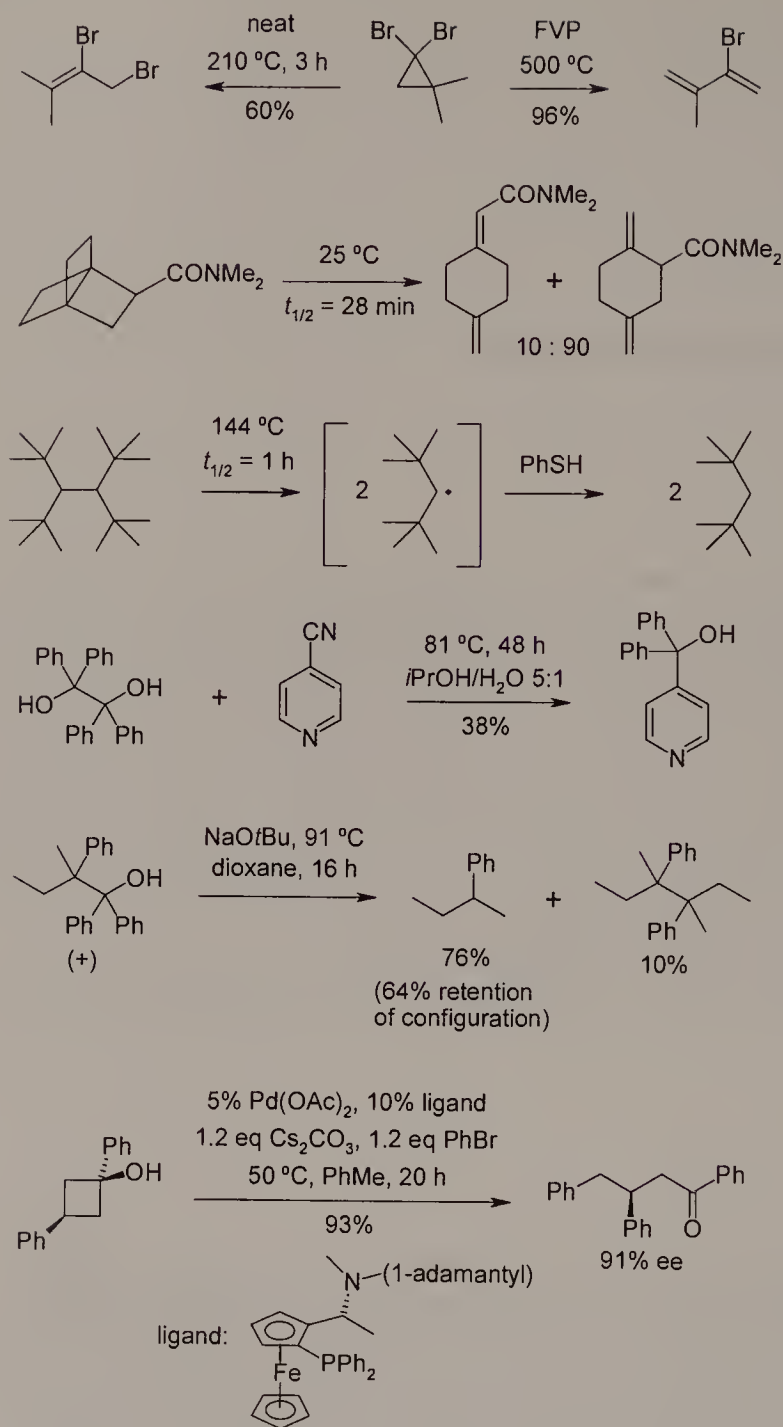
In this chapter some classes of unstable compound and their decomposition reactions will be presented, with the aim of sparing the reader unpleasant surprises in the laboratory.

3.2

Strained Bonds

Compounds in which bond angles deviate substantially from the normal values, or in which steric repulsion lengthens bonds significantly, will undergo homolytic or heterolytic C–C bond cleavage more readily and be therefore thermally less stable than comparable, unstrained compounds. Thus, cyclopropanes and ethanes with sterically demanding substituents have little thermal stability (Scheme 3.1). Transition metals readily undergo oxidative addition to C–C σ bonds if these are weakened by strain, and might therefore catalyze the rearrangement or fragmentation of strained compounds (last reaction, Scheme 3.1).

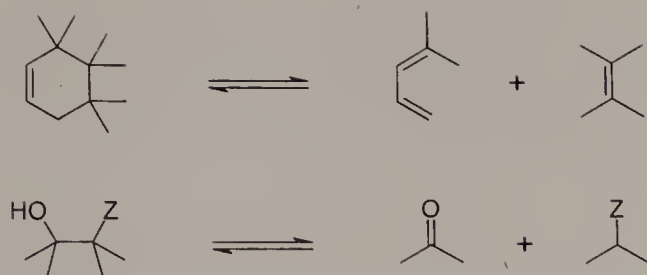
Strained bonds will be cleaved particularly readily if there is a reversible reaction by which these bonds might have been formally formed. Such reactions could be the Diels–Alder reaction, aldol additions, Michael additions, or related processes



Scheme 3.1. Thermal decomposition of strained compounds [1–8].

(Scheme 3.2). Reversible reactions are, for this reason, not usually suitable for the formation of strained bonds.

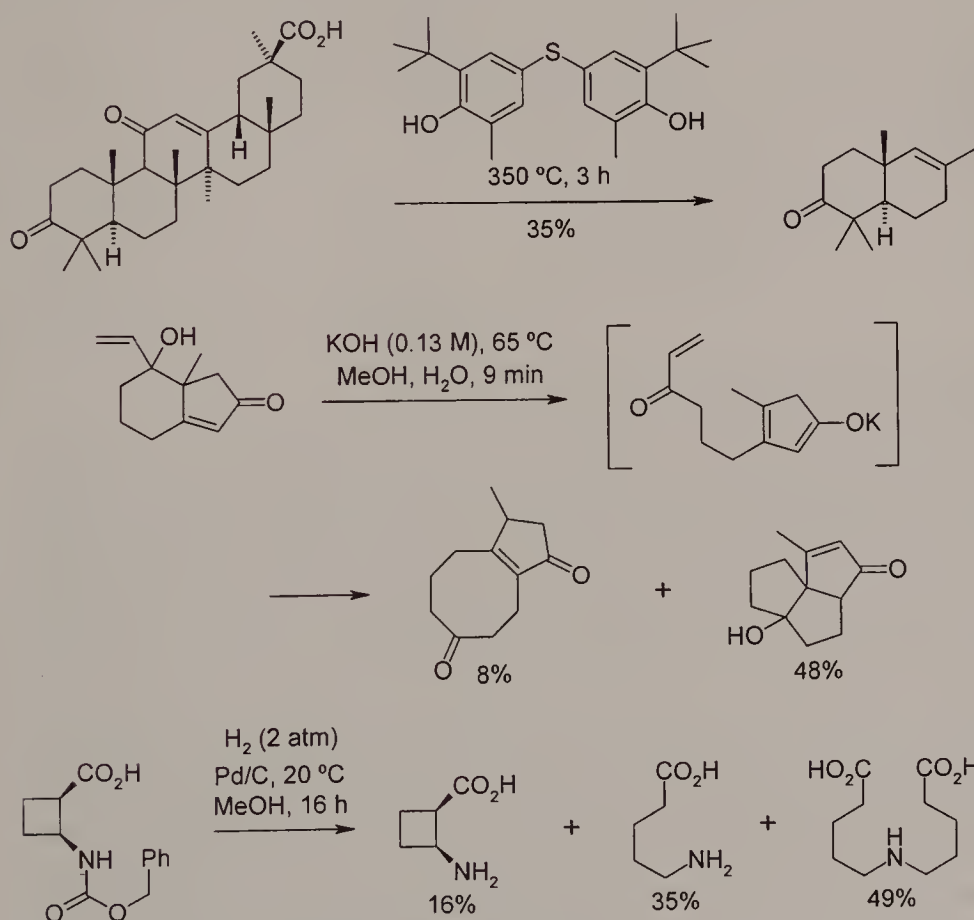
Strained cyclohexenes, such as norbornene derivatives, can undergo retro-Diels–Alder reactions even at relatively low temperatures, and this reaction can be used to prepare 1,3-dienes and alkenes (e.g. synthesis of cyclopentadiene by thermolysis of



Scheme 3.2. Fragmentation via retro-Diels–Alder cycloaddition and retro-aldol addition.

dicyclopentadiene at approximately 160 °C). In the example shown in Scheme 3.3 (first reaction) an enantiomerically pure bicyclic cyclohexanone is prepared from a readily available natural product. The radical scavenger is added to the starting material to prevent oxidation.

The second example in Scheme 3.3 illustrates the reversibility of aldol additions. The starting bicyclic ketone is a vinylogous aldol which upon treatment with base undergoes retro-aldol addition by cleavage of a strained, hexasubstituted ethane sub-

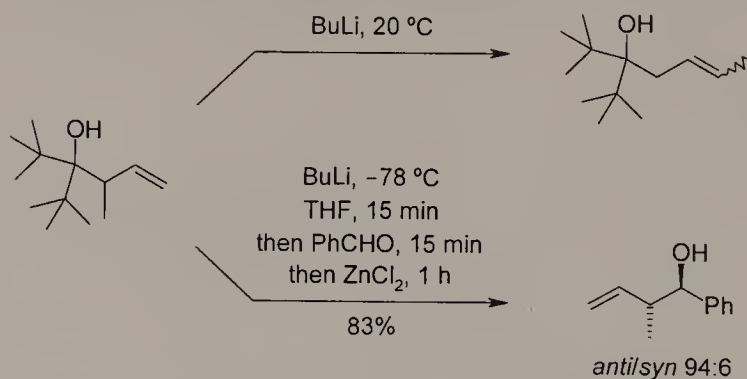


Scheme 3.3. Retro-Diels–Alder [9], retro-aldol [10] and retro-Mannich reaction [11] of strained substrates.

structure. Interestingly, the main product of this reaction also contains a similarly strained bond. Nevertheless, because these transformations are reversible, we must assume that the tricyclic ketone is thermodynamically the most stable product.

In the final example in Scheme 3.3 the starting material is the product of a formal intramolecular Mannich reaction. Accordingly, the C–C bond between the amino and the carboxyl group is particularly weak. Upon hydrogenolysis this bond is cleaved, whereby an imine or aldehyde is presumably formed as an intermediate which leads to the formation of a secondary amine as main product by reductive N-alkylation of 5-aminopentanoic acid.

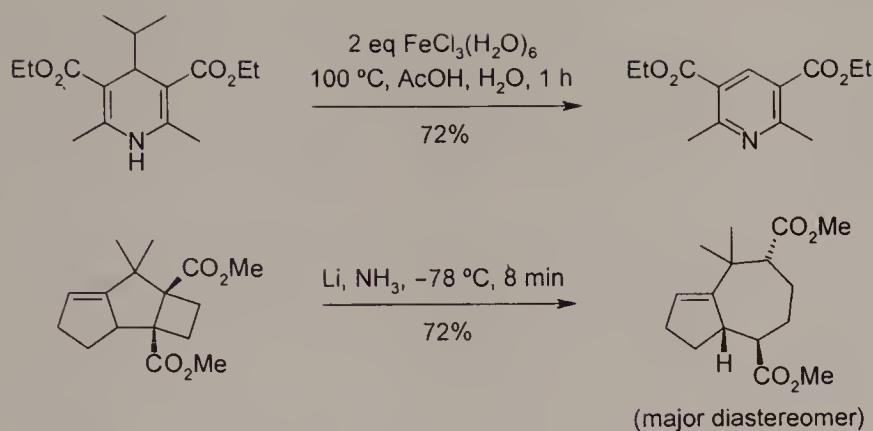
Tertiary homoallylic alcohols can formally undergo fragmentation into a ketone and an allyl anion [12, 13]. If the homoallylic alcohol contains several bulky alkyl groups its ground state energy may be sufficiently high to enable C–C bond cleavage to occur under mild reaction conditions. In the example sketched in Scheme 3.4 the tertiary alcoholate undergoes reversible fragmentation into di-*tert*-butyl ketone and an allylic organolithium compound when treated with BuLi at room temperature. Treatment of this alcoholate at low temperatures with an aldehyde activated by a Lewis acid leads to highly diastereoselective transfer of the allyl anion to the aldehyde.



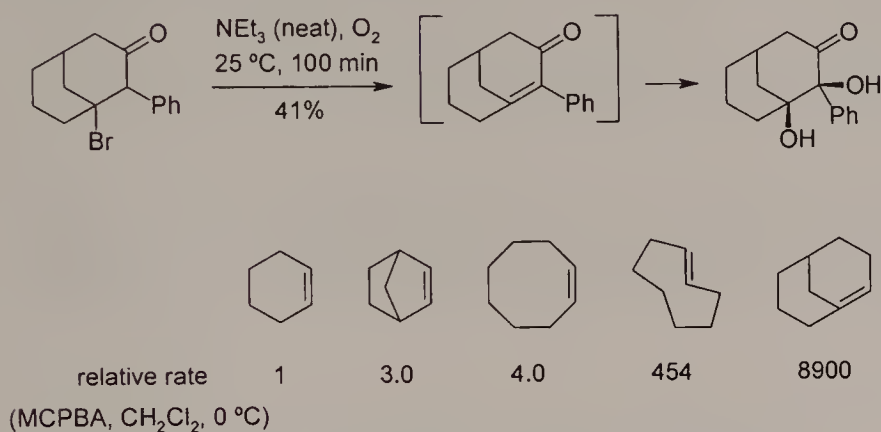
Scheme 3.4. Generation of allyl anions from bulky tertiary homoallyl alcoholates [14].

Secondary alkyl groups or benzyl groups may be cleaved from certain compounds during reactions in which radicals are formed as intermediates. This can, for instance, happen during the oxidation of 4-benzyl or 4-isopropyl dihydropyridines, which usually yields the dealkylated pyridines (Scheme 3.5). Similarly, if a strained bond connects two electron-withdrawing groups, this bond might be cleaved by SET-mediated reduction (second reaction, Scheme 3.5) [15].

If alkenes or alkynes are subjected to strain, their π bonds are weakened, and such compounds often behave chemically as diradicals. Their tendency to dimerize or polymerize will be significantly enhanced, and quick reaction with oxygen will occur in air [18, 19]. Reactions of strained alkenes which lead to a decline of strain, for example Michael additions or cycloadditions, can proceed significantly faster than with related, unstrained alkenes (Scheme 3.6).



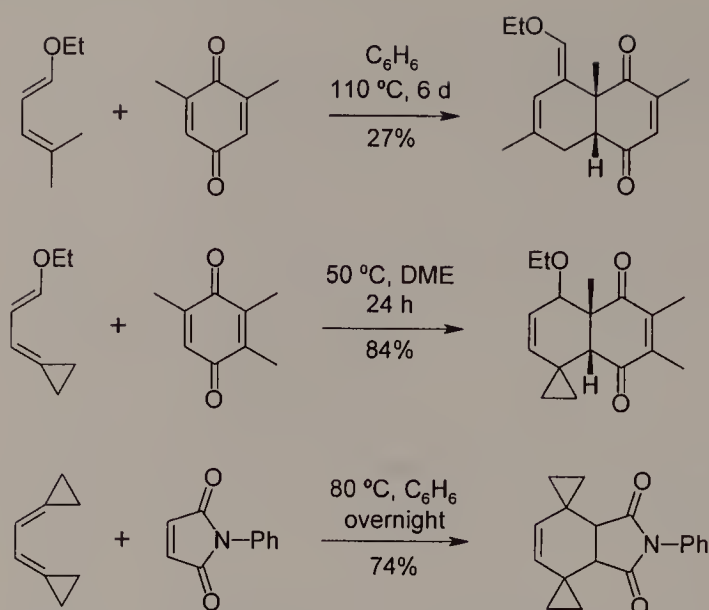
Scheme 3.5. Dealkylative oxidation of dihydropyridines [16] and reductive cleavage of cyclobutanes [17].



Scheme 3.6. Oxidation of a strained alkene by air [20] and relative rates of epoxidation of various cyclic alkenes [21].

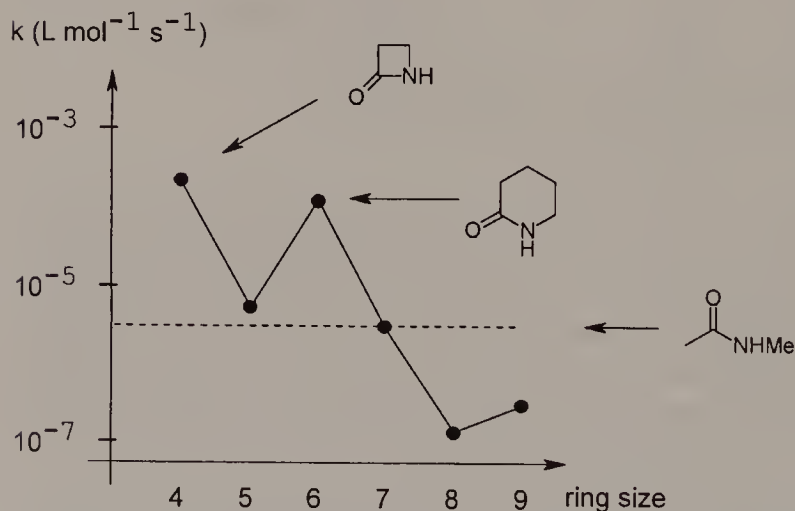
Strain can also be used to enhance the reactivity of otherwise unreactive alkenes. Non-cyclic 1,1-dimethyl-1,3-butadienes, for instance, undergo Diels–Alder reactions slowly or not at all. In the first reaction in Scheme 3.7, for example, the diene undergoes rearrangement to a terminal diene before cycloaddition. Because of the harsh reaction conditions the product is oxidized to an enol ether by the starting quinone [22]. If the terminal isopropylidene group is replaced by a cyclopropylidene group, however, the resulting dienes do not isomerize and undergo cycloaddition with dienophiles much more rapidly (Scheme 3.7).

Not all strained compounds are necessarily more reactive than less strained analogs. Reactivity will always depend on the type of reaction under scrutiny, and if the rate determining step of a given reaction is not accelerated by strain, the rate of reaction of strained and unstrained compounds will be similar. One example of such strain-independent reaction rates is the hydrolysis of lactams under basic reaction conditions (Scheme 3.8). Although β -lactams are more strained than six-membered lactams, both are hydrolyzed at approximately the same rate, presumably because the rate determining step is the addition of hydroxide to the amide bond, and not



Scheme 3.7. Diels-Alder reactions with cyclopropylidenes [22–24].

ring scission. Eight- and nine-membered lactams are more resistant to nucleophilic hydrolysis than non-cyclic amides; this might be because of an increase in transannular repulsive van der Waals interactions during the addition of hydroxide to these amides.



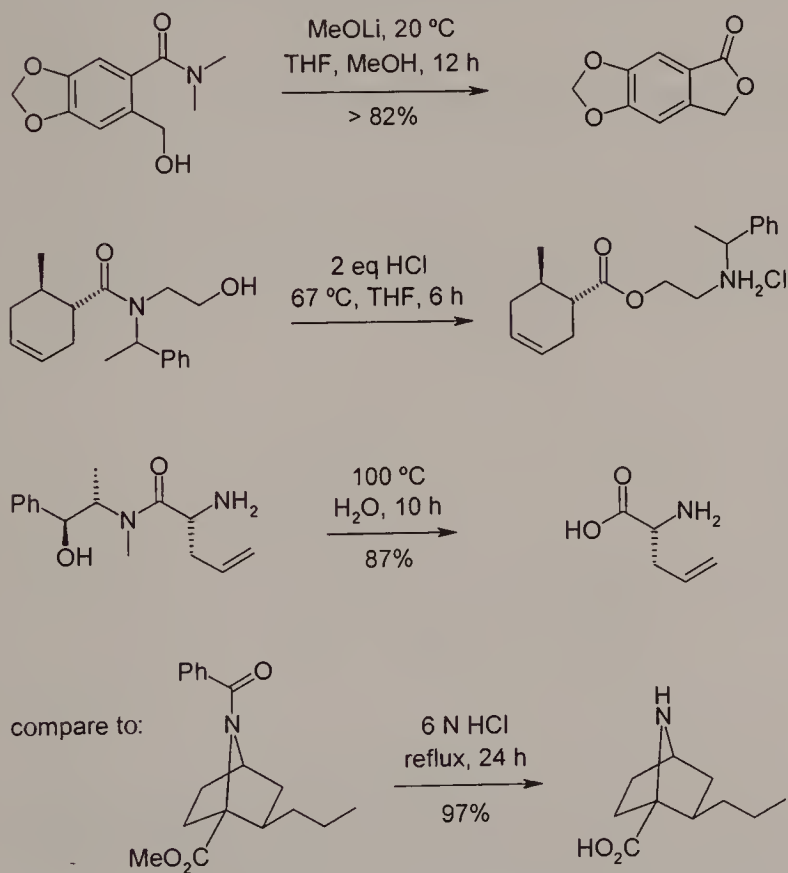
Scheme 3.8. Rates of lactam hydrolysis with aqueous base [25]. For comparison, the rate of hydrolysis of *N*-methylacetamide is shown.

3.3

Incompatible Functional Groups

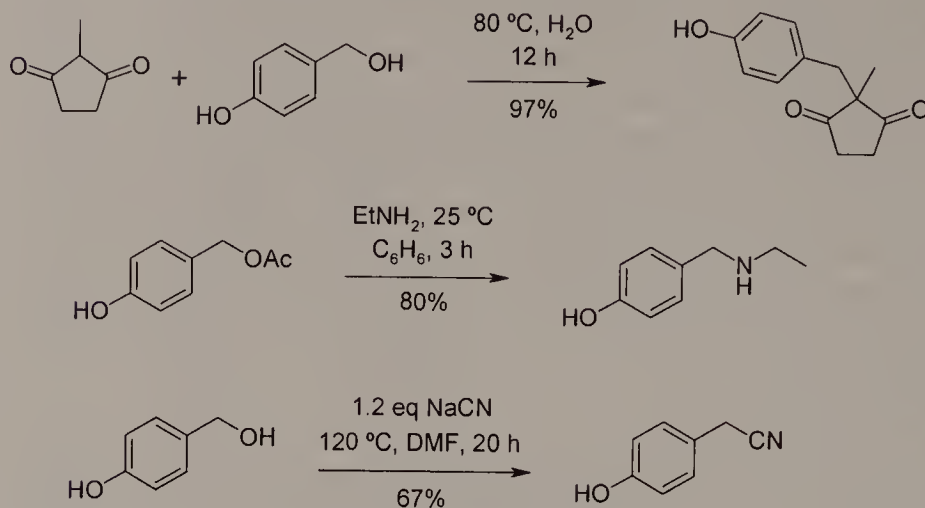
It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly. For instance, many phthalic acid, maleic acid, or 2-(hydroxymethyl)benzoic acid derivatives are notoriously sensitive because of the close proximity of the two functional groups (Scheme 3.9). Similarly, amides of 2-aminoethanols rearrange readily to esters under acidic reaction conditions[26] and undergo hydrolysis under mildly basic conditions, mainly because the hydroxyl group is close to the amide bond (Scheme 3.9). Normal amides usually require treatment with highly concentrated mineral acids at high temperatures to undergo hydrolysis (last example, Scheme 3.9).

Mannich bases (2-aminoethyl ketones) are another class of inherently unstable compounds which often undergo facile thermal elimination of the amine to yield a vinyl ketone[30]. Chemically related to Mannich bases are 2- or 4-(aminomethyl)-



Scheme 3.9. Hydrolysis of amides with and without intramolecular assistance [26–29].

phenols, which also decompose readily. For the same reason compounds of general formula $2/4-(\text{RO}/\text{R}_2\text{N})\text{C}_6\text{H}_4\text{CH}_2(\text{OR}/\text{NR}_2/\text{Hal})$ tend to be unstable, and many polymerize on standing at room temperature [31] (Scheme 3.10).

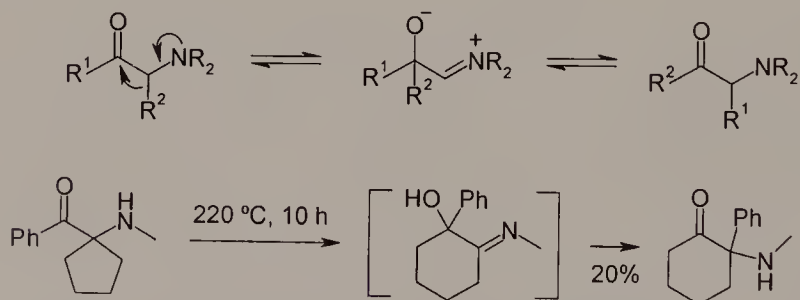


Scheme 3.10. Facile nucleophilic substitutions at 4-hydroxybenzyl derivatives [31–33].

3.4

Conjugation and Hyperconjugation of Incompatible Functional Groups

Less obvious than the reactivity discussed above is the chemical instability brought about by hyperconjugation or conjugation of incompatible groups. Methanes substituted with both amino and acyl groups, for example α -amino ketones, tend to form radicals readily (Scheme 5.69), and can undergo facile thermal rearrangements (Scheme 3.11).



Scheme 3.11. Rearrangement of α -amino ketones [34].

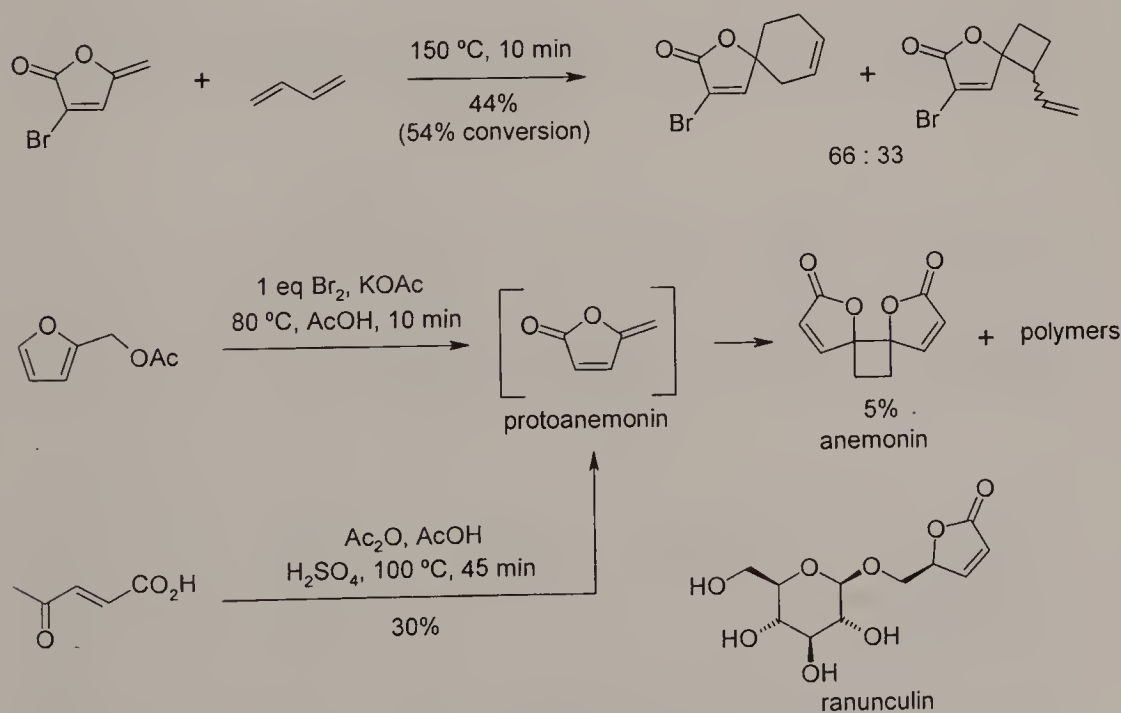
Alkenes substituted with an electron-withdrawing (Z) and an electron-donating group (X) will be less reactive than the unsubstituted alkene if the substituents are vicinal ($\text{Z}-\text{C}=\text{C}-\text{X}$; push-pull alkenes), but will generally become highly reactive when these two substituents are bound to the same carbon atom. The latter type of alkene ($\text{ZXC}=\text{CR}_2$; “1,1-captodative” alkenes) readily dimerize to yield cyclobutanes and can react with 1,3-dienes to yield products of [2 + 2] and/or [2 + 4] cycloaddi-

tion [35–37] (Scheme 3.12). This effect is probably because of the stabilization of radicals which results from substitution with both an electron-withdrawing and an electron-donating substituent (captodative effect [38, 39]).

The different reactivity of 1,2- and 1,1-acceptor/donor-substituted alkenes is paralleled by the readiness with which these compounds can be prepared. Thus, β -amino acrylates are often spontaneously formed by mixing amines with β -keto esters, and these derivatives have been used as protective groups for amines because of their low reactivity. α -Amino acrylates can, similarly, be prepared from α -keto esters [40], but this condensation reaction does not proceed spontaneously and requires chemical or azeotropic removal of water [41–43]. α -Amino acrylates are unstable compounds which must be stored at low temperatures [41] or *N*-acylated immediately after their generation [43].

A highly reactive natural product which contains such a geminally donor–acceptor substituted alkene is protoanemonin (Scheme 3.12), a toxic, skin-irritating lactone produced by various plants (ranunculaceae). The natural precursor to this compound is the glucoside ranunculin [44, 45], which yields protoanemonin enzymatically on maceration of plant tissue. Protoanemonin is unstable and quickly polymerizes or dimerizes to the less toxic anemonin.

Ground-state stabilization by hyperconjugation can modify the reactivity of organic compounds significantly, and must be taken into account when estimating the stability of certain types of compound. Di- or polysubstituted methanes can have high ground-state stability if the substituents are simultaneously σ -acceptors and π -donors, as is observed for many heteroatoms. If, on the other hand, the substitu-

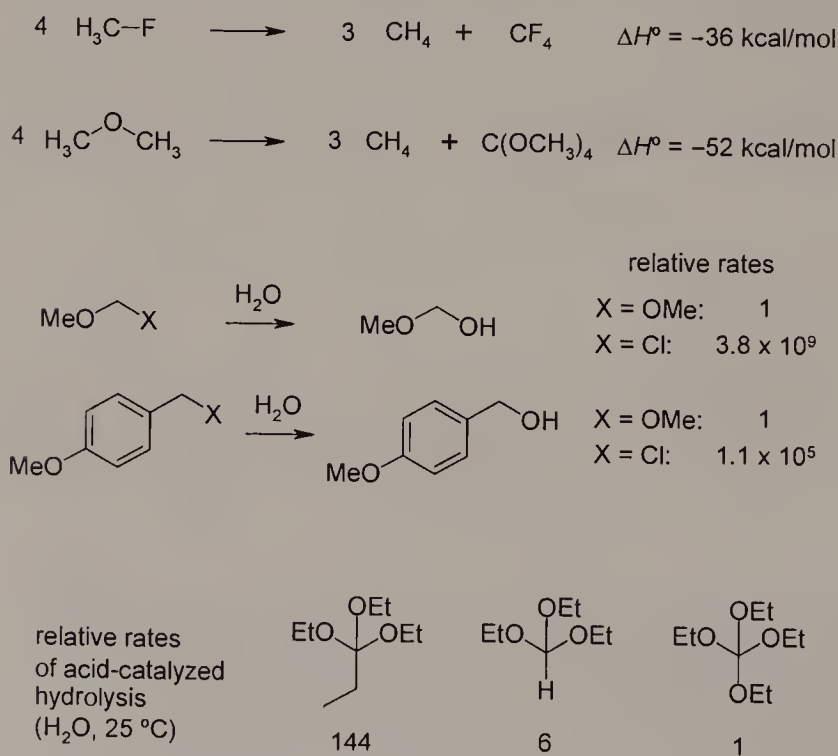


Scheme 3.12. Generation and reactions of captodative alkenes [35, 44, 46, 47].

ents are both σ - and π -acceptors (as, e.g., in malonodinitrile), strong destabilization will result [48]. The stabilization of heteroatom-substituted methanes results from hyperconjugation between the lone pairs of one heteroatom and the antibonding orbital of the C–X bond to the other heteroatom ($\sigma^*_{\text{C-X}}$) [49, 50]. This stabilization is the reason for the high exothermicity of the two isodesmic reactions shown in Scheme 3.13 [51], and for the large difference in hydrolysis rates between dimethoxymethane and chloromethyl methyl ether [52]. Dimethoxymethane is stabilized by hyperconjugation whereas in chloromethyl methyl ether this stabilization is less effective [49]. Accordingly, there is a larger difference between the rates of hydrolysis of the disubstituted methanes than between related benzyl derivatives (Scheme 3.13).

For similar reasons the stability of polyalkoxymethanes to acid-catalyzed hydrolysis is unexpectedly dependent on the number of carbon-bound alkoxy groups. Contrary to chemical intuition, orthocarbonates are more difficult to hydrolyze than orthoesters [51] (Scheme 3.13), although a carbocation substituted with three alkoxy groups is more stable than one with only two alkoxy groups. Similarly, the tendency of fluoride to add to fluorinated alkenes is much greater than that of other halides [53], despite its low nucleophilicity (see also Section 4.2.2).

These effects, which have also been called symbiosis, double bond-no bond resonance, clustering, or geminal or anomeric effect [54], can also be explained in terms of the HSAB principle: X_3C^+ will be harder than H_3C^+ if X^- is hard. Accordingly, X_3C^+ will have a higher affinity for the hard X^- than H_3C^+ will have [54].

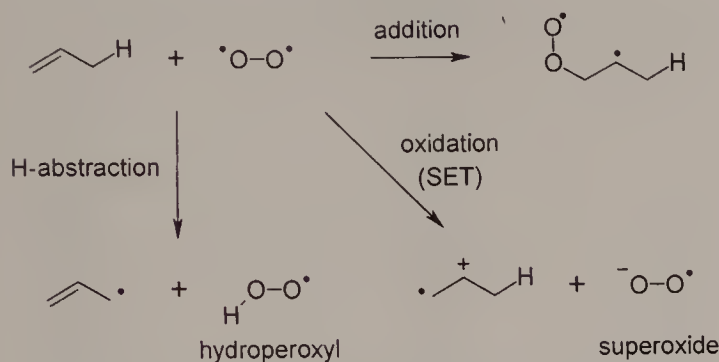


Scheme 3.13. Ground state stabilization of polyfluoro- and polyalkoxymethanes [51, 52].

3.5

Stability Toward Oxygen

Triplet oxygen is a stable and surprisingly unreactive electrophilic diradical. Its reactions with organic compounds (autoxidation) include abstraction of hydrogen atoms or single electrons and addition to reactive C–C double bonds (Scheme 3.14).

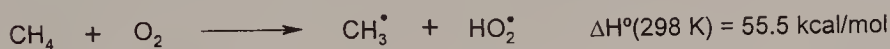


Scheme 3.14. Reactions of organic compounds with triplet oxygen.

3.5.1

Hydrogen Abstraction

The strength of the O–H bond in the hydroperoxyl radical (HO_2^\bullet) is only 49.6 kcal/mol (298 K) (Table 3.1), and thus much smaller than the strength of most C–H bonds. For this reason the cleavage of C–H bonds by oxygen is highly endothermic (Eq. 3.1) and, accordingly, most organic compounds are stable in the presence of air at moderate temperatures.



This remarkably low reactivity of triplet oxygen is in sharp contrast with the reactivity of other oxygen-centered radicals. Hydrogen peroxide ($D(\text{O–H}) = 87.1 \text{ kcal/mol}$) or aliphatic alcohols such as methanol ($D(\text{O–H}) = 104 \text{ kcal/mol}$), for instance, have much stronger O–H bonds than the hydroperoxyl radical, and the corresponding oxyl radicals will usually quickly and irreversibly abstract hydrogen atoms from alkanes to yield alkyl radicals (Table 3.1).

Most organic compounds will react with oxygen at high temperatures, but some types of compound react already at room temperature when exposed to the air. Alkanes undergo slow hydrogen abstraction by oxygen and are thereby transformed into hydroperoxides according to the radical chain mechanism sketched in Scheme 3.15. As discussed above, triplet oxygen is not reactive enough to abstract hydrogen atoms from most alkanes, so another radical-forming process will usually be required to initiate the reaction. Initiation might, for instance, be mediated by UV radiation or transition metal salts (which react with peroxides to yield alkoxyl

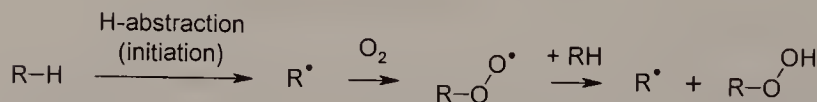
radicals [59]). As soon as carbon-centered radicals are formed they react quickly with oxygen to yield peroxy radicals, which are much more reactive than oxygen (Table 3.1) and will be able to abstract hydrogen from alkanes and in this way maintain a radical chain reaction. Peroxy radicals are quite selective, and hydrogen abstraction will occur preferentially at methine groups (R_3CH) and at benzylic or allylic positions.

Table 3.1. Bond dissociation enthalpies D (in kcal/mol at 298 K) for selected X–H bonds [$D(X-H) = \Delta H_f(X) + \Delta H_f(H) - \Delta H_f(XH)$] [55–58].

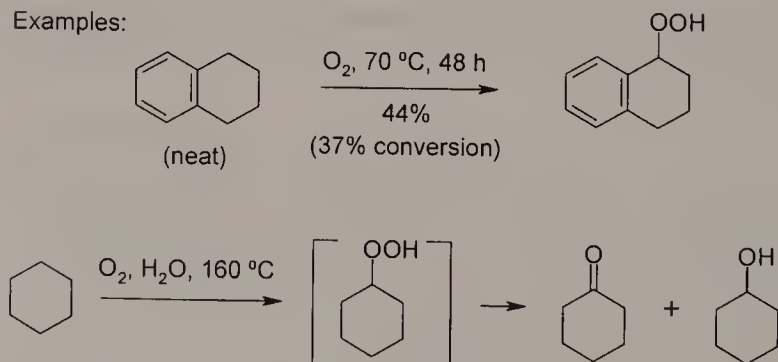
Bond	D	Bond	D
Me–H	105	O ₂ –H	49.6
H ₂ C=CHCH ₂ –H	88.8	HO ₂ –H	87.8
PhCH ₂ –H	89.8	HO–H	119
Me ₃ C–H	96.5	MeO–H	104.6
MeOCH ₂ –H	93	AcO–H	112
Ph–H	112.9	PhO–H	90
(1,3-cyclohexadien-5-yl)–H	70	2,6-(<i>t</i> Bu) ₂ -4-MeC ₆ H ₂ O–H	80.0
PhCO–H	86.9	α -tocopherol (O–H)	78.2
MeCOCH ₂ –H	98.3	Me ₂ N–H	95
Me ₃ Si–H	90	PhNH–H	86.4

The direct catalyzed or uncatalyzed oxidation of alkanes with oxygen is an important reaction in the industrial production of carboxylic acids, hydroperoxides (for production of epoxides from alkenes), alcohols, ketones, or aldehydes [60].

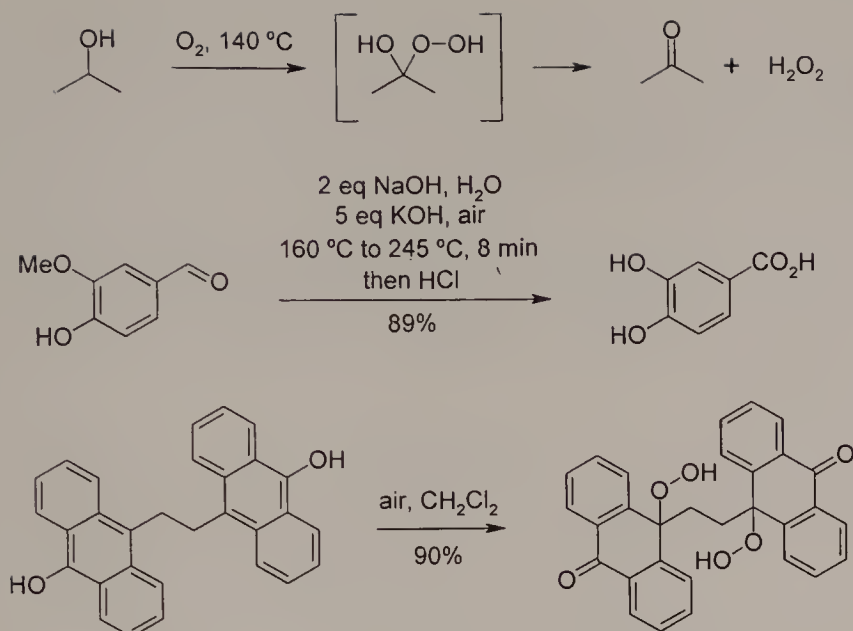
Heteroatoms or functional groups can either increase or diminish the rate of autoxidation of alkyl groups. Haloalkanes and alkanes substituted with electron-withdrawing groups are usually more resistant toward homolytic C–H bond cleav-



Examples:



Scheme 3.15. Autoxidation of hydrocarbons [61, 62].

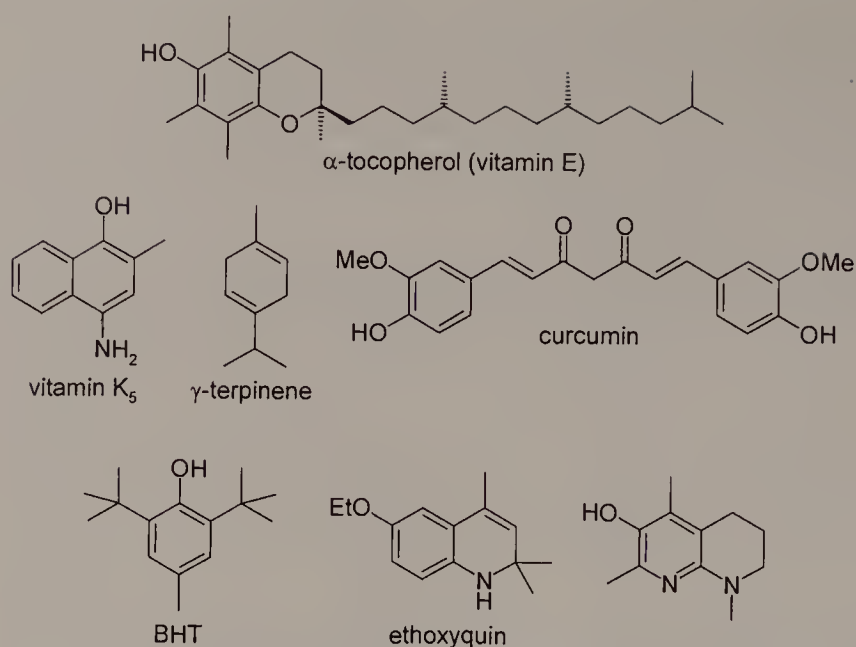


Scheme 3.16. Autoxidation of alcohols, aldehydes, and phenols [60, 63, 64].

age by oxygen or hydroperoxyl radicals whereas ethers or alcohols usually form hydroperoxides more readily than pure hydrocarbons (Table 3.1, Scheme 3.16). Aldehyde-derived acetals, aminals, or hydrates are, accordingly, particularly prone to radical-mediated autoxidation.

Autoxidation can lead to deterioration of food, drugs, cosmetics, or polymers, and inhibition of this reaction is therefore an important technical issue. The most important classes of autoxidation inhibitors are radical scavengers (phenols, sterically demanding amines [65, 66]), oxygen scavengers (e.g. ascorbic acid), UV-light absorbers, and chelators such as EDTA (to stabilize high oxidation states of metals and thereby suppress the metal-catalyzed conversion of peroxides to alkoxyl radicals) [67].

To be effective as autoxidation inhibitors radical scavengers must react quickly with peroxy or alkyl radicals and lead thereby to the formation of unreactive products. Phenols substituted with electron-donating substituents have relatively low O–H bond dissociation enthalpies (Table 3.1; even lower than arene-bound isopropyl groups [68]), and yield, on hydrogen abstraction, stable phenoxyl radicals which no longer sustain the radical chain reaction. The phenols should not be too electron-rich, however, because this could lead to excessive air-sensitivity of the phenol, i.e. to rapid oxidation of the phenol via SET to oxygen (see next section). Scheme 3.17 shows a selection of radical scavengers which have proved suitable for inhibition of autoxidation processes (and radical-mediated polymerization).

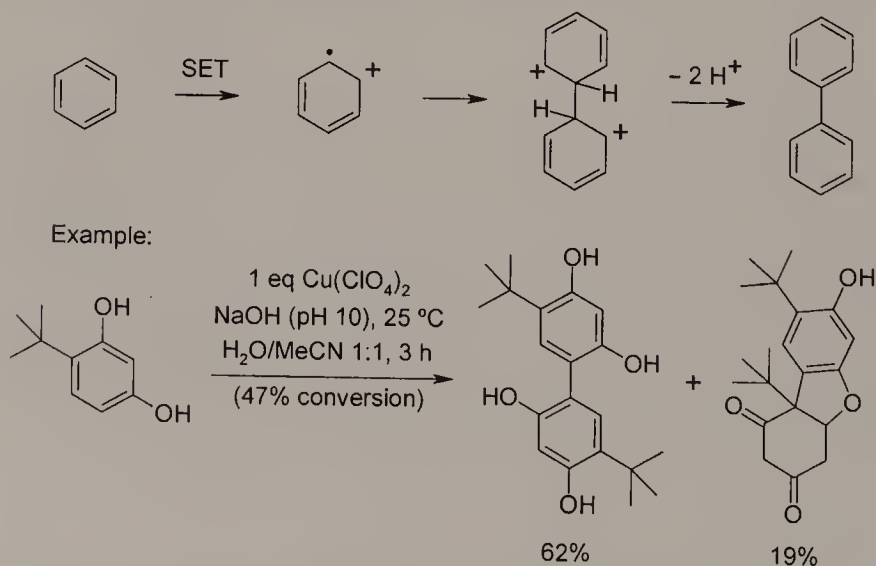


Scheme 3.17. Representative radical scavengers, suitable for the suppression of autoxidation [69–71].

3.5.2

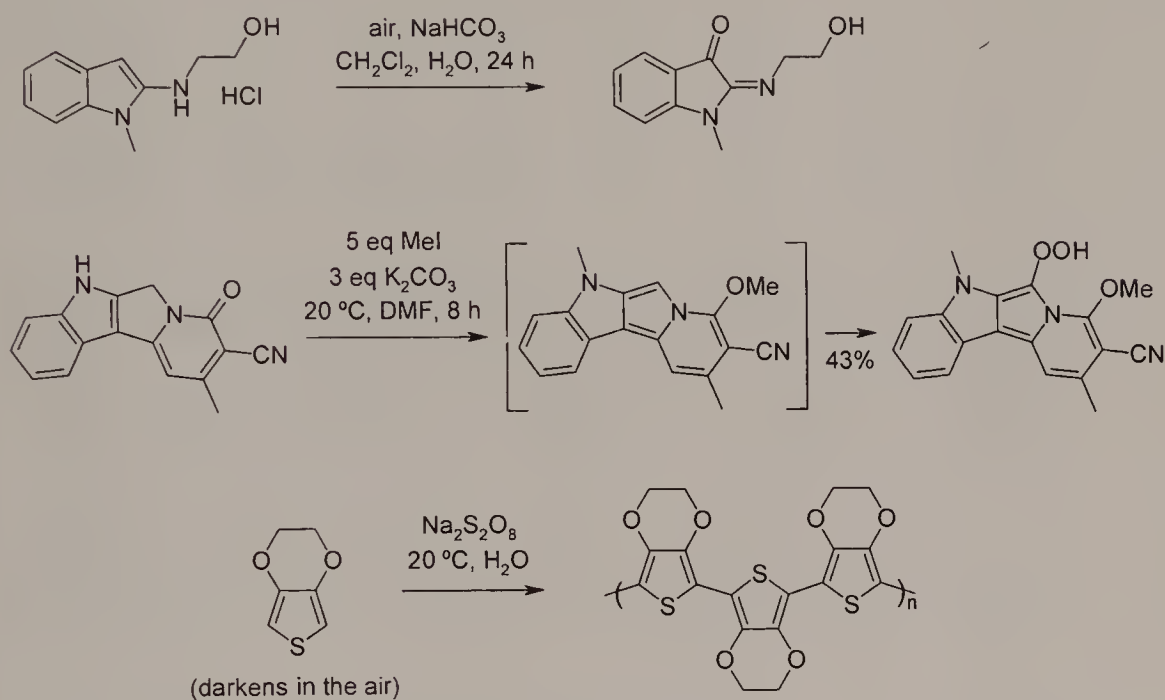
Oxidation by SET

Treatment of arenes or heteroarenes with oxidants can lead to the formation of radical cations by SET. These radical cations can dimerize, oligomerize, or react with other radicals present in the reaction mixture; deprotonation of the resulting intermediates yields the final products (Scheme 3.18).



Scheme 3.18. Oxidation of arenes via abstraction of single electrons [72].

Some electron-rich arenes or heteroarenes undergo SET even at room temperature when exposed to the air. Such compounds will usually darken quickly, even if only trace amounts of oligomers are formed by autoxidation, because these oligomers can absorb visible light very efficiently and tend to be oxidized even more readily than the monomer. Thus, older samples of aniline, alkoxyanilines, or aminophenols are usually dark or black, even if analysis by ^1H NMR does not reveal any impurities. Particularly air-sensitive are five-membered heteroarenes (pyrroles, furans, thiophenes) with electron-donating substituents. Some of these compounds polymerize on oxidation to yield materials with good electric conductivity (Scheme 3.19).

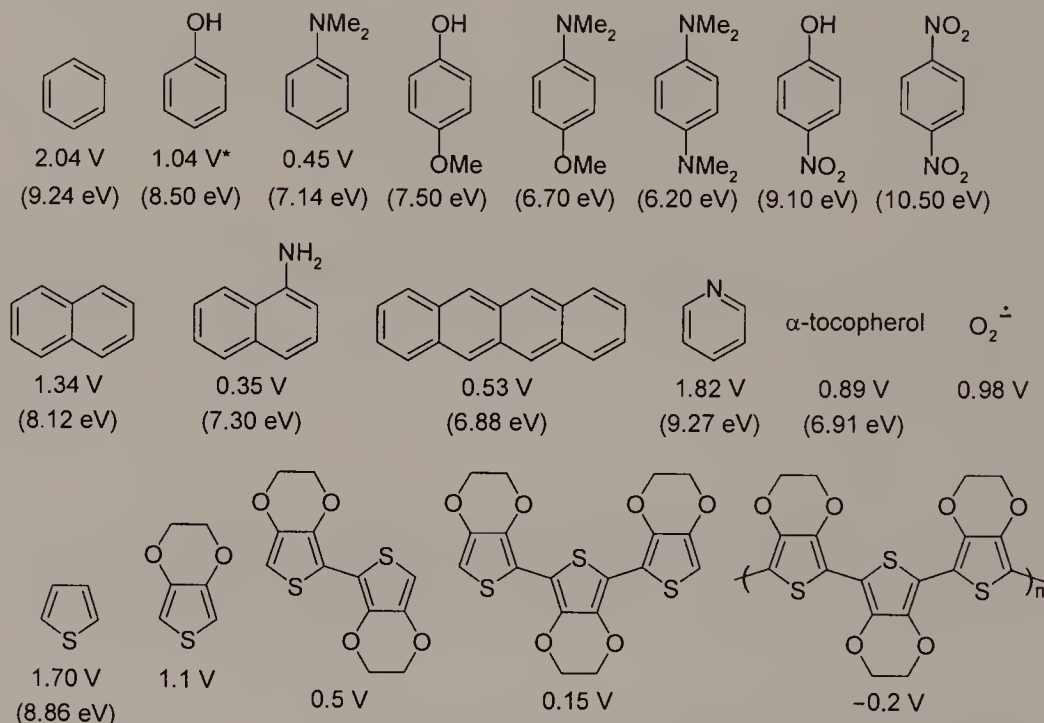


Scheme 3.19. Air-sensitive indoles, pyrroles, and thiophenes [73–75].

Arene-bound alkoxy or amino groups will facilitate oxidation by SET only if their lone electron pairs can interact with the aromatic π -system. For this reason 1,3,5-tris(dialkylamino)benzenes will be significantly more air-sensitive than, for instance, 1,2,3-tris(dialkylamino)benzenes, because steric crowding in the latter will force the lone pairs into the plane of the arene, where efficient conjugation with the aromatic π -system is impossible.

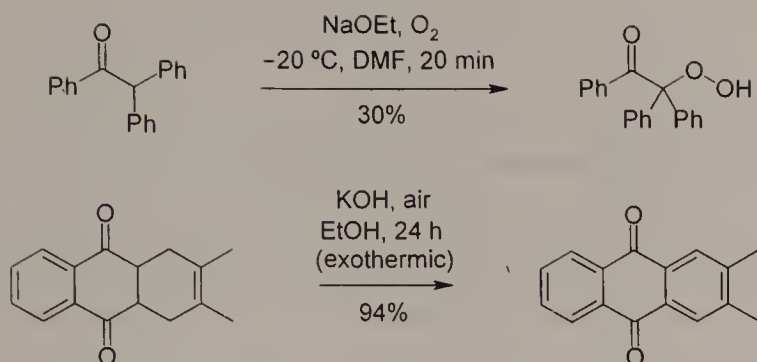
Unfortunately there is no simple correlation between gas-phase ionization potentials and solution-phase oxidation potentials for all classes of compounds, because the energy of solvation is highly dependent on molecular structure. Nevertheless, for closely related compounds there tends to be a linear correlation between ionization potentials in the gas phase and in solution [76, 77]. The air-sensitivity of electron-rich alkenes, arenes, or heteroarenes can therefore be estimated by inspecting either their gas-phase ionization potentials or their oxidation potentials in solution

(Scheme 3.20). Arenes or heteroarenes with an ionization potential smaller than approximately 7 eV or an oxidation potential smaller than 1 V will usually be susceptible to oxidation by air at room temperature. As illustrated by the examples in Scheme 3.20, electron abstraction becomes easier when the number of conjugated C–C double bonds increases. Replacing carbon in an arene or heteroarene by (the more electronegative) nitrogen usually enhances the oxidation potential and thereby the stability towards oxidants. The oxidation potential of the superoxide radical in aprotic solvents (0.98 V) corresponds approximately to the oxidation potential at which arenes become air sensitive.



Scheme 3.20. Oxidation potentials (vs Ag/Ag⁺) and gas-phase ionization potentials (in parentheses) of some arenes and heteroarenes and triplet oxygen [56, 57, 70, 74, 77–79]. *Ref[56]: 1.83 V.

Not only alkenes and arenes but also other types of electron-rich compound can be oxidized by oxygen. Most organometallic reagents react with air, whereby either alkanes are formed by dimerization of the metal-bound alkyl groups (cuprates often react this way [80]) or peroxides or alcohols are formed [81, 82]. The alcohols result from disproportionation or reduction of the peroxides. Similarly, enolates, metalated nitriles, phenolates, enamines, and related compounds with nucleophilic carbon can react with oxygen by intermediate formation of carbon-centered radicals to yield dimers (Section 5.4.6; [83, 84]), peroxides, or alcohols. The oxidation of many organic compounds by air will, therefore, often proceed faster in the presence of bases (Scheme 3.21).



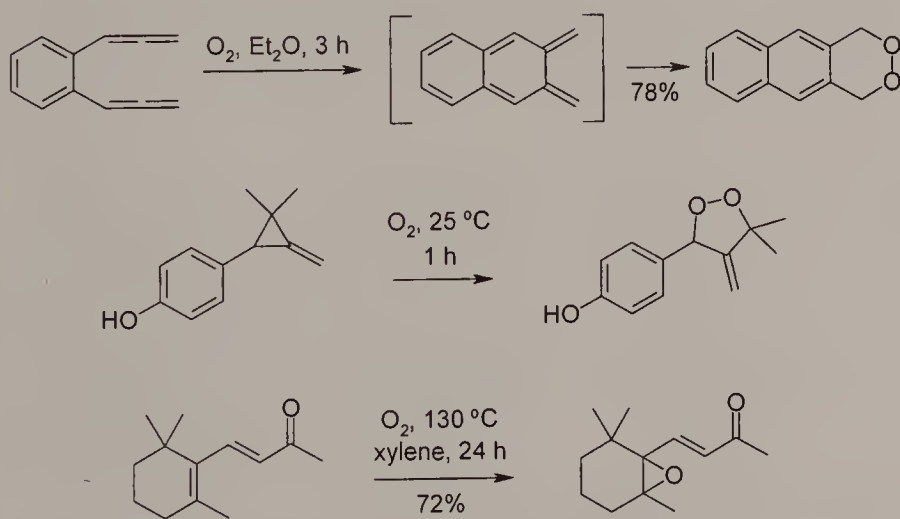
Scheme 3.21. Reaction of electron-rich organic compounds with triplet oxygen [85, 86].

3.5.3

Addition of Oxygen to C–C Double Bonds

Highly strained alkenes often behave chemically as 1,2-diradicals, and can therefore readily react with triplet oxygen (Scheme 3.6). 1,2-Quinodimethanes can also react as diradicals, and can undergo a formal [2 + 4] cycloaddition with triplet oxygen to yield cyclic peroxides (first example, Scheme 3.22). That this reaction also proceeds in the dark strongly indicates that no singlet oxygen is involved [87].

Some cyclopropanes have a high tendency to undergo homolytic ring scission and can react as 1,3-diradicals. Such compounds can be highly air-sensitive and react with triplet oxygen to yield 1,2-dioxolanes (second reaction, Scheme 3.22). 1,3-Dienes conjugated with a carbonyl group react with oxygen, and in the presence of a solvent with benzylic hydrogen atoms epoxides are formed (last example, Scheme 3.22).



Scheme 3.22. Reaction of triplet oxygen with reactive alkenes and cyclopropanes [87–89].

3.6

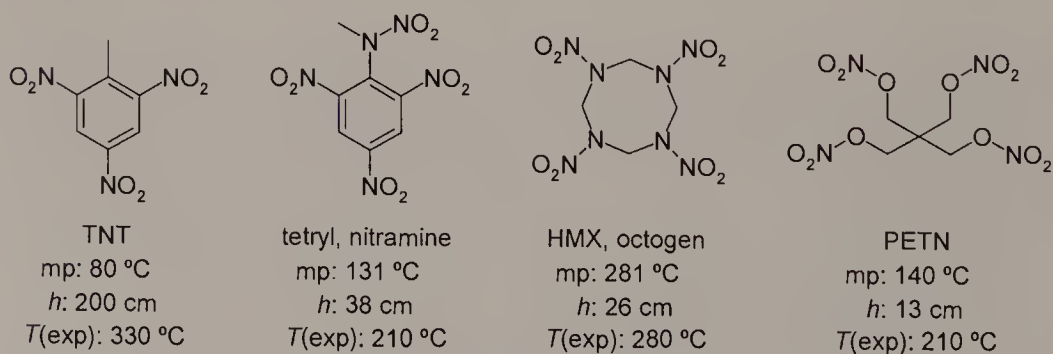
Detonations

Most organic compounds are thermodynamically unstable and will burn at the air when heated to a sufficiently high temperature. Some compounds can, however, decompose thermally into thermodynamically more stable molecules without the need for oxygen. Although most of these are nitrogen-containing compounds, alkynes also can undergo such transformations. If such a thermal decomposition is exothermic, under certain conditions the decomposition will not just proceed as a simple, self-sustained reaction (deflagration) but can continuously accelerate and finally lead to a detonation. A detonation is not just a rapid deflagration under high pressure; whereas the propagation of a deflagration is governed by transport phenomena, and will not exceed velocities of about 10 m/s, the propagation of a detonation is mediated by a hypersonic shock wave, with propagation velocities of 5–9 km/s.

Detonations can be initiated by ignition, mechanical impact, friction, or electromagnetic radiation, and physical confinement of the material is often but not always required. Thus, a sample of the potassium salt of 1-tetrazolylacetic acid placed on a surface at room temperature will explode if any part of the sample is heated to $>200\text{ }^{\circ}\text{C}$ (e.g. by a hot flint spark or a flame) [90]. If the conditions for detonation are met, the time between shock-initiation and detonation is about 1 μs only [91].

The chemistry behind the detonation of organic compounds is exceedingly complex and poorly understood, because it involves a variety of intermolecular reactions different from those observed during thermolysis in solution or in the gas phase [92–94]. The conditions required to induce detonation of organic explosives vary widely and no clear-cut structure–sensitivity relationship exists. Nevertheless, most known explosives contain characteristic functional groups, and small molecules containing several of these should be handled with great care.

In Scheme 3.23 a selection of currently used explosives is sketched, together with some of their properties. As a measure of impact sensitivity, the height h is given from which a 2.5 kg hammer must hit a 35-mg sample on sand paper to lead to an



Scheme 3.23. Selection of explosives. $h = 50\%$ impact height [91]; $T(\text{exp})$ = temperature at which the confined substance will explode within 10 s [95].

explosion with 50 % probability [91]. The temperature $T(\text{exp})$ at which these compounds will explode within 10 s when confined in a closed container is also given [95].

There is, unfortunately, no obvious correlation between the impact sensitivity of a compound, its thermal behavior, and its structure. Thus, most polynitro arenes can explode on mechanical shock or rapid heating [96], but the shock sensitivity and thermal stability varies widely. TNT, for instance, is rather insensitive toward mechanical shocks or heating, and even pentanitrotoluene and hexanitrobenzene have been prepared, and their melting points (240 °C and 260 °C, respectively) could be determined [97]. The potassium salt of the radical anion of nitrobenzene, on the other hand, is highly shock sensitive, and detonates on simple agitation [92]. Similarly, whereas nitromethane can be handled safely the dry sodium salt of deprotonated nitromethane is potentially explosive [98].

Because impact sensitivity depends on intermolecular reactions in the solid, the sensitivity of explosives depends on their purity. It is often observed that higher purity leads to increased sensitivity, but this is not always so. Small quantities of particular compounds added to an explosive can even increase its sensitivity toward shock- or ignition-induced detonation [99, 100].

Nitro group-containing explosives, such as those shown in Scheme 3.23, have additional properties which render them particularly attractive as commercial explosives. These properties include chemical inertness, high density, low melting points (what enables casting into moulds), and good synthetic accessibility. Compounds devoid of nitro groups can, however, also be potent explosives. Potentially explosive compound classes include alkynes [101], azides, azo compounds, diazo compounds, furazanes (1,2,5-oxadiazoles) [102], ozonides, perchlorates, peroxides, tetrazoles [90], and compounds containing nitrogen–halogen bonds.

Particularly dangerous are small molecules containing these functional groups, because in these the critical functionality makes up a large percentage of the total molecular weight. Thus, whereas most sulfonyl azides are sufficiently stable to be handled without special precautions, methanesulfonyl azide is hazardous and shock-sensitive [103]. Similarly, acetyl nitrate (MeCOONO_2 , explodes at 60 °C), methyl nitrate (MeONO_2 , explodes at 65 °C), dimethyl azodicarboxylate [104], diazomethane, methyl azide, vinyl azide, azidoacetonitrile, and $\text{N}_3\text{—CN}$ are particularly sensitive and dangerous, and should be handled as solutions only. Interestingly, some of these compounds, e.g. small organic azides [105, 106], are highly thermally stable at low pressures in the gas phase, but explode readily at low temperatures when condensed [107]; this indicates the importance of intermolecular reactions in the initiation and progression of a detonation. For this reason reactions with solutions of such reagents should not be performed with cold-finger condensers cooled to temperatures below the boiling point of the explosive reagents, because their condensation might readily lead to an explosion.

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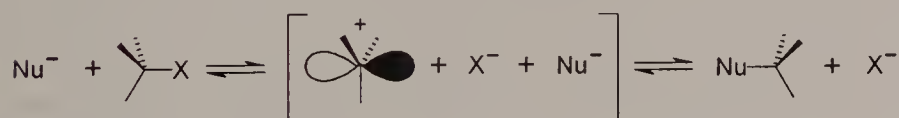
Aliphatic Nucleophilic Substitutions: Problematic Electrophiles

4.1

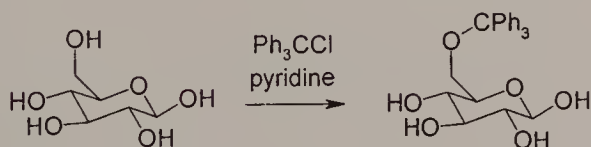
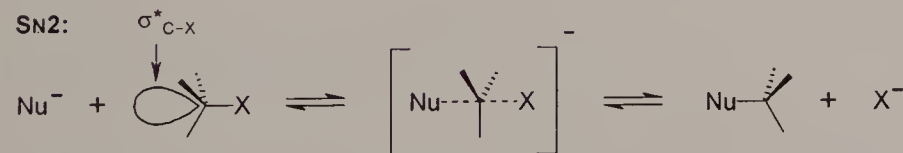
Mechanisms of Nucleophilic Substitution

Nucleophilic substitutions at sp^3 -hybridized carbon are among the most useful synthetic transformations, and have been thoroughly investigated [1–3]. The success of these reactions depends mainly on the structures of the nucleophile and electrophile, their concentration, and on the solvent and reaction temperature chosen. The structure of the electrophile in nucleophilic substitutions is of critical importance, because many unwanted side reactions result from unexpected reactivity of the electrophile.

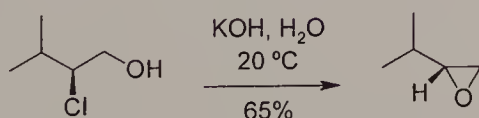
In Scheme 4.1 the mechanisms of typical monomolecular (S_N1) and bimolecular (S_N2) nucleophilic substitutions at a neutral electrophile with an anionic nucleophile are sketched. S_N1 reactions usually occur when the electrophile is sterically

 S_N1 :

Example:

 **S_N2 :**

Example:



Scheme 4.1. Mechanisms and examples of S_N1 [4] and S_N2 [5] reactions.

hindered and has a high tendency to form a carbocation. Steric hindrance will increase the activation barrier for the S_N2 pathway, and thereby enable other reaction mechanisms to become dominant. Carbocation formation is facilitated by good leaving groups, by secondary, tertiary, α -heteroatom-substituted, or conjugated (benzylic, allylic, or propargylic) alkyl groups, or by solvents of high dielectric constant. Acidic reaction conditions can also promote the formation of carbocations by protonation (i.e. improvement) of the leaving group, and thereby favor the S_N1 mechanism. Substitutions in which carbocations are formed as intermediates are usually monomolecular, that is, the rate of reaction will depend on the concentration of one of the starting materials only. Reaction of the nucleophile with the carbocation is usually much faster than the (rate-determining) formation of the carbocation, and the reaction rate will be a function of the concentration of the electrophile only.

S_N2 reactions usually occur at primary alkyl groups, and often involve soft electrophiles and nucleophiles. As shown in Scheme 4.1, the S_N2 reaction proceeds with (Walden) inversion at the central carbon, and is therefore stereospecific.

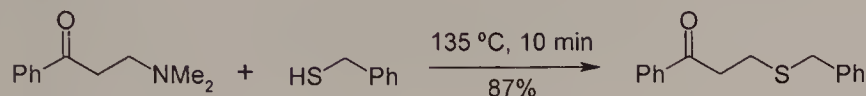
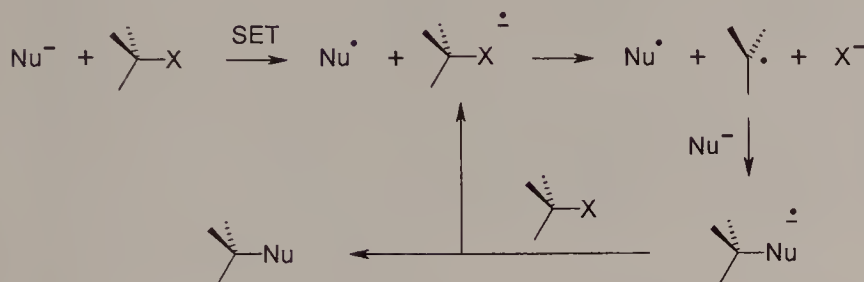
When steric or electronic factors interfere with the substitution mechanisms sketched in Scheme 4.1, a substitution may occur anyway. A variety of alternative mechanisms are available and lead to the formation of the products of aliphatic nucleophilic substitution. The most important of the alternative pathways are the elimination–addition mechanism, which is often observed for electrophiles with an electron-withdrawing group in the β position, and the radical nucleophilic substitution ($S_{RN}1$, Scheme 4.2) [6–10]. The latter, which is particularly important for tertiary substrates, nitroalkanes, nitrobenzyl halides, perfluoroalkyl halides, and some aromatic nucleophilic substitutions, is initiated by single-electron transfer (SET) from the nucleophile to the electrophile. Thereby a radical and a radical anion are formed if the nucleophile was negatively charged and the electrophile uncharged. For some substrates, but not all, SET requires light. The radical anion, which can also be generated electrochemically [11], can now release the anionic leaving group and become a neutral radical; this will react with the nucleophile to form a new radical anion. This last reaction will be particularly fast if the intermediate neutral radical is electrophilic (i.e. when the substituents at the central carbon are electron-withdrawing) and the nucleophile is electron-rich. SET from the newly formed radical anion to the electrophile yields the final product and a new radical anion.

Alternative non-chain reaction pathways have also been discussed [14]. Some radical nucleophilic substitutions, for instance, proceed with inversion at the electrophilic carbon [15]. This observation is not compatible with the formation of a free radical, but can be rationalized by the mechanism sketched in Scheme 4.3 [15], in which the two radicals formed after SET do not diffuse out of the solvent cage but react in an S_N2 -like manner with Walden inversion.

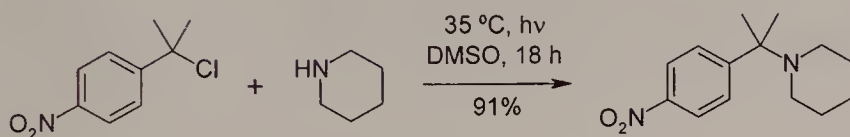
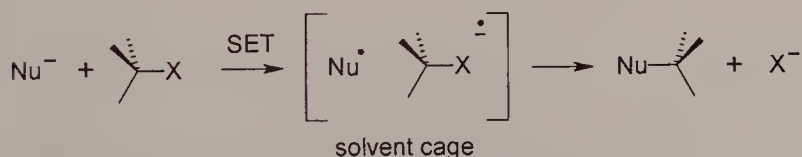
SET-induced chain reactions are usually much faster than S_N2 reactions, and if both pathways are accessible for a given pair of starting materials, products resulting from $S_{RN}1$ will usually predominate. This is, for example, observed for the first reaction sketched in Scheme 4.4 [11, 16]. Electrochemical or zinc-mediated [17] reduction of the starting pyridinium salt yields a carbanion which, on reaction with Me_2tBuS^+ , can either be methylated via S_N2 or *tert*-butylated via $S_{RN}1$. Because the nucleophile

Elimination-addition mechanism:

Example:

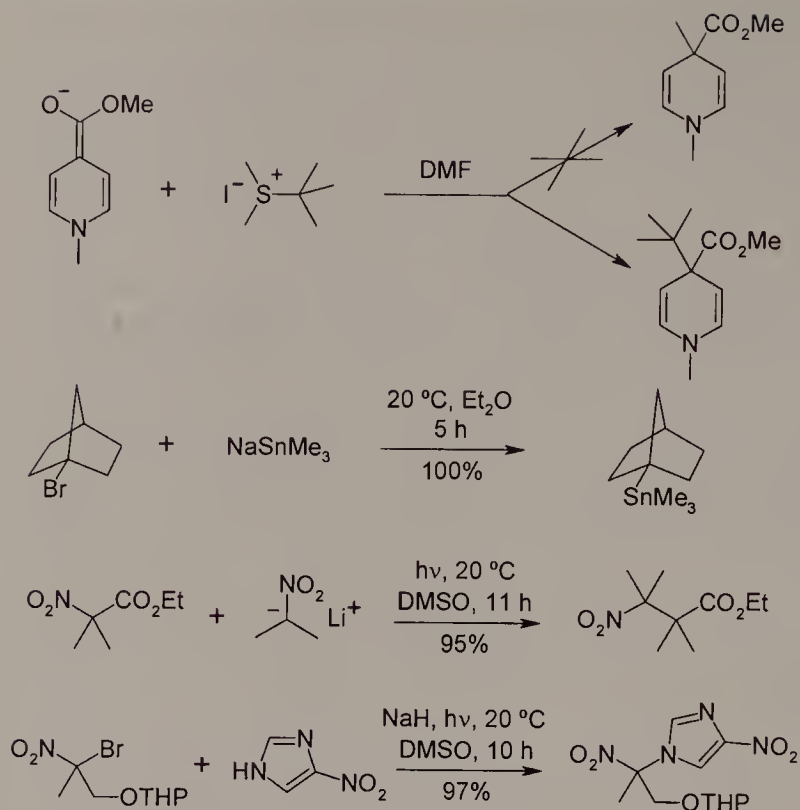
**S_{RN}1:**

Example:

**Scheme 4.2.** Mechanisms and examples of “elimination–addition” substitution [12] and of radical nucleophilic substitution [13].**Scheme 4.3.** Possible mechanism for stereospecific radical nucleophilic substitutions [15].

is a good electron donor and leads, on oxidation, to a stable radical [18], the radical pathway is preferred in this instance.

Compared with S_N1 or S_N2 reactions, relatively few examples of radical nucleophilic substitutions have been reported [6–8, 16, 22–25]. This suggests that the structural requirements of nucleophile and electrophile for such processes are more stringent than for non-radical nucleophilic substitutions. In the following sections the focus will be on the more generally applicable non-radical S_N1 and S_N2 reactions.



Scheme 4.4. Examples of radical nucleophilic substitutions [11, 19–21].

4.2

Structure of the Leaving Group

4.2.1

Good and Poor Leaving Groups

According to the mechanism of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions (Scheme 4.1), a good leaving group X should form a highly polarized bond with carbon, prone to heterolytic cleavage, and with a low-energy $\sigma_{\text{C-X}}^*$ orbital. If the displaced leaving group is unreactive and/or forms strong hydrogen bonds with the solvent chosen, its displacement will proceed more readily. Particularly good leaving groups are atoms or molecules of low basicity, such as the anions of strong acids (halides, sulfate, sulfonates, perchlorate), ethers, alcohols, and water (i.e. electrophiles of the general structure R-OR_2^+), thioethers (R-SR_2^+), aryl halides (R-HalAr^+), and nitrogen (R-N_2^+). If the basicity of the group increases, its ability to act as a leaving group usually decreases.

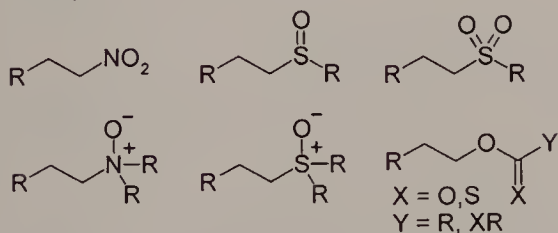
The better the leaving group, the more can the mechanism tilt towards a monomolecular ($\text{S}_{\text{N}}1$) substitution. With good leaving groups carbocation formation is faster than the $\text{S}_{\text{N}}2$ reaction and becomes the rate determining (slowest) step in the new mechanism. The reaction of the nucleophile with the carbocation is the fastest step in $\text{S}_{\text{N}}1$ reactions (and much faster than the corresponding $\text{S}_{\text{N}}2$ reaction).

Because the S_N1 reaction is no longer stereospecific and because carbocations can readily rearrange or be deprotonated (to yield an alkene), it might be advisable not to choose always the best possible leaving group, but one of moderate reactivity, also to keep the electrophilic reagent tractable. Compounds with very good leaving groups, such as alkyl triflates or diazonium salts, will often react with the solvent or undergo elimination instead of yielding the product of substitution. If substitution with a highly reactive or strongly basic nucleophile is intended, it might even be advisable to choose a poor leaving group, for example fluoride [26, 27] (last reaction in Scheme 4.10).

Some of the most common unwanted events during nucleophilic substitutions are β -elimination of HX from the electrophile to yield an alkene, rearrangement of the electrophile, reaction of the electrophile with the solvent, or no reaction at all. Although unwanted β -eliminations usually occur as a result of the structure of the alkyl group in the electrophile or because of the high basicity of the nucleophile, choosing an unsuitable leaving group might also favor the formation of alkenes. Leaving groups with a higher tendency to undergo elimination rather than substitution are those containing a group capable of abstracting a vicinal proton (Scheme 4.5), and which are, therefore, mainly used for thermal eliminations and not for nucleophilic substitutions.



Examples:

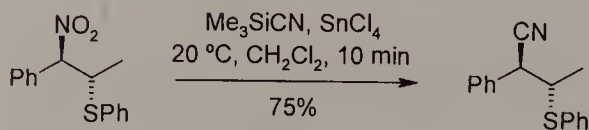
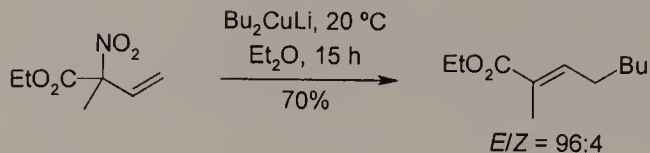


Scheme 4.5. Leaving groups with a high tendency to undergo thermal elimination.

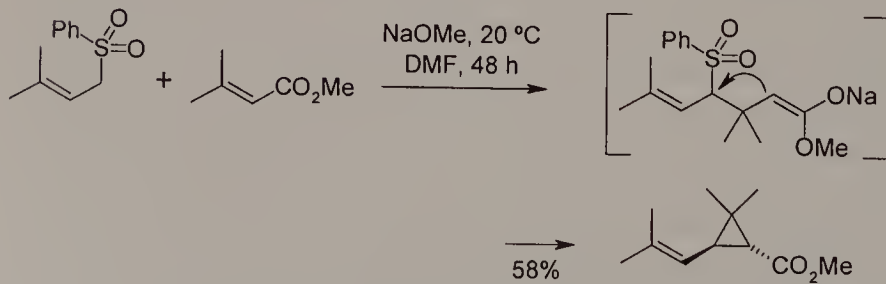
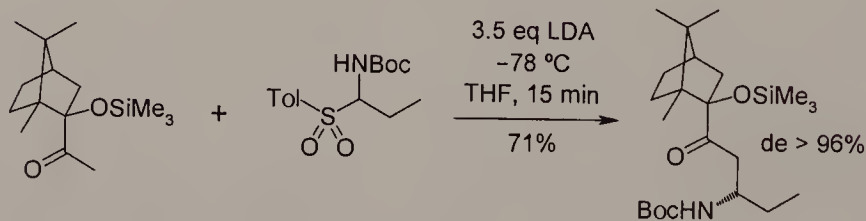
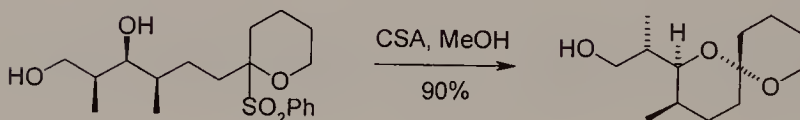
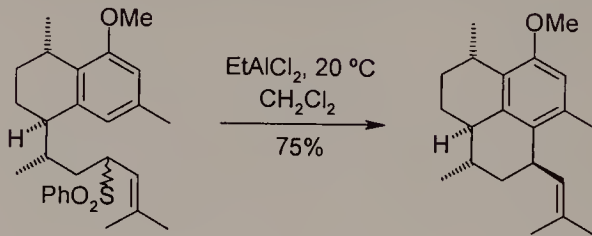
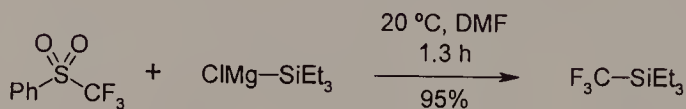
When no β hydrogen is available, however, compounds as those shown in Scheme 4.5 can be useful electrophiles in nucleophilic substitutions. Thus, $\text{Me}_3\text{S}^+\text{OH}^-$ [28], $\text{Me}_3\text{S}=\text{O}^+\text{X}^-$ [29, 30], $\text{Me}_3\text{Se}^+\text{OH}^-$ [31], $(\text{MeO})_2\text{CO}$ [32–34], or MeNO_2 [35] can all be used as electrophilic methylating reagents.

Because of the ability of some leaving groups to stabilize an α -carbanion, the pH at which the substitution is performed can be critical. Electrophiles with such leaving groups (e.g. $\text{R}-\text{NO}_2$ [36, 37], $\text{R}-\text{S}(=\text{O})_2\text{R}$ [38, 39], $\text{R}-\text{S}(=\text{O})\text{R}$ [40]) will usually undergo substitution only under neutral or acidic conditions, what limits the choice of suitable nucleophiles. Some nucleophilic displacements of nitro and sulfonyl groups, both under acidic and basic reaction conditions, are shown in Schemes 4.6 and 4.7. Allylic nitro groups can also be readily displaced by catalysis with palla-

dium(0) [36, 41]. The second example in Scheme 4.6 probably proceeds with retention of configuration because of neighboring-group participation (a thiiranium ion is formed as intermediate).



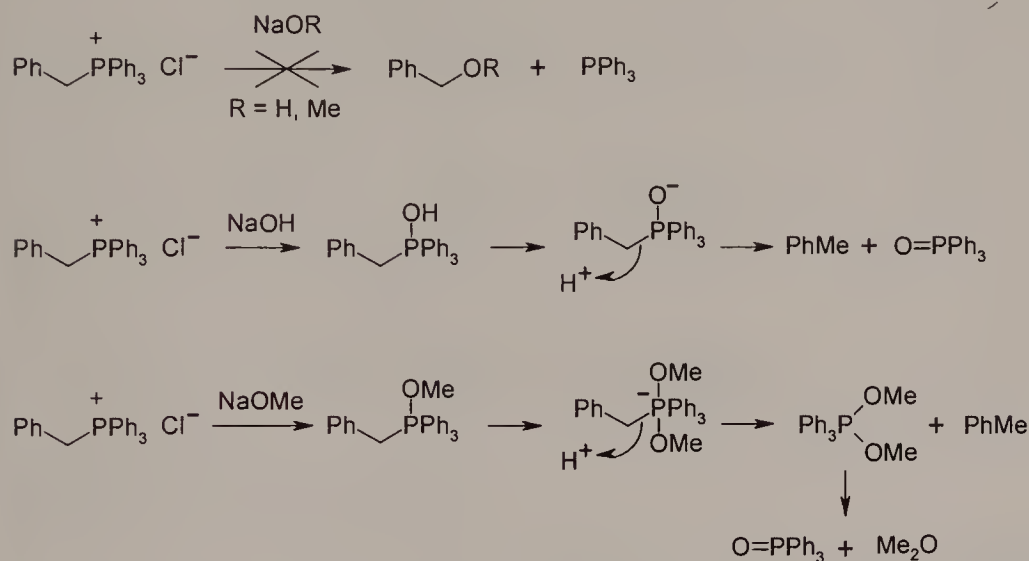
Scheme 4.6. Nucleophilic substitution of nitro groups [37, 42].



Scheme 4.7. Nucleophilic substitution of sulfonyl groups [39, 43–46].

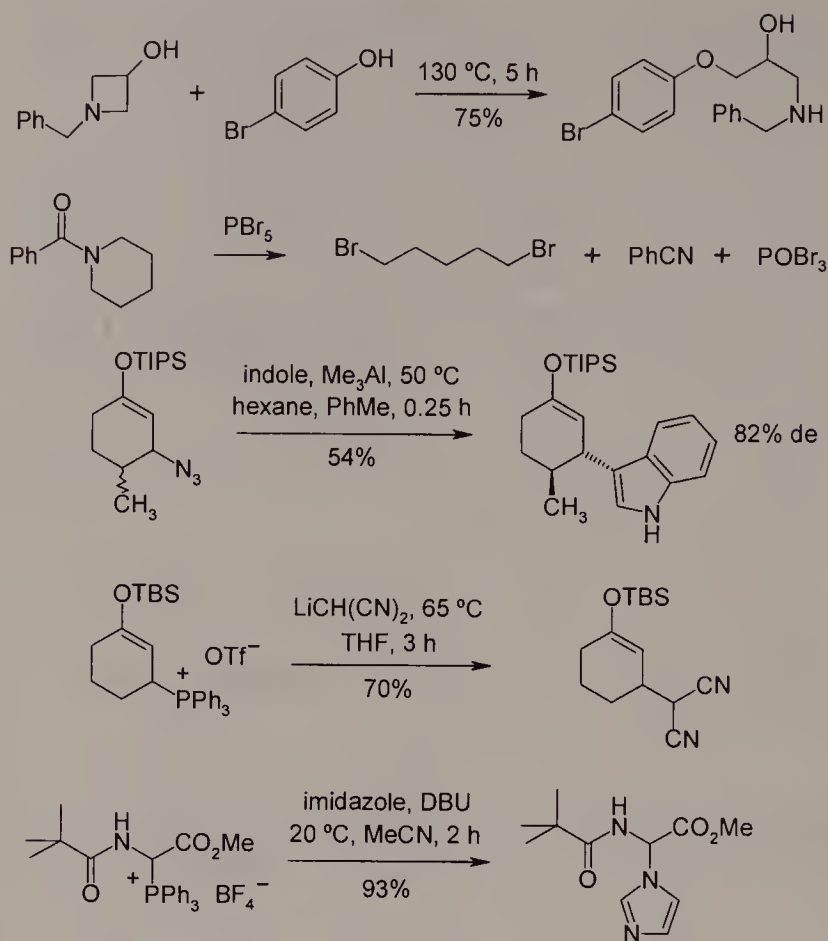
Acidic reaction conditions can also lead to protonation of some leaving groups, thereby increasing their reactivity in nucleophilic substitutions. Such groups include, for instance, alcohols, ethers, amines, amides, or alkyl fluorides.

Nucleophilic substitutions can also fail because the intended leaving group is not good enough, i.e. its bond to carbon is not strongly polarized or the basicity of the leaving group is too high. If this happens either no reaction will occur or, if a strongly basic nucleophile is used, elimination may occur instead. Some potential leaving groups can also form a bond with the nucleophile, and are thereby further deactivated. This occurs, for example, with phosphonium salts, which only rarely undergo substitution or elimination of PR_3 but are, instead, attacked by the nucleophile at phosphorus (Scheme 4.8).



Scheme 4.8. Reaction of benzylphosphonium salts with oxygen nucleophiles [47].

Further poor substrates for nucleophilic substitutions are amines, quaternary ammonium salts, amides, nitriles, and azides; these will usually undergo substitution in particularly reactive substrates only or under harsh reaction conditions. Some rare examples of successful substitutions of these leaving groups are shown in Scheme 4.9. The last reaction in Scheme 4.9 presumably proceeds via an elimination–addition mechanism.



Scheme 4.9. Examples of nucleophilic displacement of unreactive leaving groups [49–53].

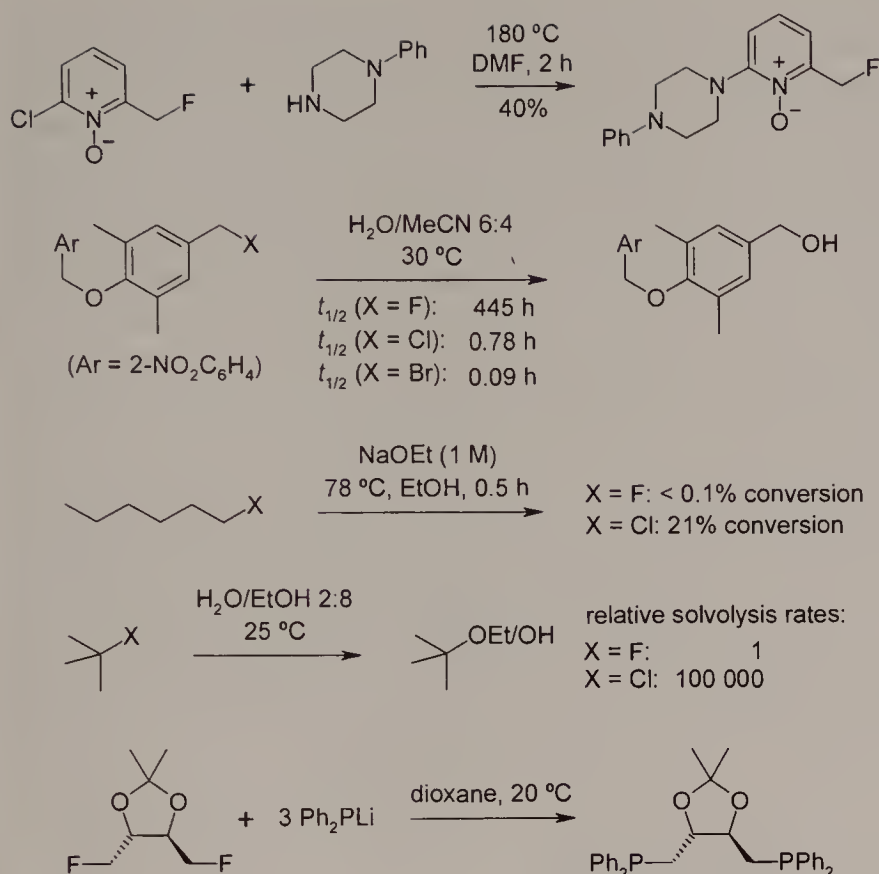
4.2.2

Nucleophilic Substitution of Fluoride

Because carbon and fluorine are of similar size, carbon-bound fluorine can undergo hyperconjugation more effectively than any other halogen and can therefore lead more readily to unexpected reactivity [54]. The reactivity of alkyl fluorides towards nucleophiles depends to a large extent on the structure of the alkyl group and on the remaining functional groups. Geminal difluoro and geminal trifluoro compounds are substantially less reactive than monofluoro compounds, because of negative hyperconjugation (Section 3.4).

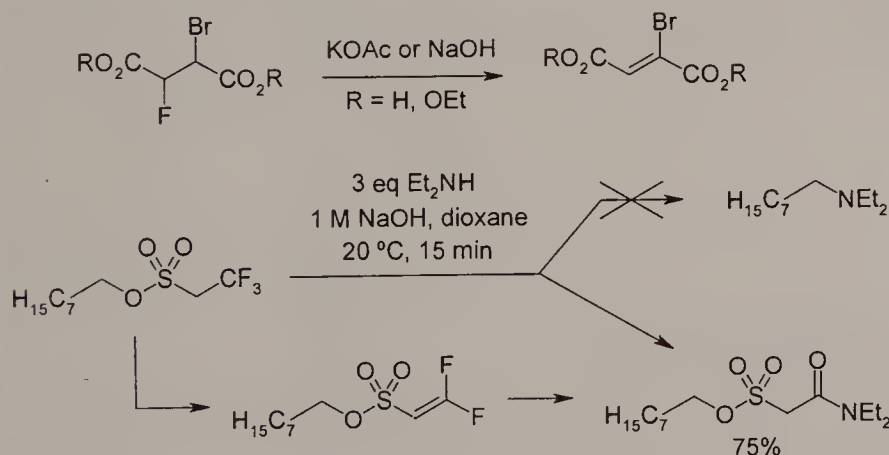
Simple alkyl fluorides are rather unreactive toward nucleophiles under neutral or basic reaction conditions, as illustrated by the first reaction in Scheme 4.10, and few examples of such reactions have been reported.

These reactions are complicated further by the pronounced tendency of some alkyl fluorides to undergo β -elimination, especially in protic solvents (strong hydrogen-bond formation with fluoride) and in the presence of vicinal electron-withdraw-



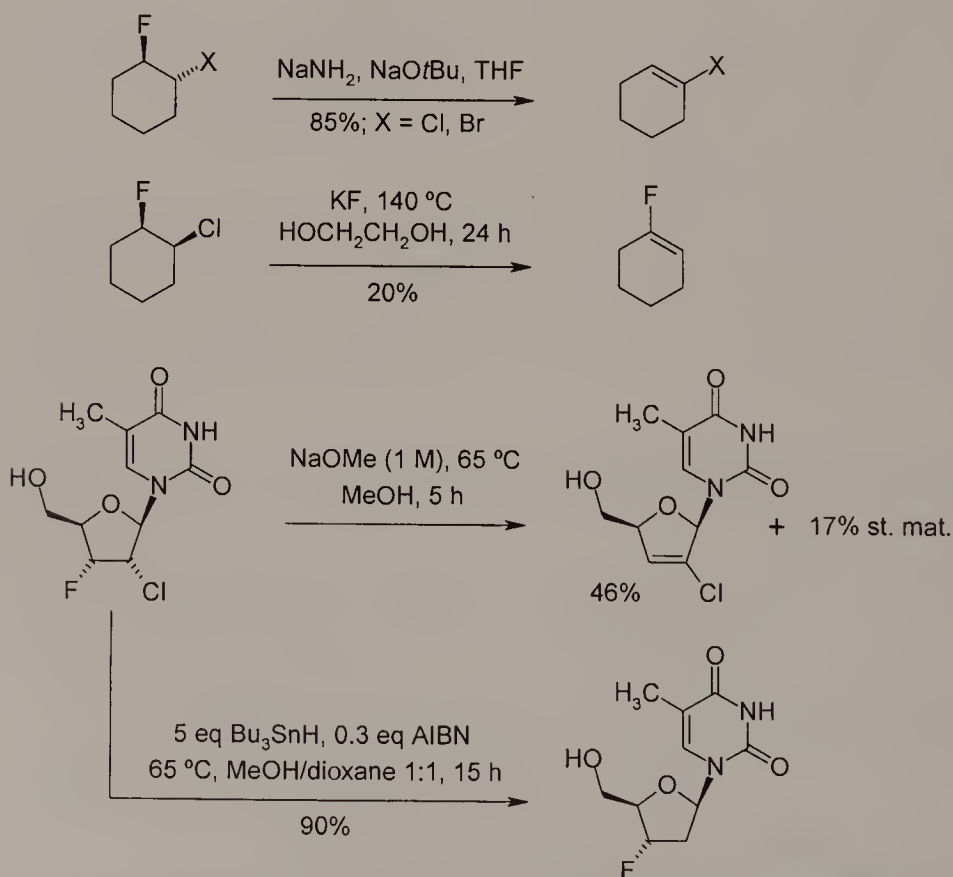
Scheme 4.10. Reactivity of alkyl fluorides toward nucleophiles under neutral or basic reaction conditions [26, 55–58].

ing groups (e.g. $\text{FCH}_2\text{CH}_2\text{Z}$) [59]. Thus, attempts to prepare β -fluoro ketones or esters from other halides usually lead to the formation of α,β -unsaturated carbonyl compounds. Similarly, 2,2,2-trifluoroethanesulfonates (tresylates) do not always undergo substitution but can eliminate fluoride instead, particularly in protic solvents [60] (Scheme 4.11).



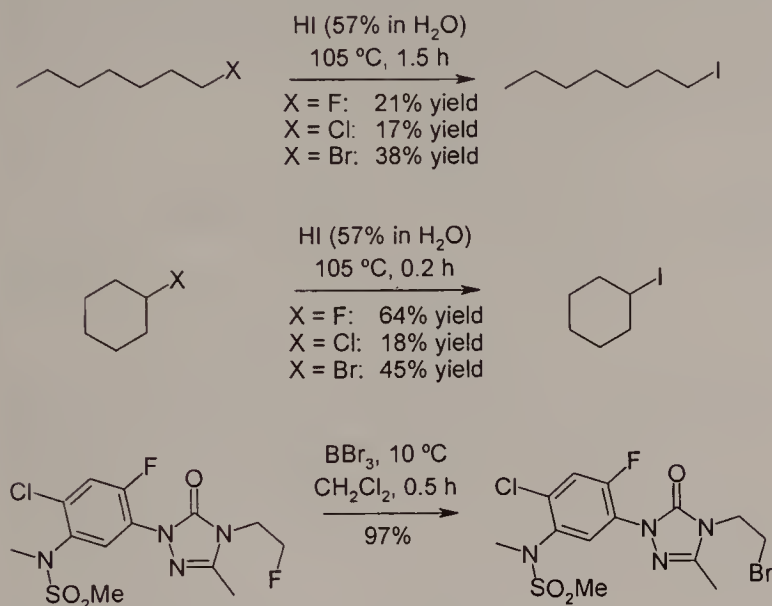
Scheme 4.11. Elimination of hydrogen fluoride from C,H-acidic substrates [61–63].

Some authors occasionally express surprise at the ready β -elimination of fluoride [64] despite the strength of the C–F bond (D_{298} Me–F 115 kcal/mol; D_{298} Me–Cl 83.7 kcal/mol [65]) and despite the lower hyperconjugative energy gain in the interaction of a β -lone pair with $\sigma^*_{\text{C–F}}$ than with the other C–Hal bonds [66]. One should not forget, however, that bond-dissociation enthalpies D refer to *homolytic* bond cleavage (i.e. the formation of radicals, not ions), and do not take into account the energy of solvation of the starting materials and products, which is particularly high for fluoride. Furthermore, fluorine seems to enhance the kinetic acidity of β protons more than that of α protons [67, 68] (and to destabilize β carbocations more than α carbocations [69]). For these reasons β -elimination of fluoride is not an unfavorable process. Some examples of the elimination of hydrogen fluoride from non-C,H-acidic substrates are sketched in Scheme 4.12. Competition experiments in which hydrogen bromide is eliminated more rapidly than hydrogen fluoride have, however, also been reported [70]. When fluoride is used as base for the dehydrohalogenation of 2-haloalkyl fluorides, vinyl fluorides are often obtained [71]; this might, however, be because of prior conversion to a vicinal difluoride by $\text{S}_{\text{N}}2$, followed by elimination of HF (second reaction, Scheme 4.12). 2-Fluoroalkyl sulfonates usually also yield vinyl fluorides on treatment with a base [71], as do 1-aryl-1-fluoro-2-haloethanes [72, 73]. As illustrated by the last example in Scheme 4.12, it is difficult to cleave C–F bonds homolytically, because of the strength of this bond.



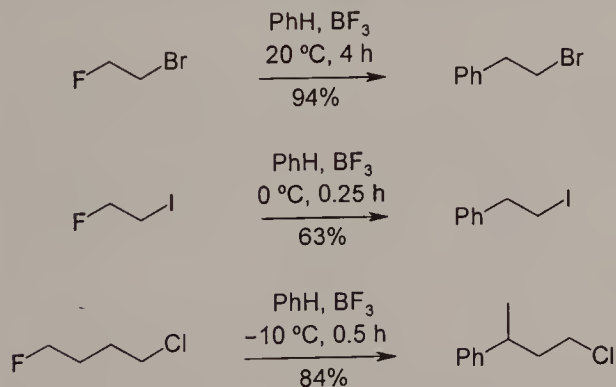
Scheme 4.12. Elimination of hydrogen fluoride from non-C,H-acidic substrates [64, 74].

Under acidic reaction conditions, however, aliphatic fluoride can be readily displaced (Scheme 4.13), especially in alkyl monofluorides. This is probably because of the strong hydrogen bonds formed by fluoride[75]. As illustrated by the second example in Scheme 4.13, for some substrates the fluorides will be even more reactive than the corresponding chlorides or bromides[76]. The first two reactions sketched in Scheme 4.13 can be driven to completion by use of higher temperatures or longer reaction times, to give almost quantitative yields of alkyl iodides.



Scheme 4.13. Nucleophilic displacement of fluoride under acidic reaction conditions [76, 77].

Lewis acids such as boron trihalides will also form stronger bonds with fluoride than with the other halogens, and can be used to abstract fluoride selectively from halogenated compounds. Some examples of Friedel–Crafts alkylations with fluoro-haloalkanes in which only fluoride is displaced are sketched in Scheme 4.14. As shown by the last example, however, hydride migrations can readily occur under such strongly acidic reaction conditions.

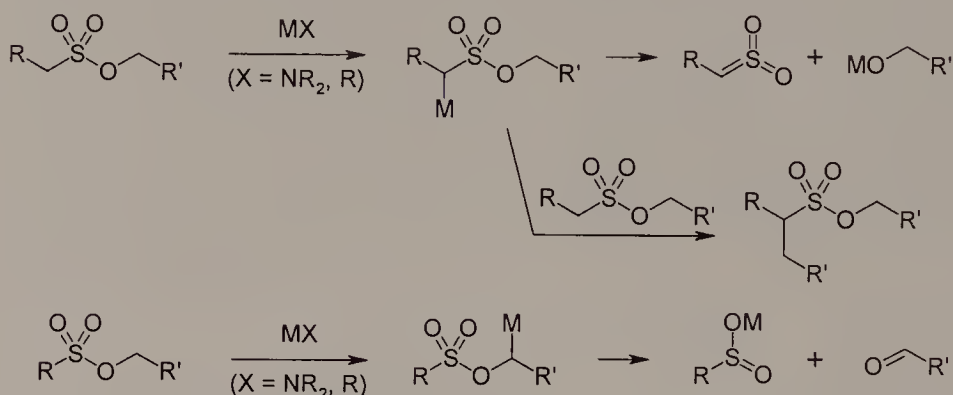


Scheme 4.14. Selective Friedel–Crafts alkylations of benzene with fluorohaloalkanes [78].

4.2.3

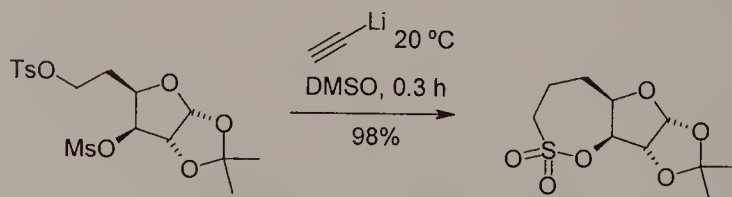
Nucleophilic Substitution of Sulfonates

Sulfonates such as mesylates or tosylates are readily prepared from alcohols under mild conditions, and are therefore attractive alternatives to halides as electrophiles. Although sulfonates often undergo clean displacement by nucleophiles, alternative reaction pathways are accessible to these intermediates, which can lead to unexpected results. If the nucleophile used is strongly basic, metalation instead of displacement of the sulfonate can occur. Some potential reactions of such metalated sulfonates include fragmentation into sulfenes and alcoholates, or into sulfinates and carbonyl compounds, or self-alkylation (Scheme 4.15).



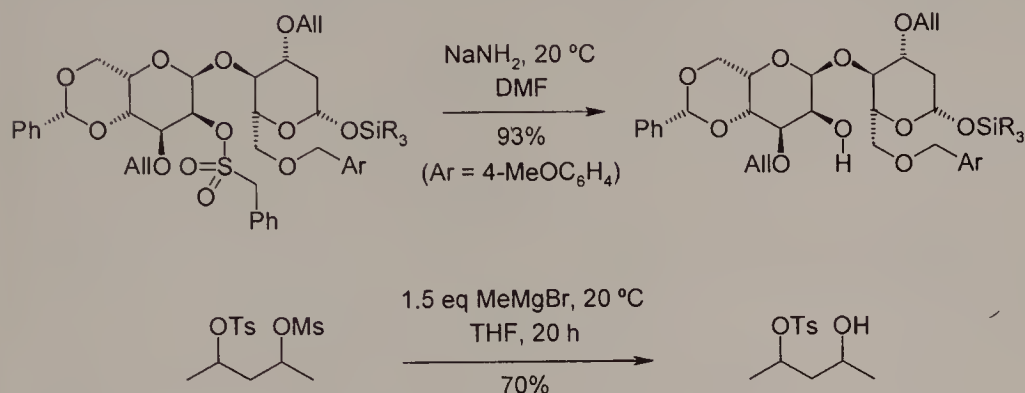
Scheme 4.15. Reactions of sulfonates with bases.

As mentioned above, 2,2,2-trifluoroethanesulfonates (tresylates) are strongly C,H-acidic and can eliminate fluoride instead of being displaced by a nucleophile (Scheme 4.11), despite the high stability of CF_3 groups. Other alkanesulfonates with a sulfur-bound C,H group can also be deprotonated if the nucleophile is sufficiently basic. Thus, methanesulfonates ($\text{p}K_{\text{a}} \approx 25$ in DMSO [79]) can be metalated by treatment with organometallic reagents such as ethynyllithium or BuLi (Scheme 4.16), and deprotonated isopropyl or neopentyl mesylate can be cleanly alkylated at carbon without C–O bond cleavage [80]. Intramolecular aldol-type condensations at mesylates can be mediated by bases as weak as triethylamine [80].



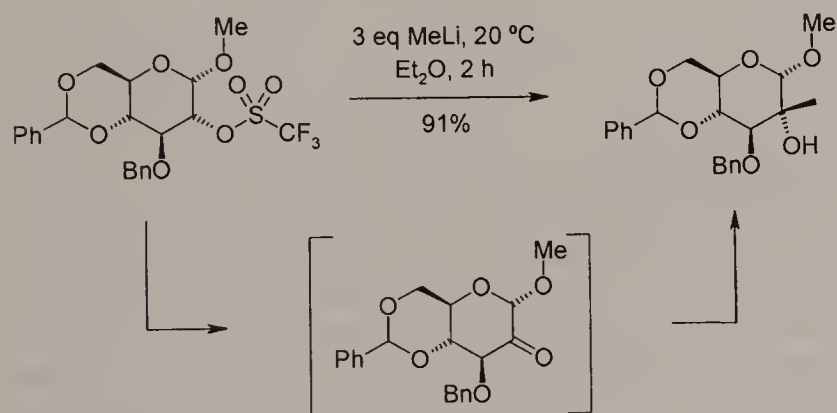
Scheme 4.16. Metalation and intramolecular C-alkylation of mesylates [81].

Sulfonates with a sulfur-bound C,H group can also eliminate alkoxide when treated with a strong base [82]. Phenylmethanesulfonic esters, for instance, are sufficiently base-labile to be useful protective groups for alcohols (Scheme 4.17).



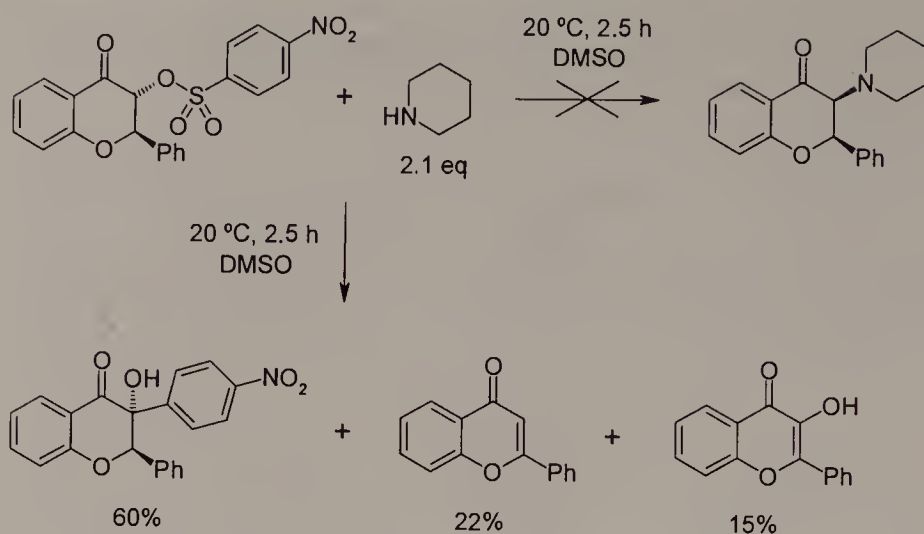
Scheme 4.17. Base-induced cleavage of sulfonates [83, 84].

Some triflates can be deprotonated at the oxygen-bound C,H group when treated with a strong base, and undergo elimination of sulfinate to yield a ketone [85–87]. If the base is an organolithium or Grignard reagent, this will add to the ketone and a tertiary alcohol will finally result (Scheme 4.18).



Scheme 4.18. Formation of tertiary alcohols from triflates via sulfinate elimination [88].

Deprotonation of sulfonates by strongly basic nucleophiles can be avoided by using arenesulfonates instead of alkanesulfonates. Arenesulfonates can, however, give rise to another type of side reaction: aromatic nucleophilic substitution. Nitroarenesulfonates are particularly prone to attack by a nucleophile at the arene [89, 90] (Scheme 4.19).



Scheme 4.19. Reaction of a 4-nitrobenzenesulfonate with piperidine [91].

4.3

Structure of the Electrophile

4.3.1

Steric Effects

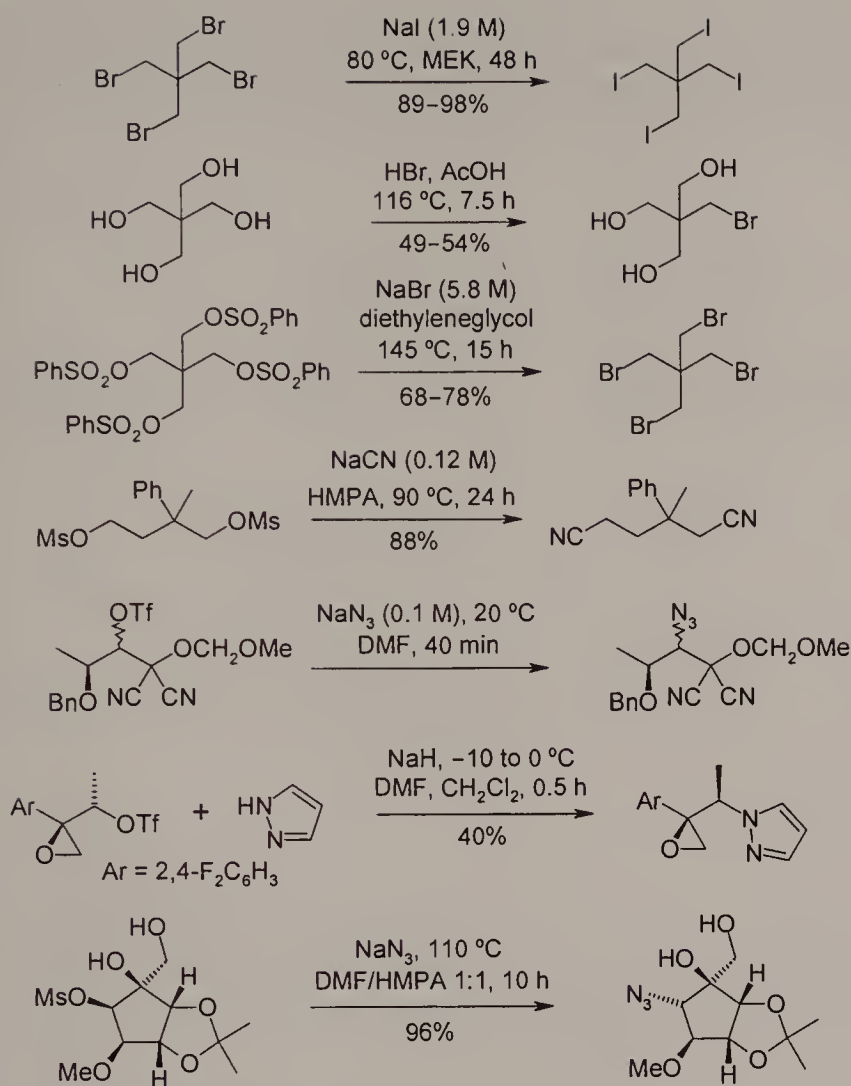
The reactivity of an electrophile is determined not only by the leaving group, but also to a large extent by steric, inductive, stereoelectronic, and field effects, all of which depend on its precise structure.

As shown in Scheme 4.1, during an S_N2 reaction at sp^3 -hybridized carbon the nucleophile approaches the electrophile from the side opposite to the leaving group. Hence, if the remaining three substituents at the electrophilic carbon are large, the nucleophile will have to overcome repulsive forces, especially so if the nucleophile also is large. This steric repulsion is believed to be the main reason for the strong dependence of bimolecular substitution rates on the structure of simple alkyl halides (Table 4.1).

Table 4.1. Average relative rates for S_N2 reactions of alkyl substrates RX [1, 92, 93].

R	Relative rate	R	Relative rate
Methyl	30	Isobutyl	0.03
Ethyl	1	Neopentyl	0.00001
1-Propyl	0.4	Allyl	40
1-Butyl	0.4	Propargyl	57
2-Propyl	0.025	Benzyl	120

Thus, alkylating agents derived from secondary or β -branched alkyl groups will usually undergo bimolecular substitution only slowly, and S_N1 or side reactions



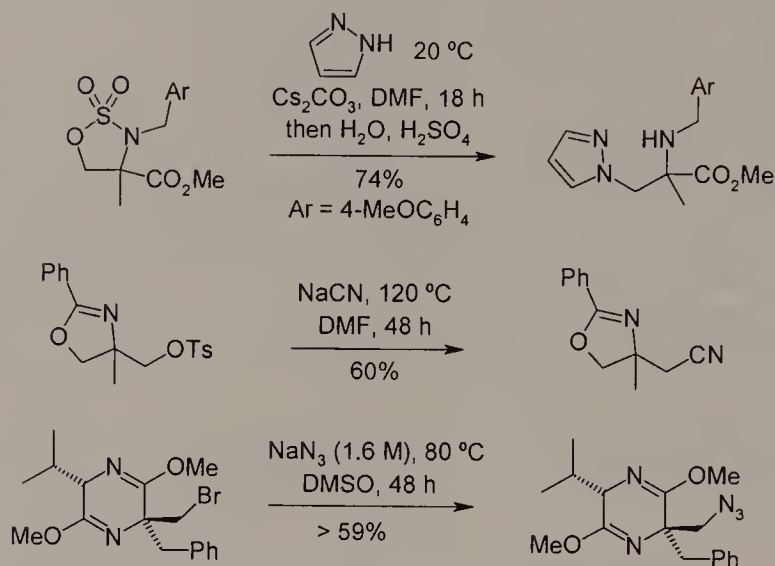
Scheme 4.20. Nucleophilic substitutions at neopentyl-type substrates [96–101].

such as elimination or rearrangement might compete efficiently. For sterically demanding secondary and tertiary substrates, substitution via the $\text{S}_{\text{N}}1$ mechanism might become the main reaction pathway, also because of the stabilization of the corresponding carbocations by hyperconjugation and inductive effects [94], and because repulsive interactions between bulky alkyl groups will be smaller in the planar carbocation.

Successful substitutions at neopentyl-type substrates can be performed, but can be accompanied by rearrangements. The best results are obtained with small nucleophiles, for example halides, azide, or cyanide. Some representative examples are shown in Scheme 4.20, to illustrate the reaction conditions required. If electron-rich nucleophiles such as thiolates are used, substitutions at neopentyl derivatives can also occur via SET [95].




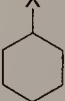




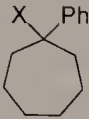

Conversion of the hydroxyl group of serine into a leaving group followed by nucleophilic substitution often leads to large amounts of acrylates [102]. In α -alkylated analogs this elimination is no longer possible, but the substrate is neopentyl-

like, and substitutions are therefore difficult. Nevertheless, despite these difficulties serine derivatives have proven to be useful intermediates for preparation of α -alkyl α -amino acids. In Scheme 4.21 representative examples of substitutions at such serine-derived substrates are sketched.



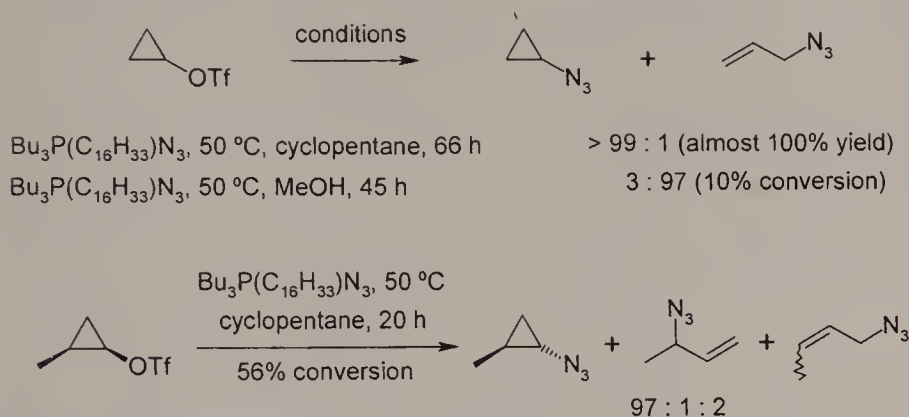
Scheme 4.21. Nucleophilic substitutions at amino acid-derived neopentyl-type substrates [103–105].

During nucleophilic substitutions the hybridization at carbon changes from sp^3 to sp^2 ; for an electrophile R_3CX this leads to widening of the angle RCR from 109° to 120° in the transition state (S_N2) or in the intermediate carbocation (S_N1). In cyclic secondary or tertiary electrophiles this required angle widening can lead either to an increase or to a relaxation of strain (Scheme 4.22).

						
relative rate (X = OTs) solvolysis in AcOH	0.0002	14	16	1.0		
relative rate (X = Br) KI in Me ₂ CO	no reaction	1.4	5.7	1.0		
						
relative rate (X = OPNB) solvolysis in Me ₂ CO/H ₂ O 8:2, 25 °C	< 10 ⁻⁵	0.13	178	1.0	51.5	515

Scheme 4.22. Relative rates of S_N1 and S_N2 reactions of cyclic substrates [106–108].

If the ring becomes more strained in the transition state nucleophilic substitution should proceed more slowly than with similar, non-cyclic electrophiles. Thus, cyclopropyl derivatives are highly resistant towards nucleophilic substitution because the RCR angle is fixed at 60° , and only rarely can products of an S_N2 reaction at cyclopropyl derivatives be obtained [109]. Instead, allyl derivatives are usually the main products (Scheme 4.23).



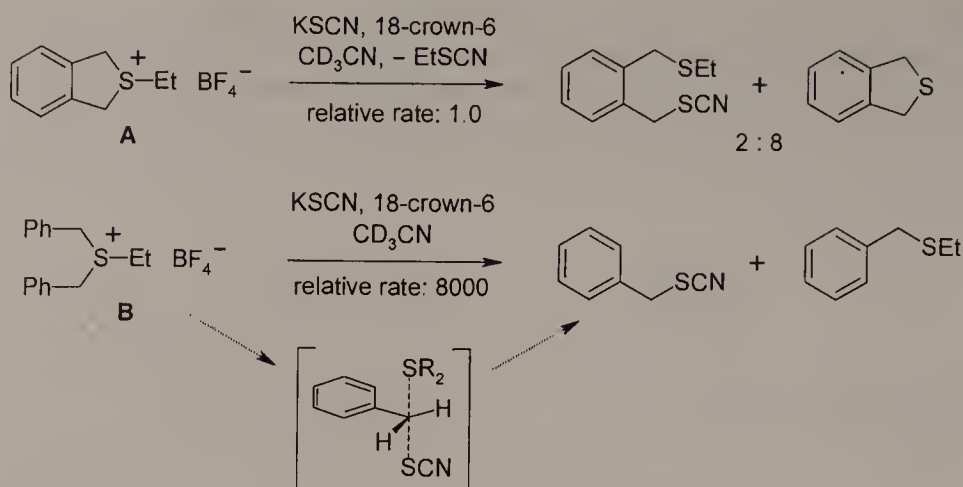
Scheme 4.23. Reaction of cyclopropyl triflates with azide [109].

4.3.2

Conjugation

The transition state of an S_N2 reaction can be stabilized or destabilized by electronic effects originating from the substituents at the reaction center. As shown in Table 4.1, allylic or benzylic substrates undergo significantly faster S_N2 reactions than similar, fully saturated substrates. This acceleration is believed to be due to conjugation of the π -system with the sp^2 -hybridized carbon atom in the transition state. Accordingly, constrained benzylic substrates in which such conjugation is not possible are not as reactive as similar, unconstrained systems. Thus, the benzylic C–S bonds in sulfonium salt **A** (Scheme 4.24) are highly unreactive, and this compound reacts with nucleophiles mainly as an ethylating reagent. In compound **A** cleavage of the benzylic C–S bond by a nucleophile has to proceed via a transition state in which the Nuc–C–SR₂⁺ trajectory is almost parallel to the arene and no conjugation with the aromatic π -system is possible. The non-cyclic sulfonium salt **B**, on the other hand, can adopt a conformation in which the Nuc–C–SR₂⁺ trajectory is orthogonal to the plane of one phenyl group. Salt **B** reacts therefore exclusively as a powerful benzylating reagent.

Conjugation in allylic or benzylic electrophiles can also stabilize the corresponding carbocations and thereby facilitate substitution by the S_N1 mechanism, as shown by the relative solvolysis rates given in Table 4.2.



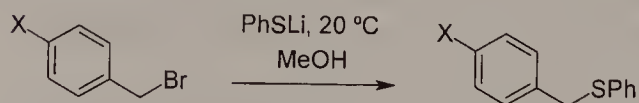
Scheme 4.24. Reactivity of benzyl ethyl sulfonium salts toward thiocyanate [110].

Table 4.2. Relative rates for the $\text{S}_{\text{N}}1$ reaction of tosylates R-OTs with ethanol at 25°C [1].

R	Relative rate	R	Relative rate
Ethyl	0.26	PhCH_2	100
2-Propyl	0.69	Ph_2CH	$\sim 10^5$
Allyl	8.6	Ph_3C	$\sim 10^{10}$

The effect of substituents at the arene on the reactivity of benzylic electrophiles depends on the type of nucleophile used [111]. Benzylic substrates with electron-withdrawing ring substituents react more rapidly with anionic nucleophiles in bimolecular substitutions than comparable unsubstituted electrophiles, but slower with neutral nucleophiles [111–113]. Because donor-substituted benzylic systems tend to undergo rapid $\text{S}_{\text{N}}1$ reactions, the reactivity of benzylic electrophiles toward negatively charged nucleophiles usually reaches a minimum for unsubstituted benzylic electrophiles and increases on substitution with either electron-withdrawing or electron-donating substituents [114–117] (Scheme 4.25).

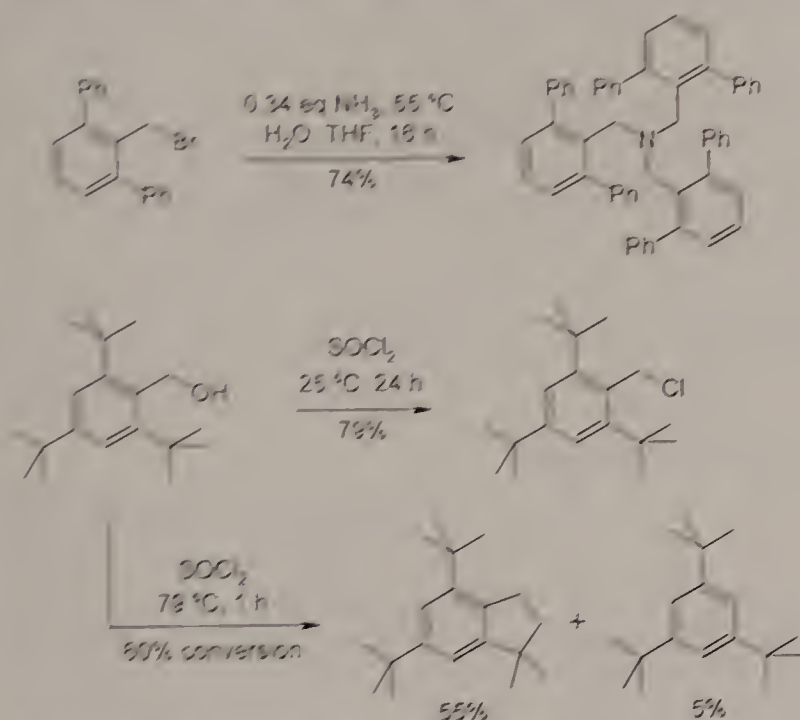
Donor-substituted benzylic electrophiles usually undergo clean $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ reactions to yield the expected products in high yield. The favorable electronic effect of the aryl group seems to dominate the reaction, and sterically demanding substitu-



X =	OMe	Me	H	Br	NO_2
relative rates:	4.6	1.5	1.0	2.4	6.9

Scheme 4.25. Relative rates of the S -benzylation of thiophenol with benzyl bromides [115].

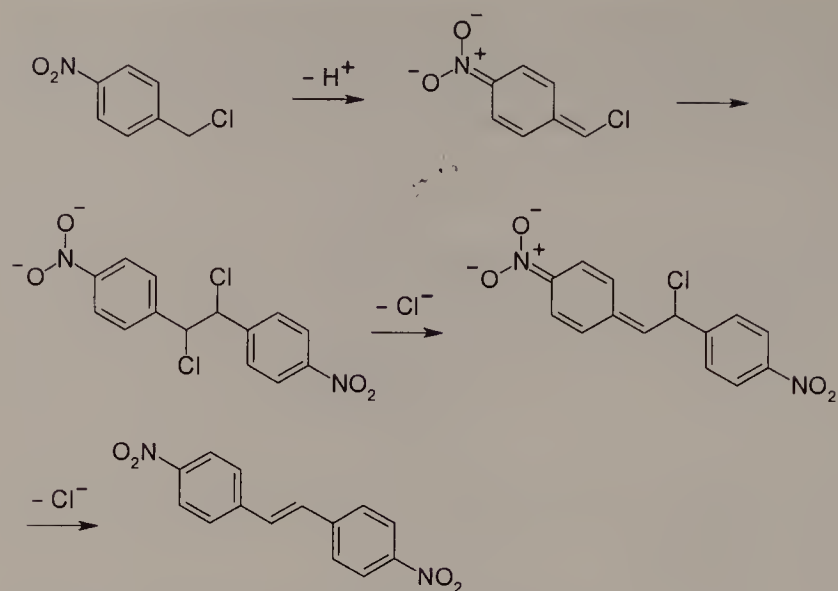
ents in the *ortho* positions usually have no strong rate-diminishing effect. Even 2,6-diphenyl or 2,6-di-*tert*-butylbenzyl derivatives undergo high-yielding benzylic substitution (Scheme 4.26). Under acidic conditions, however, reaction of the benzylic cation with the *ortho* substituents can occur (Scheme 4.26).



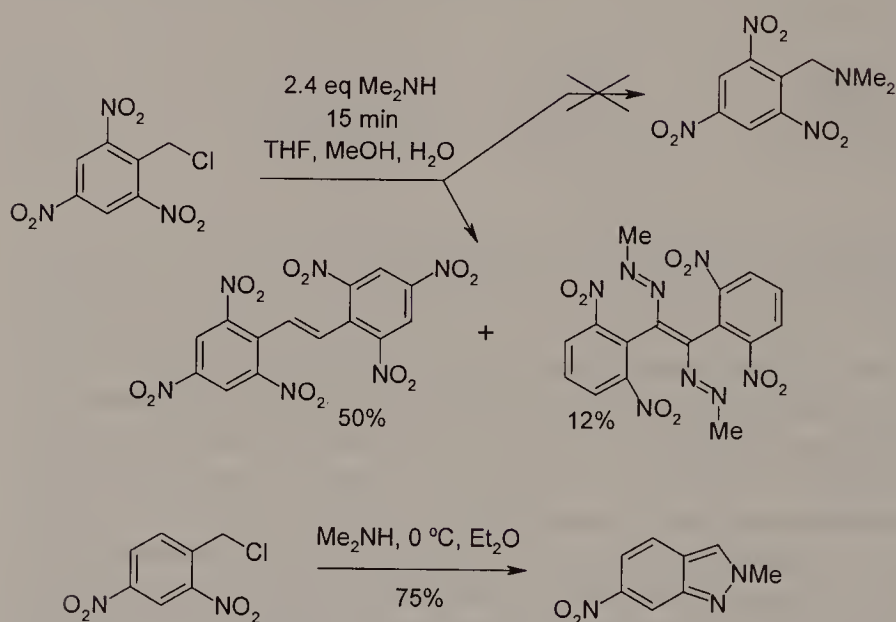
Scheme 4.26. Nucleophilic substitution at sterically demanding benzylic substrates [112, 113].

Benzylic electrophiles bearing electron-withdrawing groups at the arene do not always yield the expected products of nucleophilic substitution on treatment with a nucleophile. One important side reaction is the dimerization of these compounds to yield 1,2-diarylethenes (stilbenes). This dimerization does not require such highly activated systems as the example sketched in Scheme 4.28, but can even occur with, for example, 2- or 4-nitrobenzyl chloride [120, 121]. The latter compounds are converted into the corresponding stilbenes by treatment with KOH in ethanol [120]. Diarylmethyl halides behave similarly and can yield tetraarylethenes on treatment with a base. These reactions presumably proceed via the mechanism sketched in Scheme 4.27, in which the amphiphilic character of the nitro group plays a decisive role (metalated nitroalkanes or 4-nitrobenzyl derivatives can act as nucleophiles and as electrophiles).

If the arenes are very electron-deficient direct attack of the nucleophile at the arene might also compete with displacement of the benzylic leaving group, to yield complex structures such as that shown in Scheme 4.28. 2-Nitrobenzyl halides can also react with amines to yield, instead of simple products of nucleophilic substitution, 2*H*-indazoles [122] (Scheme 4.28). 4-Nitrobenzyl halides, however, yield the expected benzyl amines on treatment with amines [123].

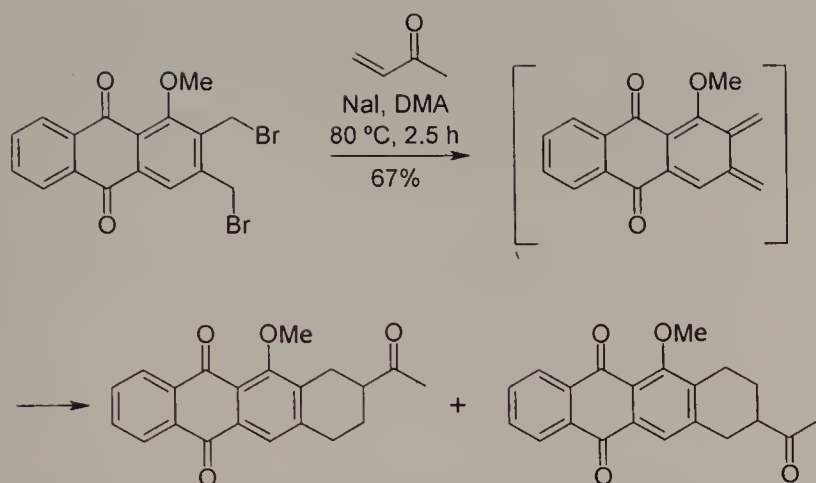


Scheme 4.27. Dimerization of nitrobenzyl halides.



Scheme 4.28. Reactivity of nitrobenzyl halides toward amines [122, 124].

Other benzylic electrophiles which can lead to unexpected products are 1,2- or 1,4-bis(halomethyl)benzenes. On treatment with a nucleophile, oxidation of the nucleophile instead of nucleophilic substitution may occur, followed by the formation of highly reactive quinodimethanes, which can either oligomerize or undergo addition or cycloaddition reactions (Scheme 4.29). The outcome of these reactions can, however, be controlled by choosing the right conditions, as demonstrated by the numerous report of successful S_N2 reactions at 1,2- or 1,4-bis(halomethyl)benzenes (see, e.g., Ref. [125]).



Scheme 4.29. Formation of quinodimethanes from 1,2-bis(bromomethyl)benzenes and iodide [126].

4.3.3

Electrophiles with α -Heteroatoms

4.3.3.1 α -Heteroatoms with Lone Electron Pairs

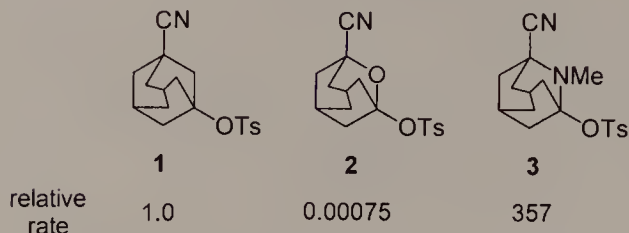
The rates of S_N1 and S_N2 reactions are usually strongly enhanced when atoms with an unshared electron pair are directly attached to the reaction center, as in α -halomethyl ethers, thioethers, or amines (Scheme 4.30). Only the halogens do not lead to an enhancement of S_N2 reactivity, but to inhibition of bimolecular substitution reactions (Scheme 4.30). In S_N1 reactions, however, α -halogens can both increase or reduce the rate of substitution [127].

	<chem>PhCH2Cl</chem>	<chem>AcOCH2Cl</chem>	<chem>MeOCH2Cl</chem>			
relative rate (NaI in acetone, 50 °C)	1.00	1.37	4.66			
	<chem>HCH2Br</chem>	<chem>MeCH2Br</chem>	<chem>FCH2Br</chem>	<chem>ClCH2Br</chem>	<chem>BrCH2Br</chem>	<chem>ICH2Br</chem>
relative rate (NaI in acetone, 20 °C)	191	1.00	0.53	0.06	0.017	0.04

Scheme 4.30. Relative rates of substitution at α -substituted methyl derivatives [112, 128].

An unshared electron pair can usually only assist nucleophilic displacements if this lone pair and the antibonding (σ^*) orbital between carbon and the leaving group are either antiperiplanar or synperiplanar. If such a conformation cannot be achieved, α -heteroatoms can even reduce the rate of S_N2 or S_N1 reactions. Scheme 4.31 shows some examples of conformationally constrained, tertiary tosylates for which hyperconjugation between the heteroatom lone pairs and the antibonding C–OTs orbital is not possible [129]. Thus, although α -alkoxyalkyl sulfonates

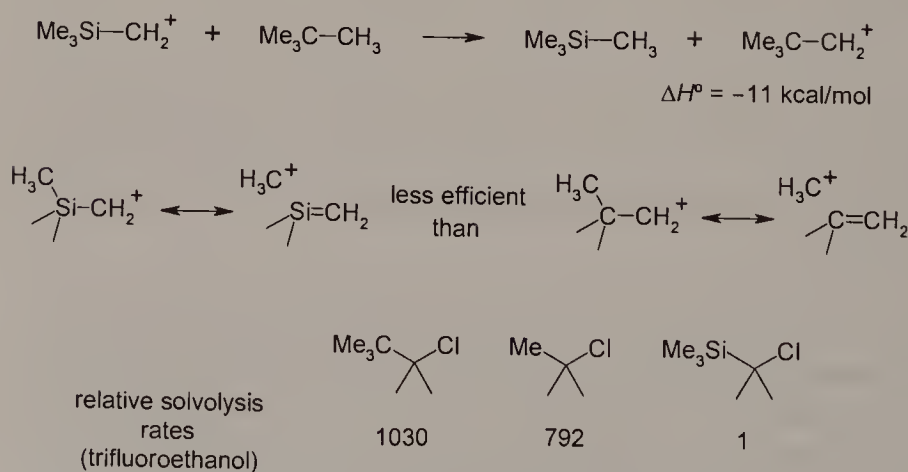
usually undergo S_N1 reactions much more rapidly than simple *tert*-alkyl sulfonates, compound **2** is much less reactive than its carbon analog **1**. The α -aminoalkyl tosylate **3**, however, reacts faster than **1**, indicating that despite the unfavorable geometry substantial stabilization of the transition state leading to the corresponding carbocation is still possible in this substrate [129].



Scheme 4.31. Relative rates of solvolysis of tosylates in EtOH/H₂O 8:2 at 25 °C [129].

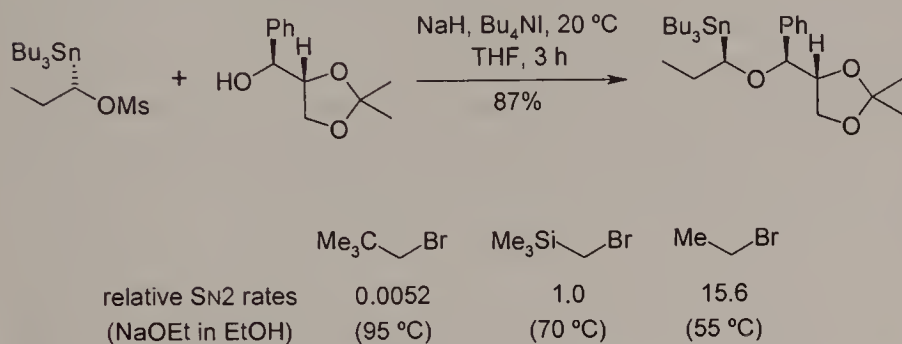
4.3.3.2 α -Silicon and α -Tin Electrophiles

(Trialkylsilyl)methyl halides and related electrophiles (R_3SiCH_2X) have rather peculiar reactivity which would be difficult to infer by simple comparison with carbon analogs. Although silicon is less electronegative than carbon, and a trimethylsilyl group is therefore a better σ -donor than a *tert*-butyl group, carbocations are strongly destabilized by silyl groups relative to alkyl groups (but stabilized relative to hydrogen) [130–132]. This destabilization is because of the weak hyperconjugation between σ_{C-Si} bonds and the empty p orbital on carbon (orbital size and energy mismatch; silicon does not readily form π bonds with carbon or other second-period elements) and the electrostatic destabilization brought about by the partial positive charge on silicon (bound to four more electronegative atoms). For these reasons S_N1 reactions of electrophiles such as Me_3SiCR_2X proceed more slowly than with comparable alkyl derivatives (Scheme 4.32).



Scheme 4.32. Destabilization of carbocations by R_3Si groups [130, 131].

Because of the destabilization of α -trialkylsilyl carbocations, electrophiles such as $\text{Me}_3\text{SiCH}_2\text{X}$ undergo rearrangement-free $\text{S}_{\text{N}}2$ reactions rather than $\text{S}_{\text{N}}1$ reactions, even under conditions where neopentyl derivatives ($\text{Me}_3\text{CCH}_2\text{X}$) would undergo solvolysis and rearrangement [131]. These $\text{S}_{\text{N}}2$ reactions at $\text{Me}_3\text{SiCH}_2\text{X}$ proceed much more rapidly than at comparable neopentyl derivatives (Scheme 4.33), because the long C–Si bonds reduce steric crowding. Electrophiles such as $\text{Me}_3\text{SiCH}_2\text{I}$ can, for instance, be used to *N*-alkylate amines (DMSO, 100 °C, 2–3 h [133]). Similarly, α -trialkylstannyl halides or sulfonates undergo clean $\text{S}_{\text{N}}2$ reactions under relatively mild reaction conditions (Scheme 4.33).



Scheme 4.33. $\text{S}_{\text{N}}2$ reactions at α -trialkylsilyl and α -trialkylstannyl electrophiles [134–136].

For electrophiles such as $\text{Me}_3\text{SiCH}_2\text{X}$ strong ground-state destabilization has been observed for $\text{X} = 4$ -nitrobenzoate [130]. For $\text{X} =$ halide, on the other hand, this ground-state destabilization is significantly smaller, and it may therefore be advisable to choose carboxylates or sulfonates as leaving groups when alkylations with α -silyl-substituted electrophiles are to be performed.

4.3.3.3 α -Boron Electrophiles

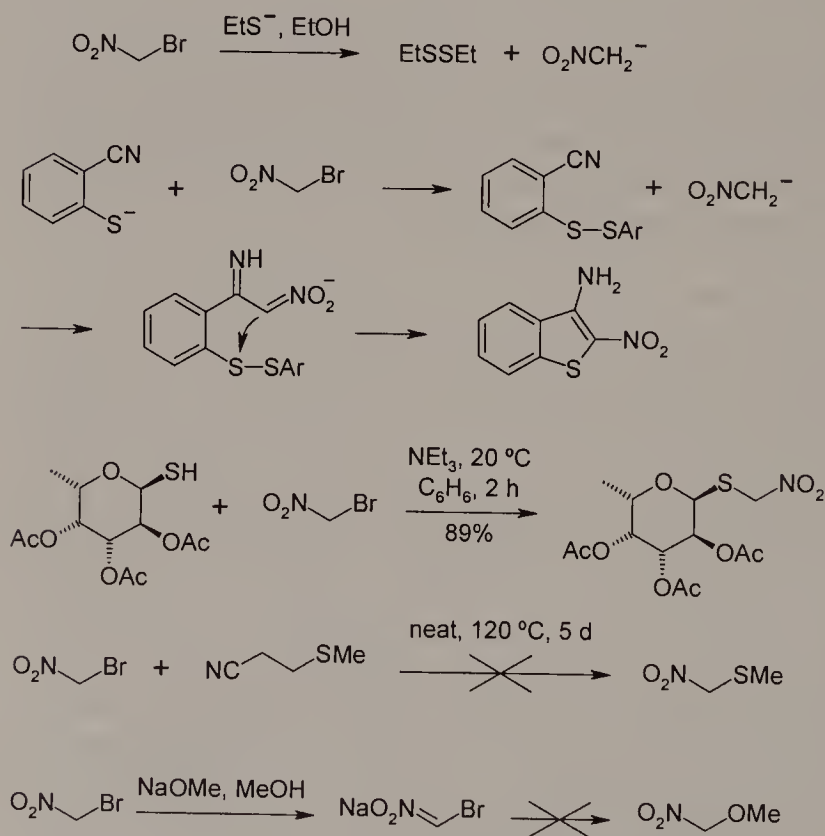
The reactivity of electrophiles with an electron-deficient heteroatom such as boron in the position α to the reaction center depends on whether $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ reactions are being considered. By analogy with α -halo ketones or electron-poor benzyl or allyl halides rate enhancement for bimolecular substitutions would be expected, and is indeed found. Thus, α -chloroalkyl boronic esters undergo halide exchange in non-ionizing solvents at significantly higher rates than comparable boron-free compounds [137–139]. These and other bimolecular nucleophilic substitutions at α -haloalkyl boronic esters usually proceed via initial attack of the nucleophile at boron, followed by intramolecular halide displacement [140]. In $\text{S}_{\text{N}}1$ reactions, on the other hand, the $\text{B}(\text{OR})_2$ group has a slight rate-diminishing effect if compared with a methyl group but a rate-enhancing effect relative to hydrogen (Scheme 4.34), and thus behaves similarly to the SiR_3 group. Amines [141] and carbamates [142] can also be *N*-alkylated with α -haloalkyl boronates, but the products resulting from alkylation of amines are not stable and can rearrange to aminoboronates $\text{R}_2\text{NB}(\text{OR})_2$ ([141] and references cited therein).

relative rate SN2 (NaI in Me ₂ CO)	6000	1600	4000	1.0	
relative rate SN1 (H ₂ O/EtOH 1:1)		100		1.0	10000

Scheme 4.34. Relative rates of SN1 and SN2 reactions of α -bromo boronic esters [138, 140].

4.3.3.4 α -Nitro Electrophiles

α -Nitroalkyl halides do not usually undergo attack at carbon with simultaneous displacement of the halide, but react as halogenating or oxidizing reagents instead, because of the ability of nitroalkanes to act as leaving groups [143]. Because of the high acidity of nitroalkanes, the precise reaction conditions can have a decisive influence on the course of the reaction. Under basic reaction conditions the nitroalkane will be deprotonated and usually become even less susceptible to nucleophilic attack. As shown in Scheme 4.35, reactions of bromonitromethane with nucleophiles can, nevertheless, yield products of nucleophilic halide displacement, but

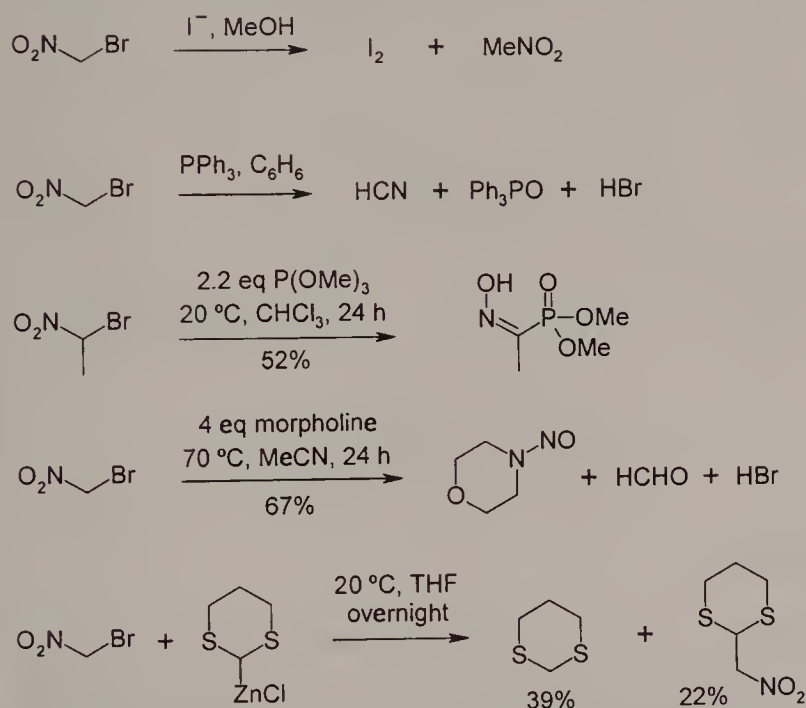


Scheme 4.35. Reactions of 1-halo-1-nitroalkanes with sulfur and oxygen nucleophiles [144–146]. Ar = 2-cyanophenyl.

these reactions might proceed via a more intricate mechanism than a simple bimolecular substitution.

The oxidizing power of bromonitromethane is illustrated further by its reactions with iodide and phosphines[145], which do not yield products of nucleophilic substitution but the oxidized nucleophiles only (Scheme 4.36). Phosphites are also oxidized by bromonitromethane[145], but with higher homologs, for example 1-bromo-1-nitroethane, products of nucleophilic substitution can be isolated[147] (Scheme 4.36).

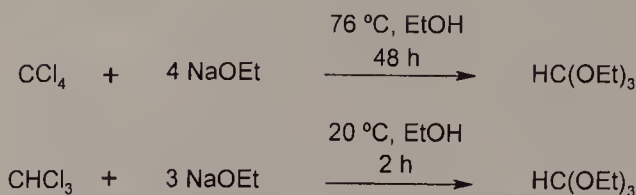
The fact that products of type $\text{Nu}-\text{CR}_2-\text{NO}_2$ can be unstable, in particular if the group Nu has an unshared electron pair, and that nitroalkanes are efficient one-electron oxidants with a pronounced tendency to undergo radical reactions, add further uncertainty to the outcome of these reactions. Thus, the reaction of amines with bromonitromethane, for instance, is assumed to yield nitromethylamines initially; these, however, decompose to *N*-nitrosoamines[148] (Scheme 4.36).



Scheme 4.36. Reactions of 1-halo-1-nitroalkanes with iodide[145] and with phosphorus[145, 147], nitrogen[148], and carbon[149] nucleophiles.

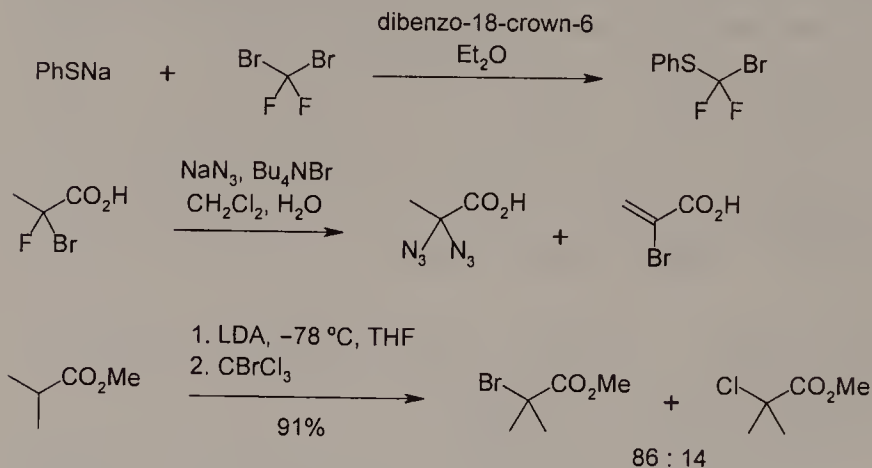
4.3.3.5 Electrophiles with More than one α -Heteroatom

The reactivity of methanes substituted with more than two heteroatoms is not easy to predict. Tetrahalomethanes react with nucleophiles usually at the halogen with displacement of X_3C^- . CHCl_3 or PhCCl_3 , however, undergo clean substitution with strong nucleophiles. Treatment of CCl_4 or CHCl_3 with alcoholates, for instance, yields trialkyl orthoformates (HC(OR)_3) in both cases[150, 151] (Scheme 4.37). The first step of the reaction of CCl_4 with alcoholates is probably reduction of CCl_4 by the alcoholate to yield CHCl_3 and ethyl hypochlorite or diethyl peroxide.



Scheme 4.37. Preparations of triethyl orthoformate [151, 152].

Electrophiles which enable four substitutions at the same carbon atom include Cl_3CNO_2 and Cl_3CSCl ; both compounds yield tetraalkyl orthocarbonates on treatment with alcoholates [150]. In polyhalomethanes selective substitutions of the most reactive halide are possible [153] but not always easy to perform (Scheme 4.38).



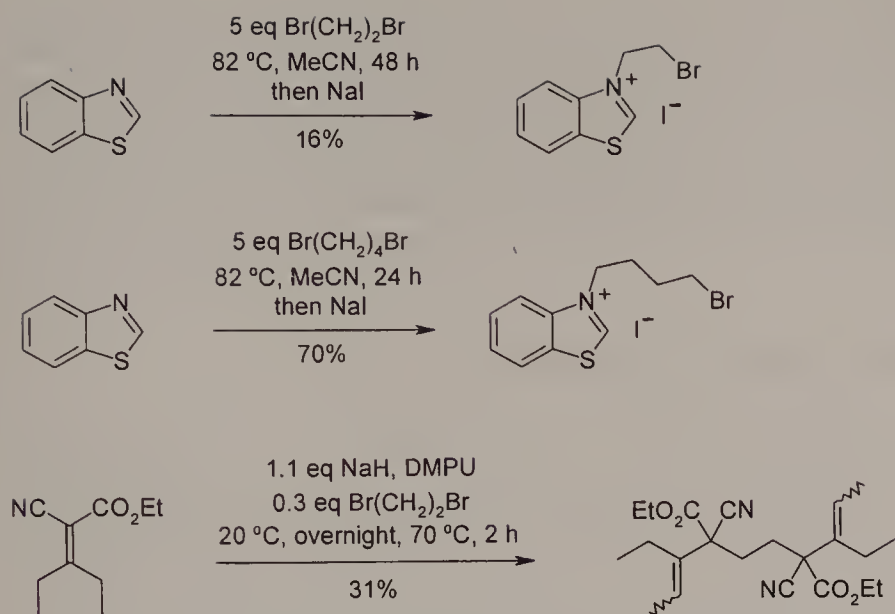
Scheme 4.38. Nucleophilic substitutions at polyhalomethanes [43, 70, 154].

4.3.4

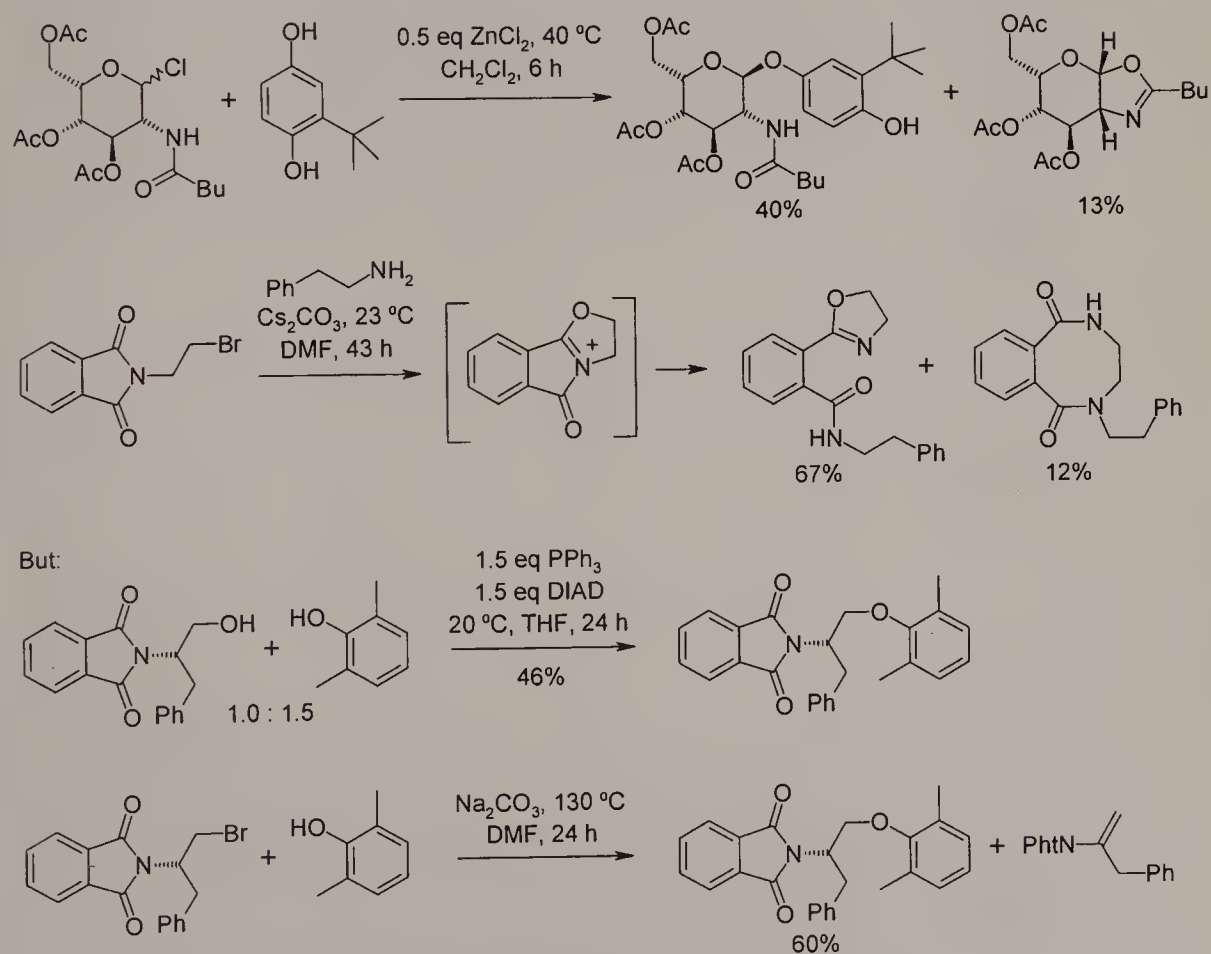
Electrophiles with β -Heteroatoms

Two opposing effects mainly modulate the reactivity of electrophiles with a heteroatom (N, O, S, Hal) in the β position – enhancement of $\text{S}_{\text{N}}1$ reactivity by neighboring-group participation (Section 4.3.6) and a reduction of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactivity by the inductive, electron-withdrawing effect through σ bonds. The second of these two effects has only a weak impact on $\text{S}_{\text{N}}2$ reactions, and electrophiles with β -heteroatoms usually have a $\text{S}_{\text{N}}2$ reactivity similar to that of the related, heteroatom-free electrophiles. In $\text{S}_{\text{N}}1$ reactions, however, neighboring-group participation can significantly enhance the reactivity of electrophiles.

1,2-Dihaloethanes are usually slightly less reactive toward nucleophiles than, for example, the corresponding propyl halides [155]. Although several successful nucleophilic substitutions at 1,2-dichloroethane or 1,2-dibromoethane have been performed (Section 10.6), several examples of poor results with these electrophiles have also been reported (Scheme 4.39).



Scheme 4.39. Alkylations with 1,2-dihaloethanes and 1,4-dihaloalkanes [155, 156].



Scheme 4.40. Alkylations with 2-(acylamino)ethyl halides and alcohols [157–159].

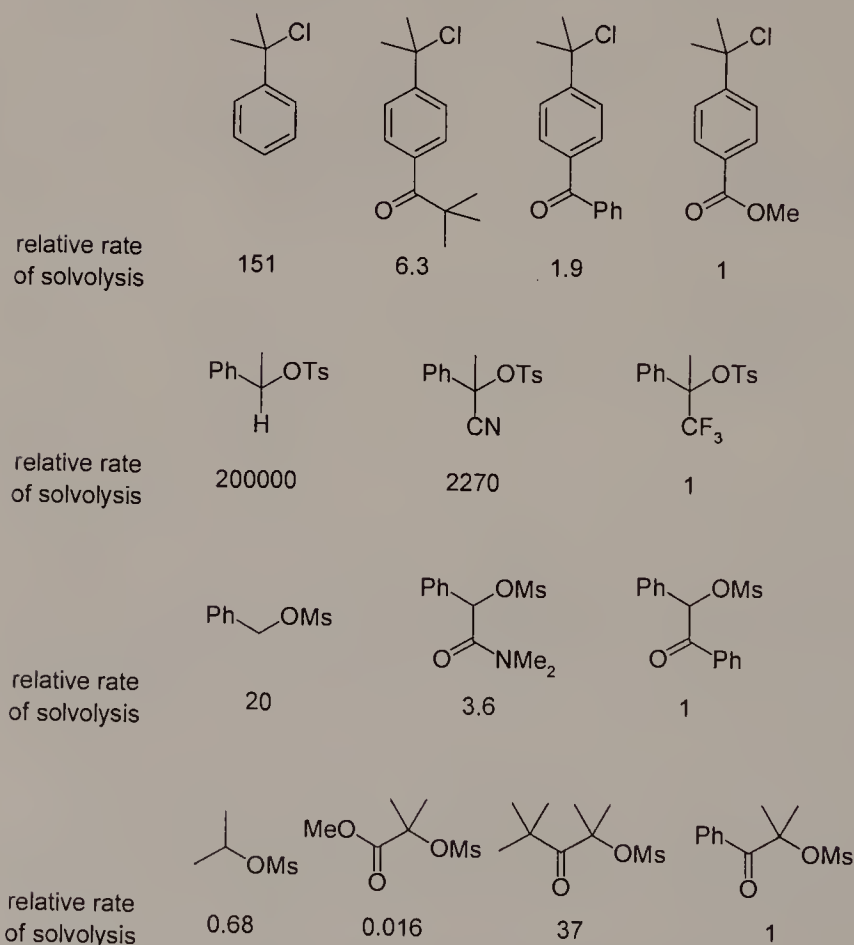
Other problematic electrophiles are 2-(acylamino)ethyl halides and related compounds. Although numerous successful nucleophilic substitutions with such substrates have been described in the literature, occasionally a side reaction becomes dominant. If the leaving group is hard or if the reaction conditions chosen are conducive to the formation of carbocations, intramolecular *O*-alkylation of the electrophile will lead to the formation of oxazolines (Scheme 4.40). This cyclization can sometimes be avoided by choosing a softer leaving group.

4.3.5

Electrophiles with α -Electron-withdrawing Groups

Substitutions at α -nitro (Section 4.3.3.4) and nitrobenzyl electrophiles (Section 4.3.2) have been discussed above.

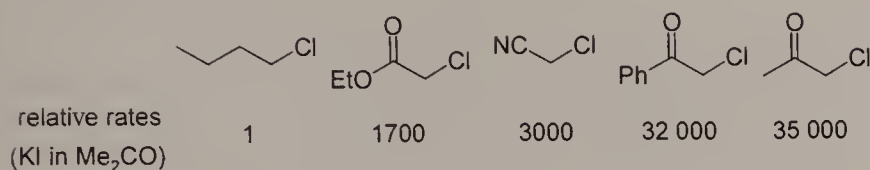
The rate of substitutions proceeding via free carbocations should decrease when electron-withdrawing groups are linked to the central carbon, and accelerated by carbocation-stabilizing groups. This is, however, not always observed. α -Carbonyl groups, for instance, sometimes have only a small rate-lowering effect, and can even enhance the rate of some S_N1 reactions [160, 161] (last row, Scheme 4.41). This



Scheme 4.41. Relative rate of S_N1 reactions of α -acceptor-substituted electrophiles [160, 162, 163].

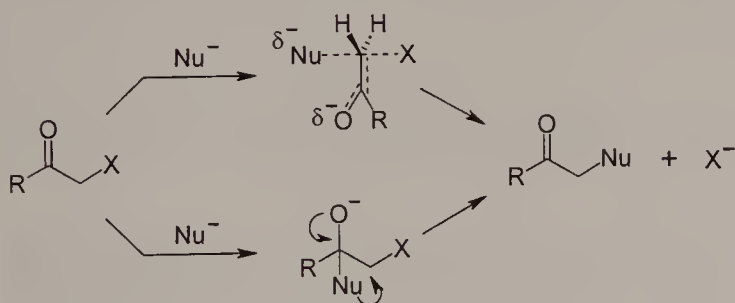
might be because of conjugation of the carbonyl group with the carbocation[161] ($R_2C^+-C=O \leftrightarrow R_2C=C-O^+$) or ground-state destabilization of the electrophile[162] (e.g. by steric crowding or dipole–dipole interaction). Usually, however, α -carbonyl groups reduce the rate of S_N1 reactions significantly [161].

For S_N2 reactions the effect of electron-withdrawing groups is less easy to predict than for S_N1 reactions. α -Halo ketones, α -halo nitriles, or haloacetic acid derivatives undergo bimolecular substitutions at much higher rates than unfunctionalized alkyl halides (Scheme 4.42).



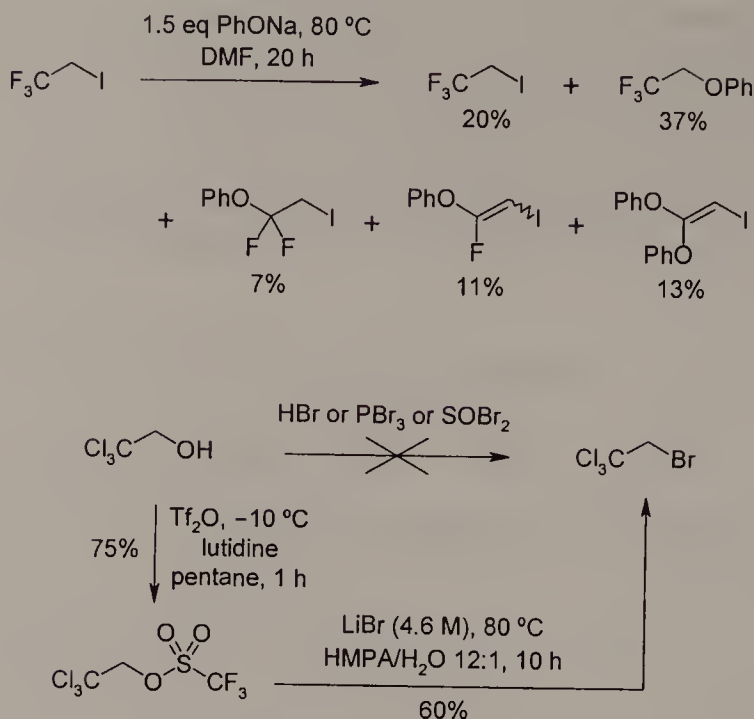
Scheme 4.42. Relative rates of S_N2 reactions of electrophiles substituted with electron-withdrawing groups [164, 165].

This effect is believed to result from an enolate-type transition state [166] or from a reaction mechanism in which the nucleophiles initially add to the carbonyl group and then undergo intramolecular 1,2-migration with simultaneous displacement of the leaving group [167] (Scheme 4.43). The latter proposal would also explain the strong decrease of reactivity of phenacyl derivatives on introduction of *ortho* substituents on the arene. In these *ortho*-substituted phenacyl derivatives addition of nucleophiles to the carbonyl group would lead to significant steric crowding and is therefore more difficult than in unsubstituted aryl ketones [168].



Scheme 4.43. Possible mechanisms of S_N2 reactions at α -carbonyl electrophiles.

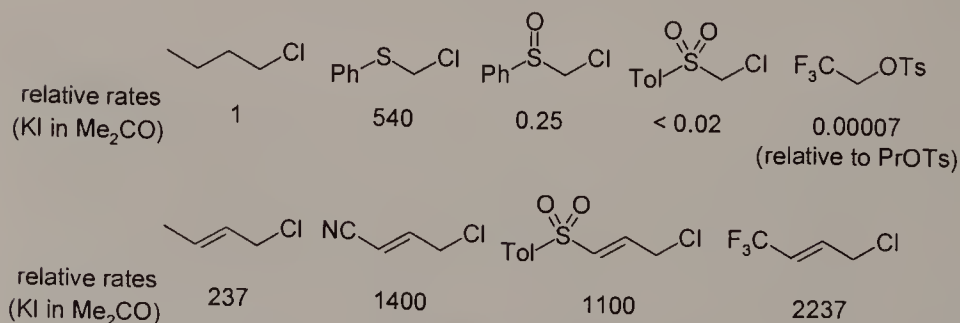
α -Sulfonyl [165] or α -trifluoromethyl halides [169] are, in contrast, much less reactive in S_N2 reactions than comparable, unsubstituted alkyl halides (Schemes 4.44 and 4.45). Fluorinated electrophiles of the type $C_nF_{(2n+1)}CH_2X$ are so unreactive [164, 169–176] that usually only thiolates or similarly powerful nucleophiles will be alkylated by them. If weaker nucleophiles have to be 2,2,2-trifluoroethylated, triflates [177] or phenyliodonium salts [178, 179] must usually be used to achieve acceptable reaction rates. Similarly, 2,2,2-trichloroethyl derivatives Cl_3CCH_2X react only sluggishly with nucleophiles [180] (Scheme 4.44).



Scheme 4.44. Substitution reactions at 2,2,2-trihaloethyl derivatives [180, 181].

If sulfonyl- or trifluoromethyl groups are separated from the reacting center by a vinyl group, however, a slight increase of the rate of $\text{S}_{\text{N}}2$ reactions relative to the unsubstituted allylic substrates is observed [182] (Scheme 4.45). This indicates that the rate-diminishing effect of sulfonyl- and trifluoroalkyl groups is probably due to steric or electrostatic effects [164, 169, 183], which are only active in close proximity to these groups and disappear in the corresponding vinylogous electrophiles. It has also been proposed that the $\text{S}_{\text{N}}2$ -inhibiting effect of the trifluoromethyl group is because of electrostatic repulsion between the nucleophile and the partial negative charge on the fluorine atoms [184].

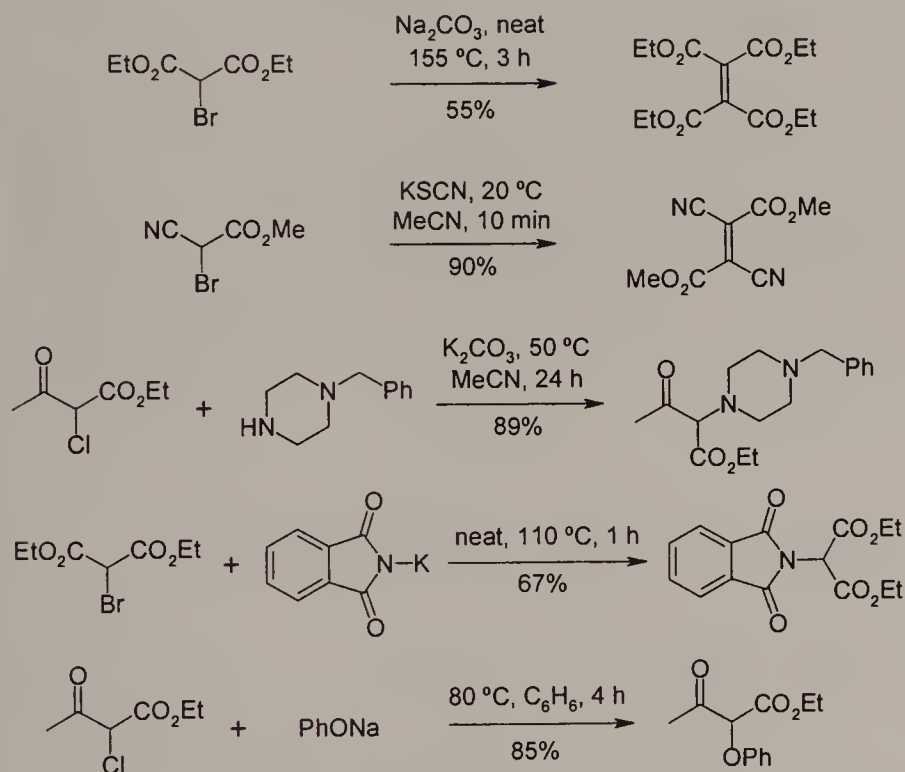
The enhanced reactivity of 3-cyano-, 3-sulfonyl-, and 3-(trifluoromethyl)allyl chlorides compared with that of allyl or 2-buten-1-yl chloride can also be explained by a mechanism analogous to that sketched in Scheme 4.43, in which the nucleophile

Scheme 4.45. Relative rates of $\text{S}_{\text{N}}2$ reactions [164, 165, 182].

first undergoes rapid addition to the electron-poor double bond and then displaces the leaving group by 1,2-migration [182].

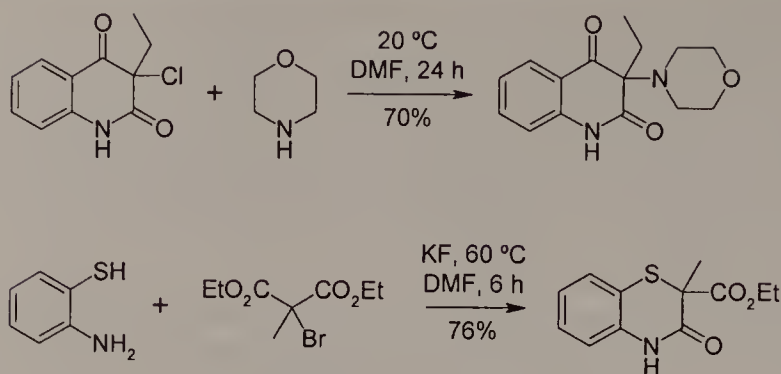
A frequent side reaction of electrophiles bearing electron-withdrawing groups is attack of the nucleophile at the leaving group and not at carbon [143]. This reactivity pattern is characteristic of 2,2-dihalo and 2-halomalonic acid derivatives [185] and α -nitroalkyl halides (Section 4.3.3.4), i.e. substrates in which the alkyl group is strongly C,H-acidic and, therefore, is itself a good leaving group. Tetrahalomethanes can also react in this way [154] (Scheme 4.38).

Halomalonic acid derivatives, 1-halo-1-nitroalkanes [186], and related electrophiles can, upon treatment with a base, also dimerize to yield substituted ethylenes, in the same way as nitrobenzyl halides (see above). The reaction conditions required for this dimerization do not differ much from those required for successful nucleophilic substitution (Scheme 4.46), and if substitution is desired a low concentration of the electrophile should be maintained during the reaction to minimize dimerization.



Scheme 4.46. Dimerizations and substitutions of electrophiles of type Z_2CHX [187–191].

Tertiary substrates of the type Z_2CRX can sometimes also undergo nucleophilic substitution (Scheme 4.47), although nucleophilic attack at the leaving group to yield the reduced electrophile (Z_2CHR) will often compete [192]. These reactions probably proceed via (destabilized) carbocations or via SET.

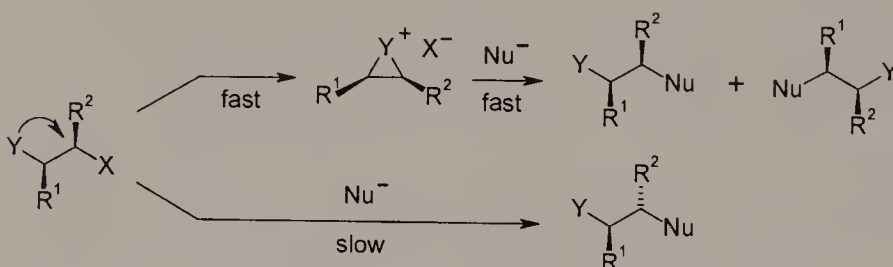


Scheme 4.47. Nucleophilic substitutions at substrates of type Z_2CRX [193–195].

4.3.6

Neighboring-group Participation

Heteroatoms with an unshared electron pair can enhance the S_N1 -reactivity of electrophiles not only when bound directly to the reacting carbon, but also when positioned further away. In such instances nucleophilic substitutions can occur with retention of configuration and/or rearrangement, because the substitutions are in fact two sequential S_N2 reactions proceeding via a cyclic intermediate (Scheme 4.48). The reactivity of such electrophiles will be increased by neighboring-group participation if both the cyclization and the reaction of the resulting intermediate with a nucleophile are faster than the direct S_N2 reaction of the starting material with the nucleophile.



Scheme 4.48. Nucleophilic substitution with neighboring-group participation.

Groups capable of enhancing the reactivity of electrophiles by neighboring-group participation include NR_2 , OR , SR , I , Cl , and Br , but phenyl groups, alkenes, alkynes, and $C-C$ σ bonds can also have this effect. The preferred ring sizes formed are three-, five-, and six-membered rings [196–200], although a few examples of four- [201] and seven-membered [202] rings have also been reported. Illustrative examples of substitutions at substrates with neighboring-group participation are sketched in Scheme 4.49. The last example in Scheme 4.49 proceeds via the base-induced formation of an epoxide.



participation [201, 203–208].

acceptable yields (see, e.g., Scheme 6.11).

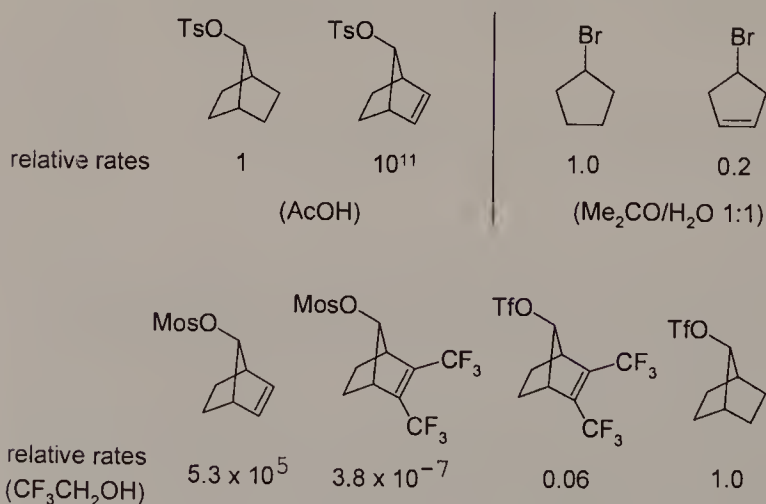
groups is observed only rarely.

	$\text{PhS-CH}_2\text{-Cl}$	$\text{PhS-CH}_2\text{-CH}_2\text{-Cl}$	$\text{PhS-(CH}_2)_3\text{-Cl}$	$\text{PhS-(CH}_2)_4\text{-Cl}$	$\text{PhS-(CH}_2)_5\text{-Cl}$
relative rates					
solvolysis in MeOH (relative to HexCl)	33 000	150	1.0	130	4.3
KI, Me ₂ CO (relative to BuCl)	540	0.79	3.1	1.8	1.4

Scheme 4.50. Relative rates of S_N1 and S_N2 reactions of chloroalkyl thioethers [164].

One example of neighboring-group participation without the formation of cationic intermediates is the aminolysis of 2-bromoethanols (last example, Scheme 4.49). In this instance epoxide formation and opening must be faster or as fast as direct bimolecular substitution of bromide by the amine; otherwise no rearranged product would be observed.

There are also instances in which neighboring groups reduce the reactivity of an electrophile. Thus, as shown in Scheme 4.50, the β -phenylthio group actually reduces the rate of S_N2 reactions compared with an ethyl group. As discussed above, electrophiles with one or more fluorine atoms in the β position are strongly deactivated toward nucleophilic substitution [169]. Similarly, the other halogens located β to the reaction center reduce the rate of bimolecular substitution reactions by approximately a factor of 3.6 [209]. Some homoallyl halides or electrophiles containing electron-deficient C–C double bonds can also react more slowly than comparable saturated compounds. Thus, although *anti*-7-tosyloxynorbornene solvolyzes (with retention of configuration) much faster than the corresponding norbornane, because of anchimeric assistance by the double bond [210], 4-bromocyclopentene is less reactive than bromocyclopentane [211] (Scheme 4.51). This surprising effect probably results from the high strain-energy of norbornenes. The energy required to force 4-bromocyclopentene into a suitable conformation for anchimerically assisted



Scheme 4.51. Relative solvolysis rates of norbornane and cyclopentane derivatives [210–212].

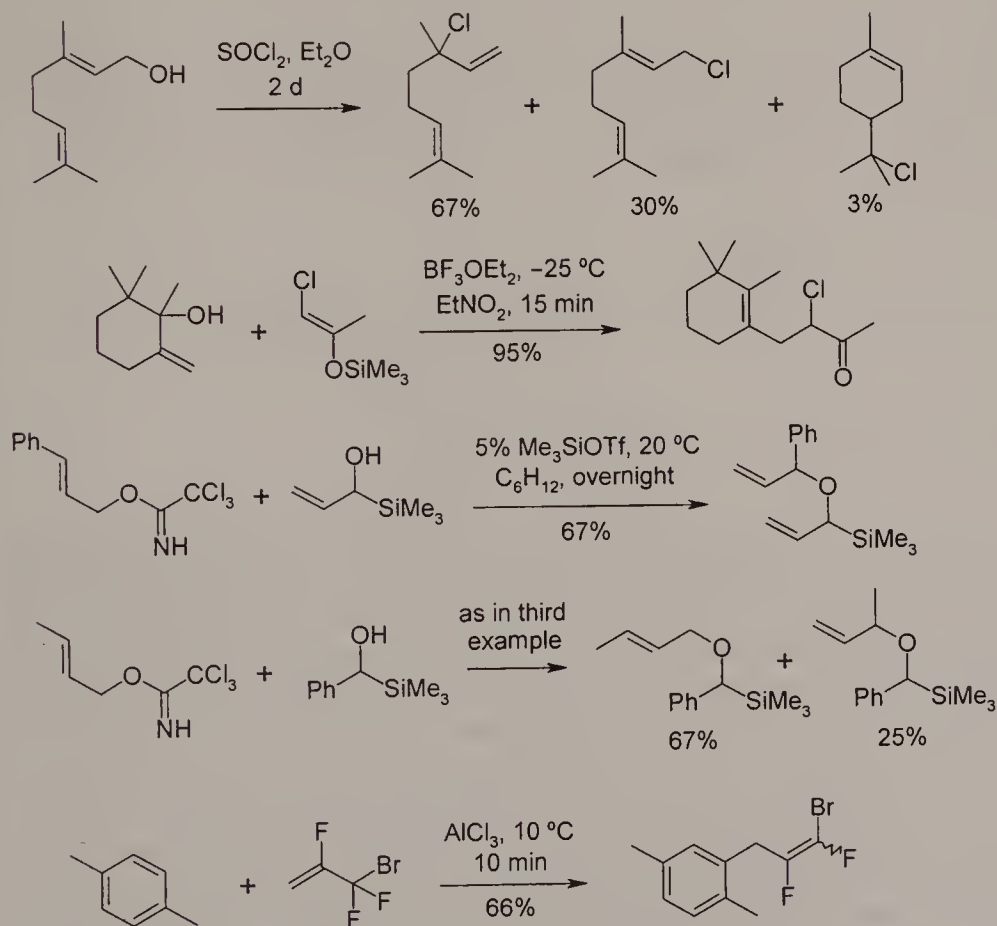
bromide displacement is larger than the activation energy for an unassisted S_N1 or S_N2 reaction [211]. Accordingly, neighboring-group participation of double bonds in flexible cyclic or non-cyclic substrates will usually have only a minor effect on reactivity.

The capacity of a homoallylic C-C double bond to assist nucleophilic displacements is, furthermore, a function of its electron density. Electron-withdrawing substituents at the alkene will reduce its electron-donating capability, and electron-deficient alkenes can even reduce the rate of nucleophilic displacements relative to the corresponding saturated compounds (Scheme 4.51).

4.3.7

Allylic and Propargylic Electrophiles

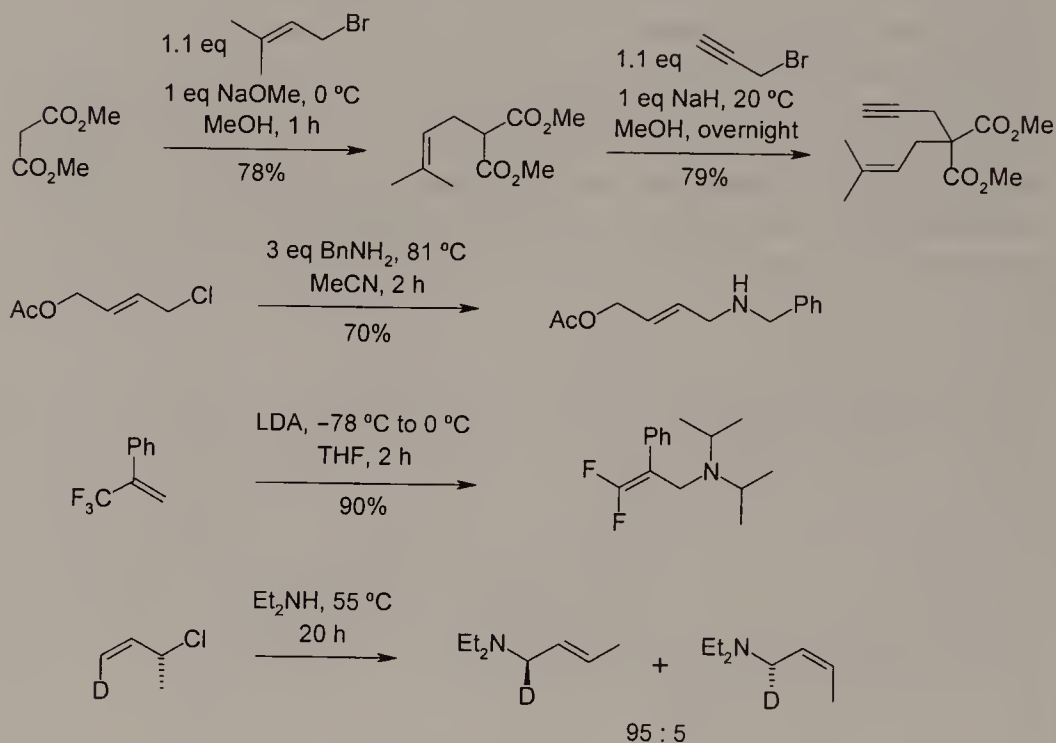
Allylic electrophiles can react with nucleophiles either with or without allylic rearrangement [213]. The outcome of such reactions will depend on whether or not an allylic carbocation is formed as intermediate, and on the steric requirement and hardness of the two electrophilic centers and the nucleophile. Bimolecular substitutions at allylic electrophiles which occur with rearrangement are called S_N2' reactions.



Scheme 4.52. S_N1 -type allylic substitutions [214–217].

In S_N1 -type substitutions the nucleophile will generally tend to add to the carbon which forms the better-stabilized carbocation, while avoiding too much steric crowding. The regioselectivity of such reactions is often difficult to predict and to control (Scheme 4.52).

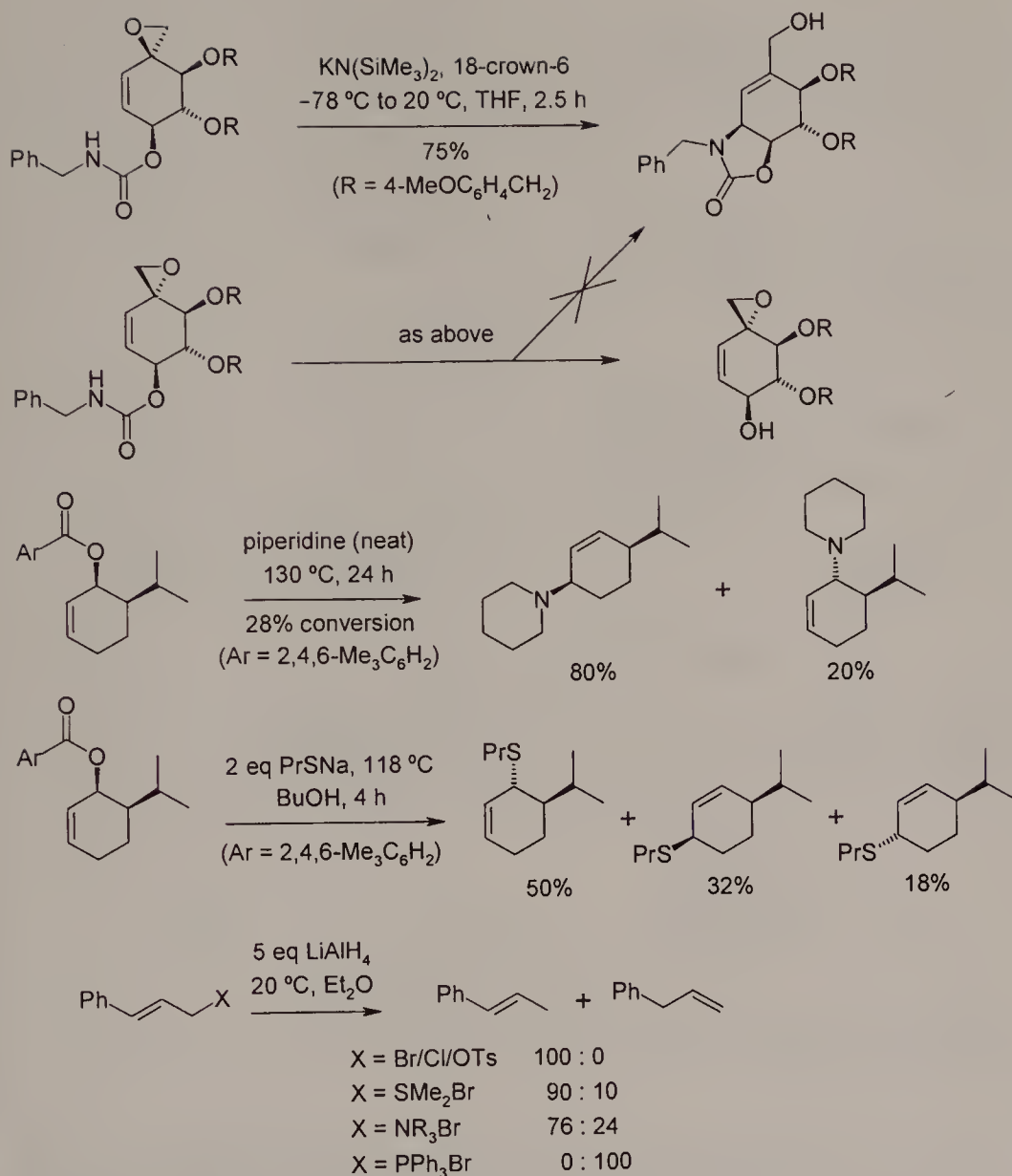
The regioselectivity of bimolecular allylic substitutions, on the other hand, is often easier to control, and can sometimes be reversed by slight modification of the starting materials or reaction conditions. In uncatalyzed, bimolecular substitutions the nucleophile will usually add to the sterically less demanding site of the allylic system (Scheme 4.53).



Scheme 4.53. S_N2 and S_N2' at allylic electrophiles [218–221].

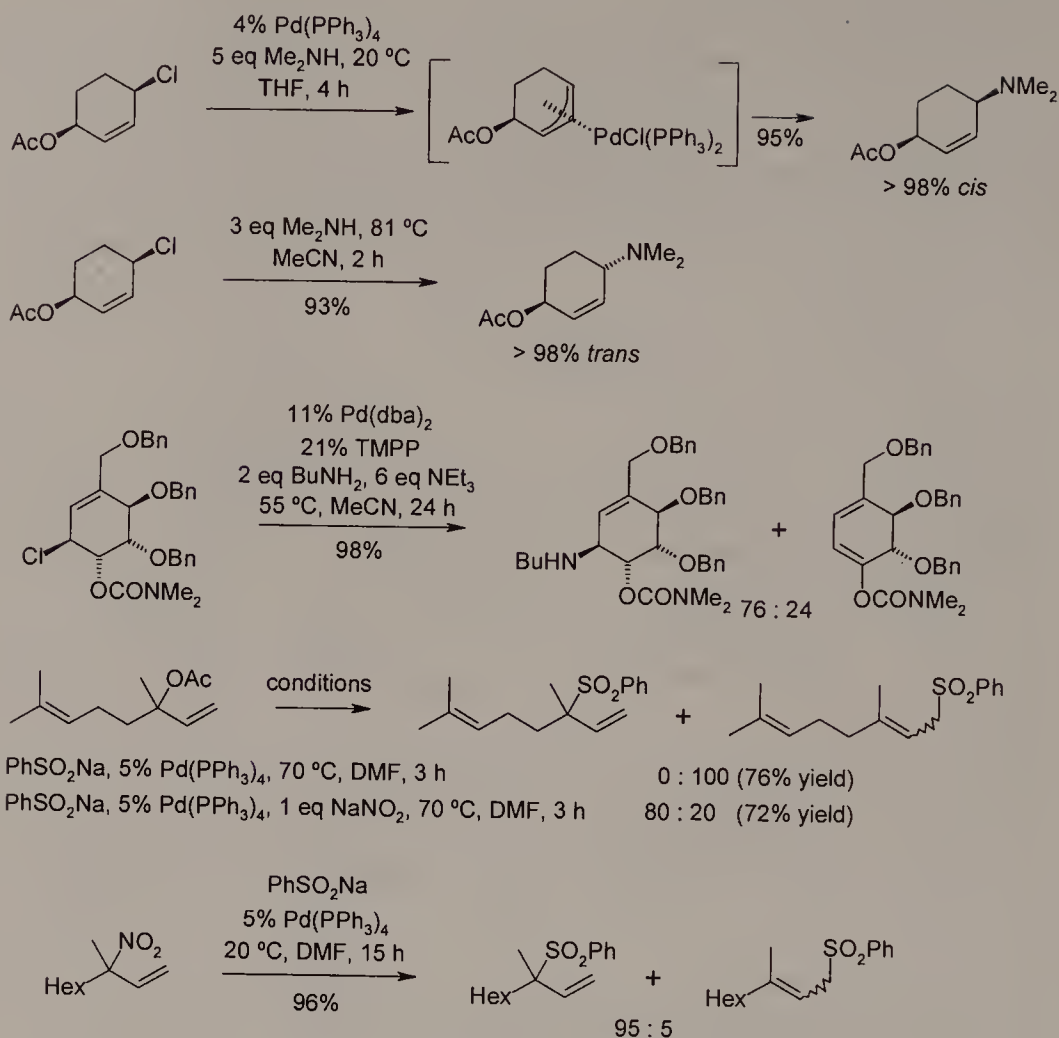
As shown by the last example in Scheme 4.53, S_N2' reactions can proceed with high stereoselectivity. During an S_N2' reaction the plane in which the alkene lies and the C–C–X plane are perpendicular to each other, and the nucleophile attacks the alkene preferentially from the side of the leaving group (first three reactions, Scheme 4.54). This is, however, not always so. Both regio- and stereoselectivity depend on the nucleophile, on the leaving group, and on the precise reaction conditions, and are not always easy to predict (Scheme 4.54).

Allylic electrophiles react readily with Pd(0) complexes to yield η^3 -allyl Pd(II) complexes, which retain electrophilic character and react with nucleophiles to yield the product of allylic substitution and Pd(0). Thus, catalytic amounts of Pd(0) provide an additional mechanism (in addition to S_N1 , S_N2 , and S_N2') by which an allylic substitution can proceed. Because the metal generally attacks the allylic electrophile



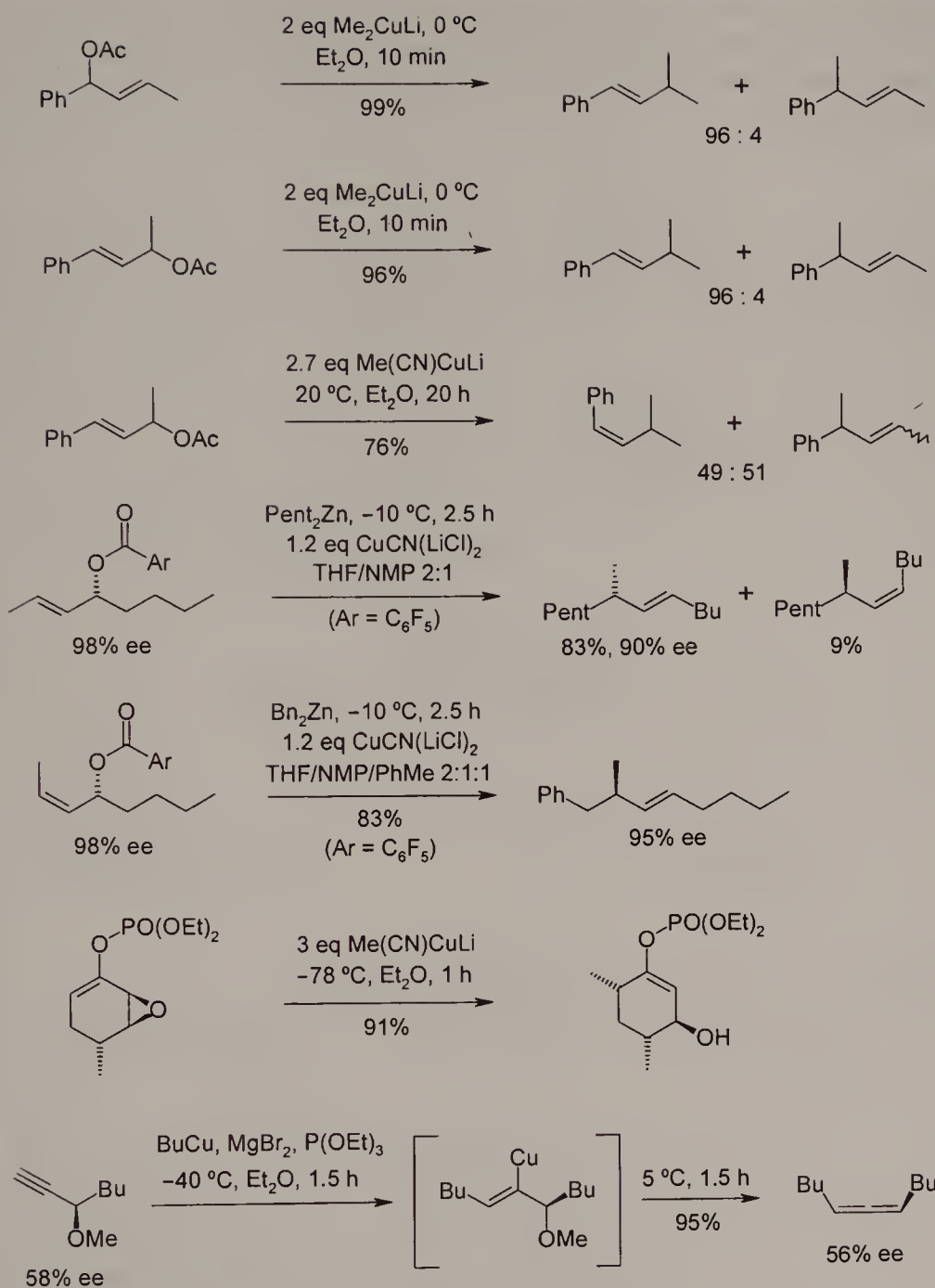
Scheme 4.54. Regio- and stereoselectivity of $\text{S}_{\text{N}}2'$ reactions [222–224].

from the side opposite to the leaving group, and is itself displaced by nucleophiles in the same fashion (Scheme 4.55) [225]. $\text{Pd}(0)$ -catalyzed allylic substitutions often proceed with overall retention of configuration. If the starting material or product can be isomerized by the catalyst, the thermodynamically most stable product will usually be isolated from $\text{Pd}(0)$ -catalyzed allylic substitutions. Thus, reaction of allylic acetates with sulfinate in the presence of $\text{Pd}(0)$ yields exclusively the thermodynamically most stable product (fourth reaction, Scheme 4.55). Isomerization of the product can be suppressed by addition of NaNO_2 (which deactivates the catalyst) or by using allylic nitro compounds as electrophiles which liberate nitrite during the course of the reaction [41].



Scheme 4.55. Uncatalyzed and Pd(0)-catalyzed S_N2 reactions at allylic substrates [41, 221, 226].

Organocopper reagents, being soft nucleophiles, often lead to S_N2' reactions when treated with allylic [227–229] or propargylic [230–232] electrophiles. Although highly stereoselective reactions with clean attack from the opposite side of the leaving group can be achieved [233] (Scheme 4.56), these reactions might still require careful optimization of the conditions to achieve high-yielding, stereoselective product formation, because the precise structure of the organocopper reagent and the solvent can have a decisive impact on the selectivity (Scheme 4.56).



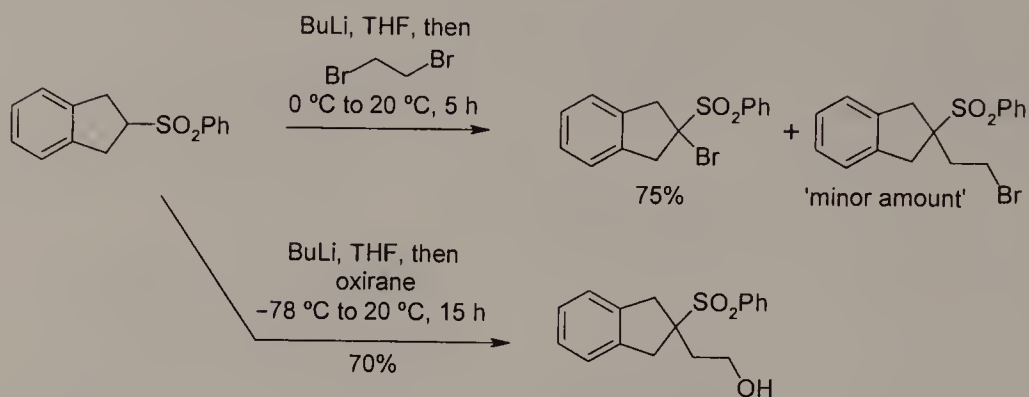
Scheme 4.56. Nucleophilic substitutions at allylic electrophiles with organocopper reagents [230, 234–237].

4.3.8

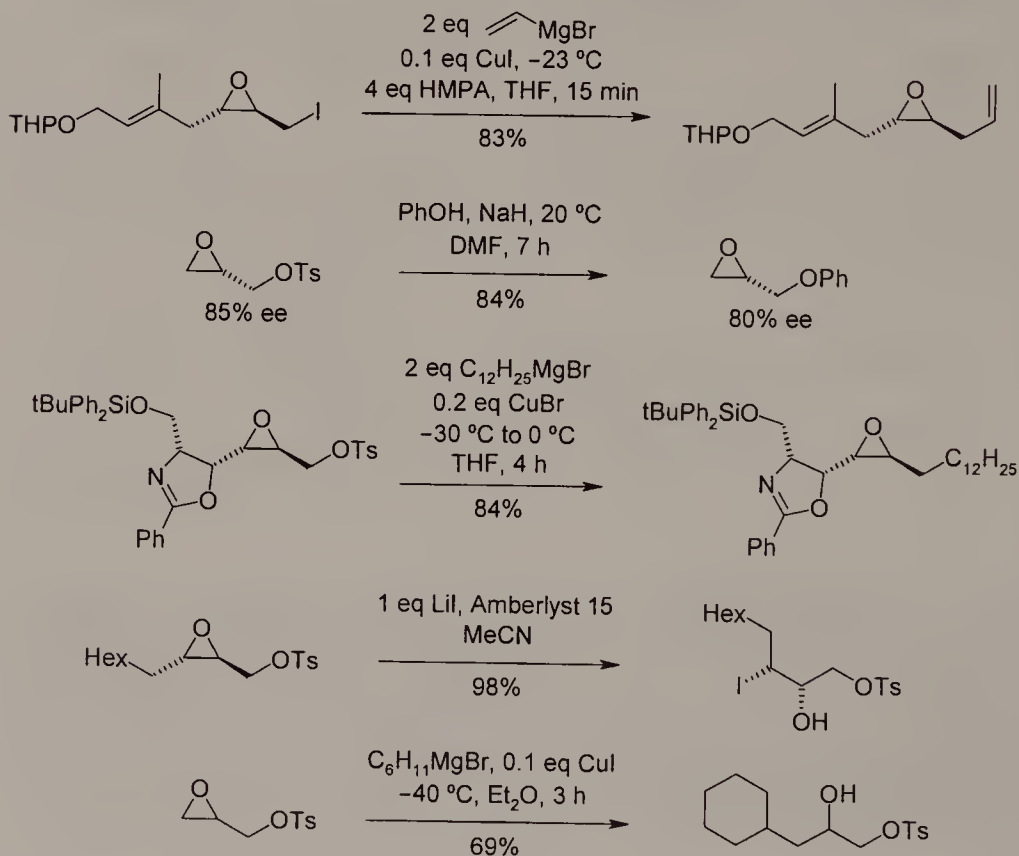
Epoxides

Epoxides are readily accessible, valuable synthetic intermediates. Because of the high ring strain, epoxides are much more reactive than ethers, and usually react swiftly with nucleophiles either under basic or acidic reaction conditions to yield

β -substituted ethanols. Epoxides are often superior to electrophiles such as 1,2-dihaloethanes or protected 2-haloethanols, because epoxides undergo fewer side reactions than these synthetically equivalent but often unreactive, alternative electrophiles (Scheme 4.57).



Scheme 4.57. Alkylations of a sulfone with 1,2-dibromoethane and oxirane [238].

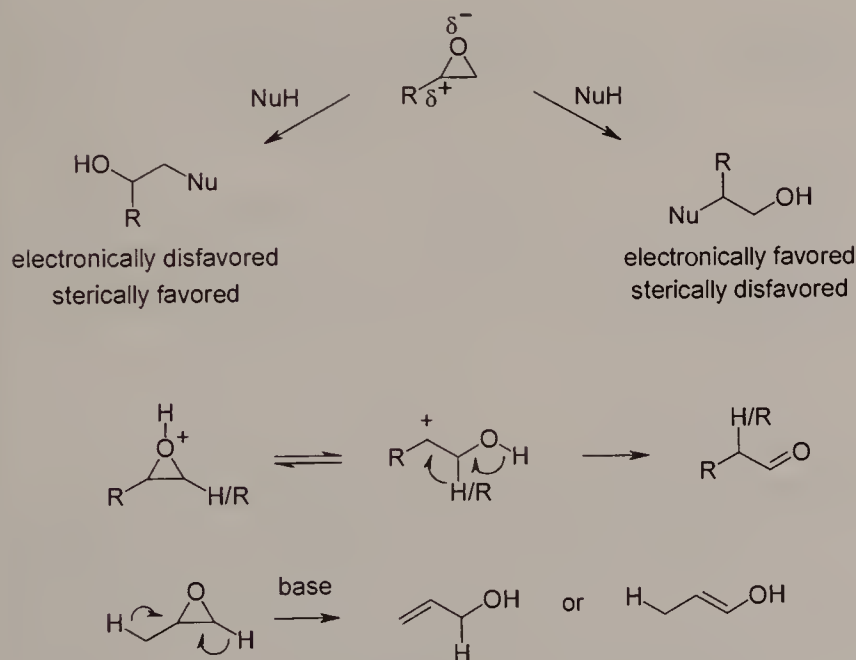


Scheme 4.58. Reactivity of epoxides vs sulfonates and other electrophiles [243–246]. All reactions required careful monitoring to avoid reaction of both electrophilic sites.

The reactivity of epoxides is similar to that of sulfonates. Compounds containing both an epoxide and a sulfonate can react at either of these functional groups with

nucleophiles, depending on the precise structure of the reacting partners (Scheme 4.58) [239]. In most of the reported reactions of carbon nucleophiles with sulfonate-containing epoxides the epoxide is cleaved first [240–243]. As illustrated by the second and third examples in Scheme 4.58, this is, however, not always true (see also Scheme 4.20).

Epoxides with two different substituents at C-2 and C-3 can yield, upon reaction with a nucleophile, two different alcohols. The regioselectivity of this reaction is governed mostly by steric but also by electronic factors [247]. Substituents which generally facilitate nucleophilic substitutions will also enhance the reactivity of the carbon atom of an epoxide to which they are attached. If the nucleophile is sterically demanding the outcome of a reaction can often be predicted, but not so for small nucleophiles. To make matters worse, groups which favor electronically the formation of one product often retard its formation by steric crowding (Scheme 4.59). Instead of reacting with a nucleophile to yield a β -substituted ethanol, epoxides can also undergo acid or base-mediated rearrangements (Scheme 4.59) or act as oxidants while themselves being reduced to alkenes.

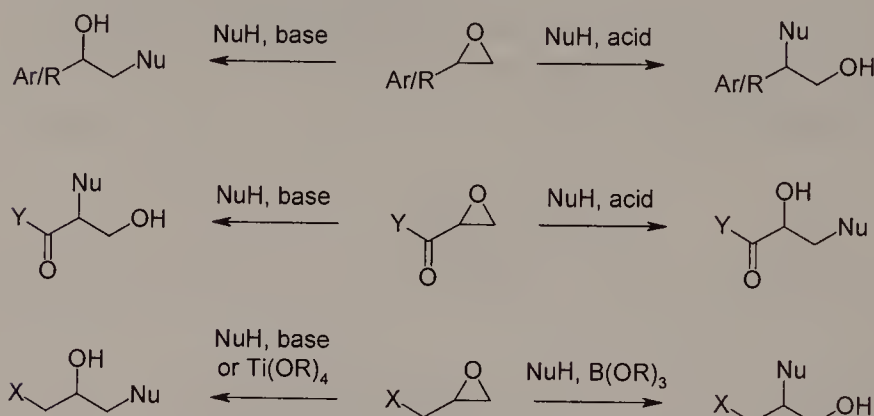


Scheme 4.59. Ring opening of epoxides by nucleophilic attack or acid or base-mediated rearrangement. R = carbocation-stabilizing, sterically demanding group.

Rough guidelines for the prediction of regioselectivity in epoxide ring openings are summarized in Scheme 4.60. Under neutral or basic reaction conditions alkyl- or aryl-substituted epoxides react with most nucleophiles at the less substituted carbon atom [248–253]. Under acidic reaction conditions, however, product mixtures or preferential attack at the most substituted carbon atom can be observed. Acids can usually be used to enhance the reactivity of epoxides and to promote substitution at the site of an epoxide which forms a carbocation more readily.

Epoxides bearing a carbonyl group or vinylogous analogs of such compounds react with nucleophiles under neutral or basic reaction conditions usually at the carbonyl group-bearing carbon atom. This observation is in accord with the increased reactivity of α -halo carbonyl compounds discussed above (Section 4.3.5). Because of the destabilization of carbocations by carbonyl groups, acidic conditions will favor substitution at the non-carbonyl-substituted carbon atom.

Heteroatoms with higher electronegativity than carbon (e.g. nitrogen, oxygen, or the halogens) inductively destabilize carbocations at the β position. Epoxides of the type shown in the last equation of Scheme 4.60 therefore react preferentially at the unsubstituted carbon atom. Only in the presence of certain Lewis acids, capable of chelate formation with simultaneous activation of the substituted carbon atom, is the alternative regiochemistry observed.



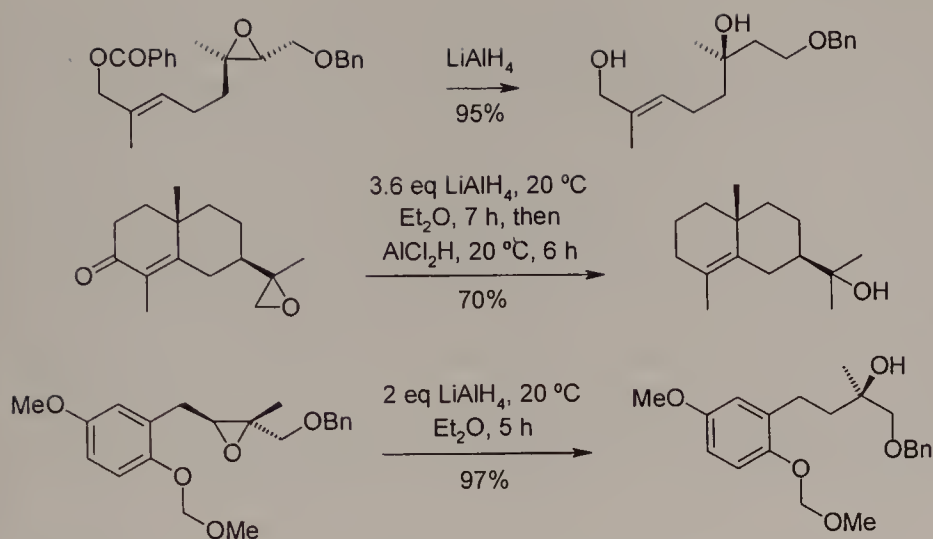
Scheme 4.60. Typical regioselectivity of the ring opening of epoxides. $\text{Y} = \text{Ar}$, R , NR_2 , OR ; $\text{X} = \text{NR}_2$, OR , Hal .

4.3.8.1 Epoxide Opening by Hydride

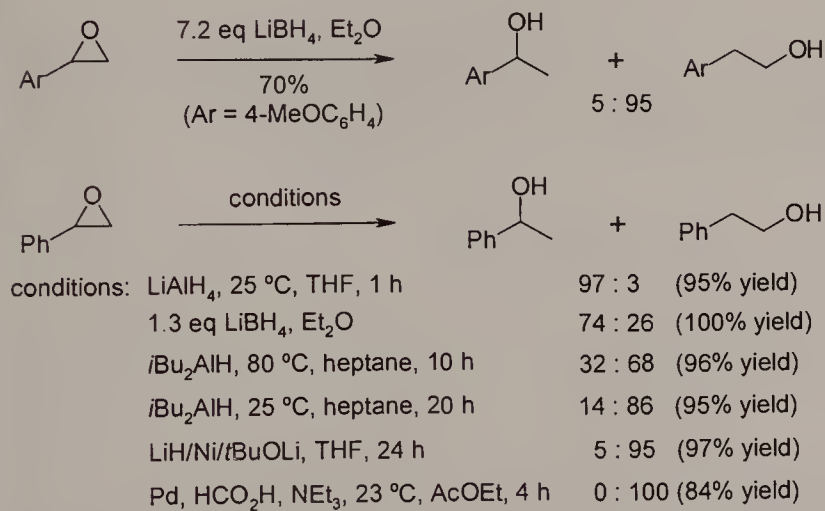
Treatment of epoxides with reducing agents can lead to the formation of either an alkene or an alcohol. Reducing agents such as phosphorus derivatives [254], R_3SiI [255], and some metals [185, 256] can convert epoxides into alkenes, whereas hydrogen in the presence of a catalyst or hydride-donating reagents generally only cleave one C–O bond of epoxides to yield alcohols. If nucleophilic attack of hydride at the least substituted carbon atom is desired, LiAlH_4 in ethers can be a suitable reagent (Scheme 4.61).

Styrene oxides can be reduced selectively to either 2-arylethanols or 1-arylethanols. Attack of hydride at the non-benzylic carbon atom can sometimes be achieved with LiAlH_4 , but most reducing agents, in particular under acidic reaction conditions, will lead to cleavage of the benzylic C–O bond (Scheme 4.62).

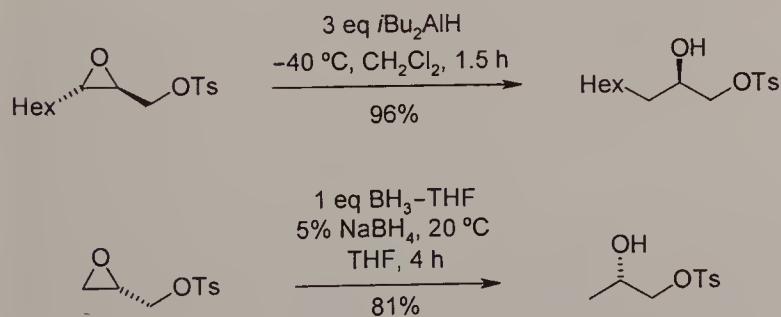
Epoxides with an oxymethyl substituent (RO-CR_2) usually react with nucleophiles at the non-oxymethyl-substituted carbon atom, because of the carbocation-destabilizing effect of this group. This is also observed for hydride as nucleophile, as illustrated by the examples in Scheme 4.63.



Scheme 4.61. Reductive ring opening of epoxides [257–259].



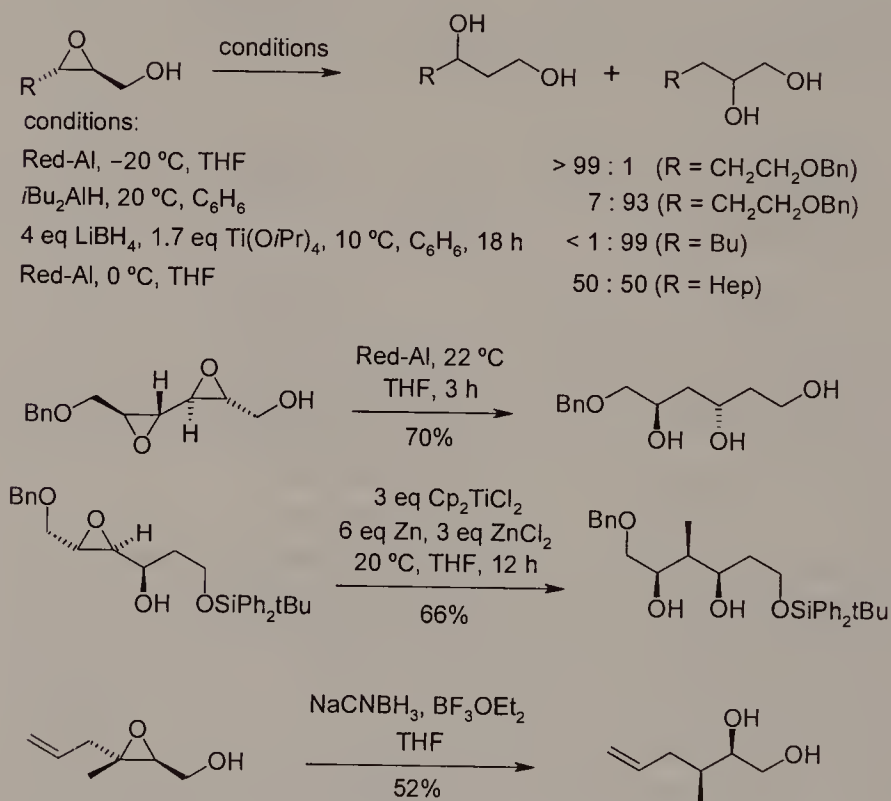
Scheme 4.62. Reductive ring opening of styrene oxides [250, 260–262].



Scheme 4.63. Reductive ring opening of tosyloxymethyl epoxides [243, 263].

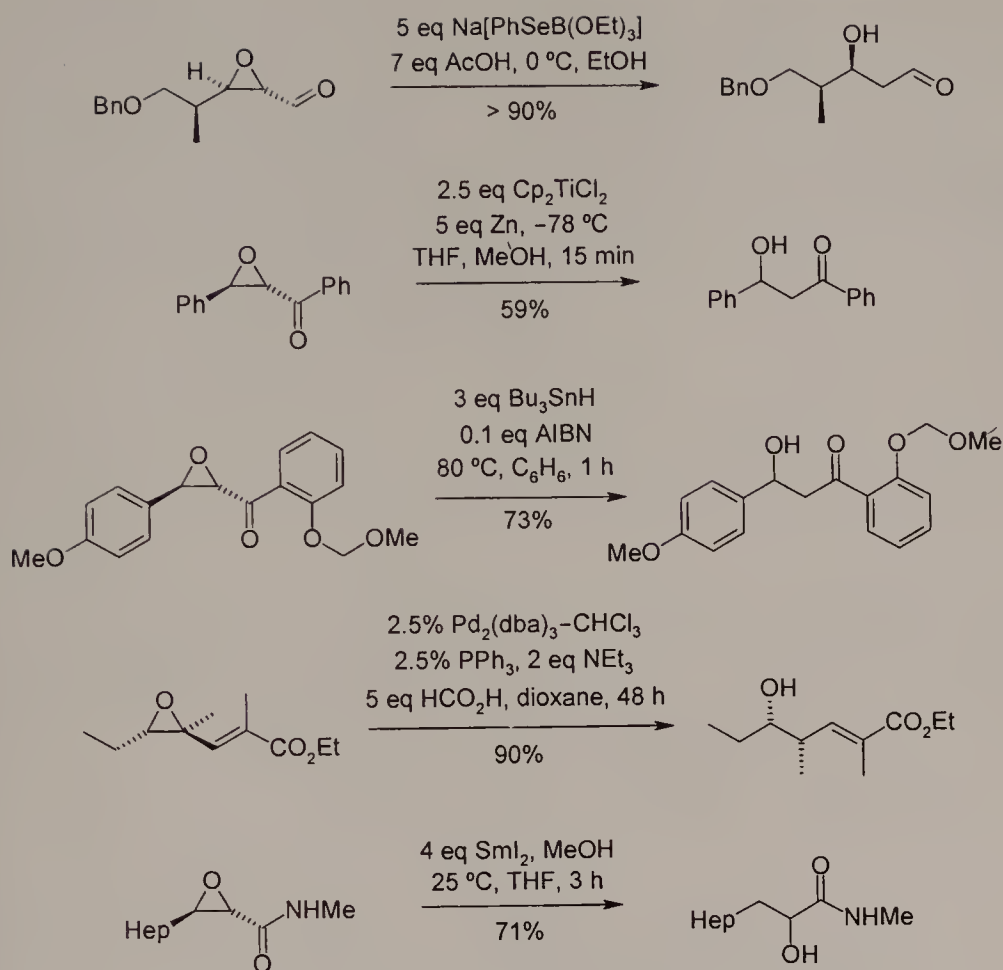
Hydroxymethyl epoxides can be reduced to yield either 1,2- or 1,3-diols. The regioselectivity of this reaction is critically dependent on the structure of the epoxide and on the precise reaction conditions, as illustrated by the examples in Scheme 4.64. Titanium(IV) alcoholates promote attack of hydride at C-3 [264] (to yield 1,2-diols), as does $i\text{Bu}_2\text{AlH}$ in non-coordinating solvents such as benzene, hexane, or dichloromethane [265, 266]. Pure 1,3-diols can be obtained by treatment of hydroxymethyl epoxides with LiAlH_4 or Red-Al ($(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{AlH}$) in THF [259, 267, 268], or by single-electron transfer with Cp_2TiCl_2 [269] (Scheme 4.64).

Treatment of hydroxymethyl epoxides with $\text{NaCNBH}_3/\text{BF}_3\text{OEt}_2$ usually leads to attack of hydride at the most highly substituted carbon atom and preferentially to the formation of 1,2-diols (last example, Scheme 4.64). If in a given epoxide cleavage of the C–O bond to the most highly substituted carbon atom leads to formation of a 1,3-diol, mixtures of products can result from use of this reagent [270].



Scheme 4.64. Reduction of hydroxymethyl epoxides [264, 266, 267, 269, 271].

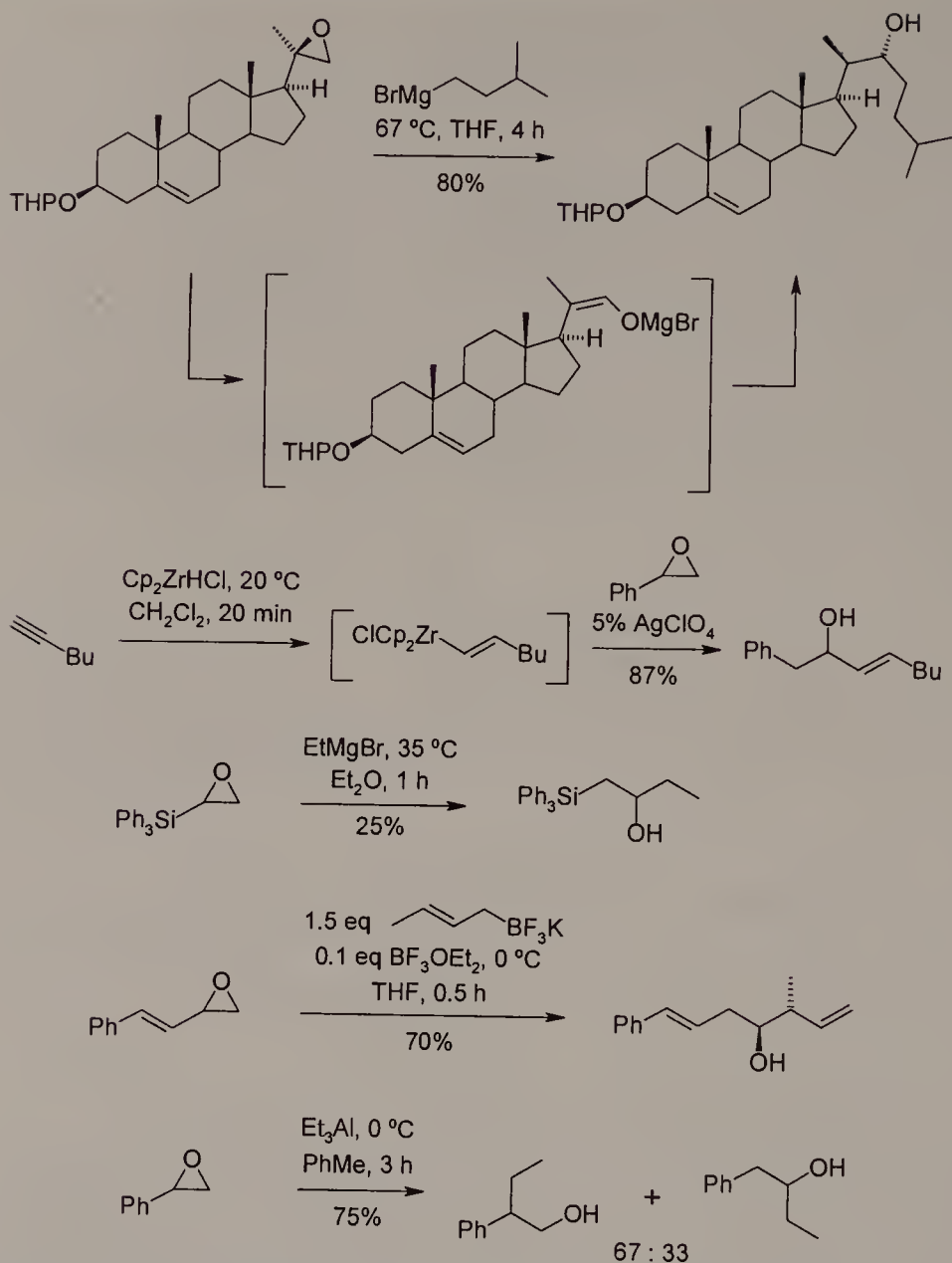
In epoxides substituted with electron-withdrawing groups the C–O bond closest to the electron-withdrawing group will usually be cleaved (Scheme 4.65) [272–274]. This is also observed for reductions proceeding via radicals [273]. Reductions with SmI_2 in methanol, however, can lead to reversal of this regioselectivity with some substrates (last reaction, Scheme 4.65) [275].



Scheme 4.65. Regioselective reductive ring opening of epoxides substituted with electron-withdrawing groups [275–279].

4.3.8.2 Epoxide Opening by Carbon Nucleophiles

Organometallic compounds such as Grignard reagents, organolithium compounds, cuprates, or enolates can react with epoxides to yield 2-substituted ethanol. Because epoxides can rearrange to carbonyl compounds when treated with bases or acids under rather mild conditions [280–288] (e.g. upon treatment with LiClO₄ [289], MgBr₂ [290], or lithium halides [291]), the type of organometallic reagent used can be of critical importance to the outcome of such reactions. Strongly basic organometallic compounds, such as organolithium or Grignard reagents, usually lead to rapid isomerization of epoxides to enolates [292] or to allyl alcoholates. If isomerization to a ketone or aldehyde is more rapid than addition of the organometallic reagent to the epoxide, the main product can result from addition to the newly formed carbonyl compound (Scheme 4.66). Highly substituted epoxides are particularly prone to such transformations. Rearrangements such as those shown in Scheme 4.66 can sometimes be suppressed by addition of bases (e.g. PPh₃ or Me₂S [293]) to the reaction mixture.



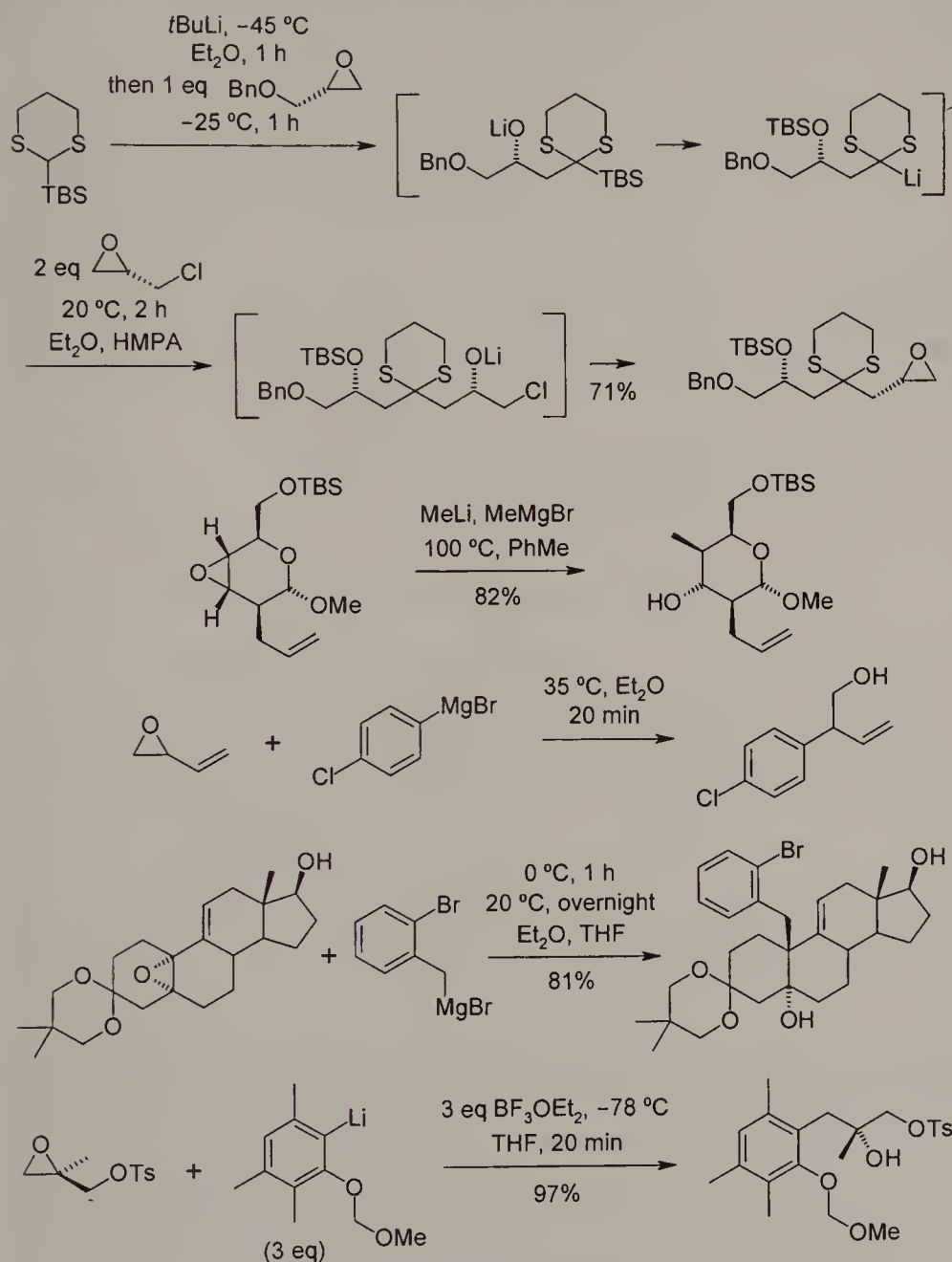
Scheme 4.66. Rearrangement of epoxides followed by addition of organometallic reagents [284, 290, 293–295].

Although the reactivity of epoxides toward organometallic reagents can be enhanced by the addition of Lewis acids [241, 243, 251, 296], this can also lead to cleavage of other ethers present in the reaction mixture, for example THF or Et_2O [238, 240]. Strong Lewis acids, for example trityl cations [297], can also enhance the amount of products resulting from rearranged epoxides.

Few types of epoxide react with Grignard or organolithium reagents in the absence of catalysts without rearrangement. These include oxirane, which has been extensively used to transform these organometallic reagents into 2-substituted

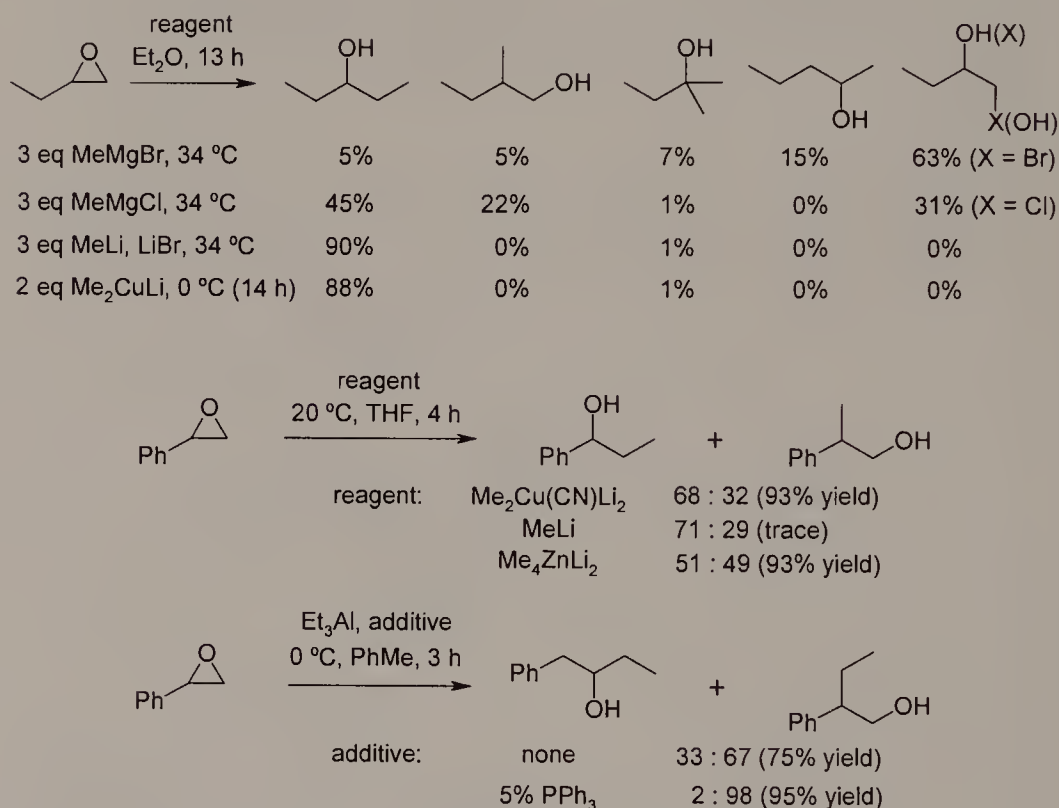
ethanols [298, 299], and oxymethyl oxirane derivatives (e.g. glycidol derivatives) [300, 301], which are also quite resistant toward rearrangement. Other epoxides, however, react only slowly with Grignard or related reagents, and tend to give poor yields of 2-substituted ethanols [302, 303].

Carbon nucleophiles which do not readily trigger the rearrangement of epoxides include lithiated dithianes [295, 304], lithiated sulfones [238], lithiated diarylphosphine oxides [240, 305], lithium enolates [306], and allylic organolithium or organomagnesium compounds [298, 307–310] (Scheme 4.67).



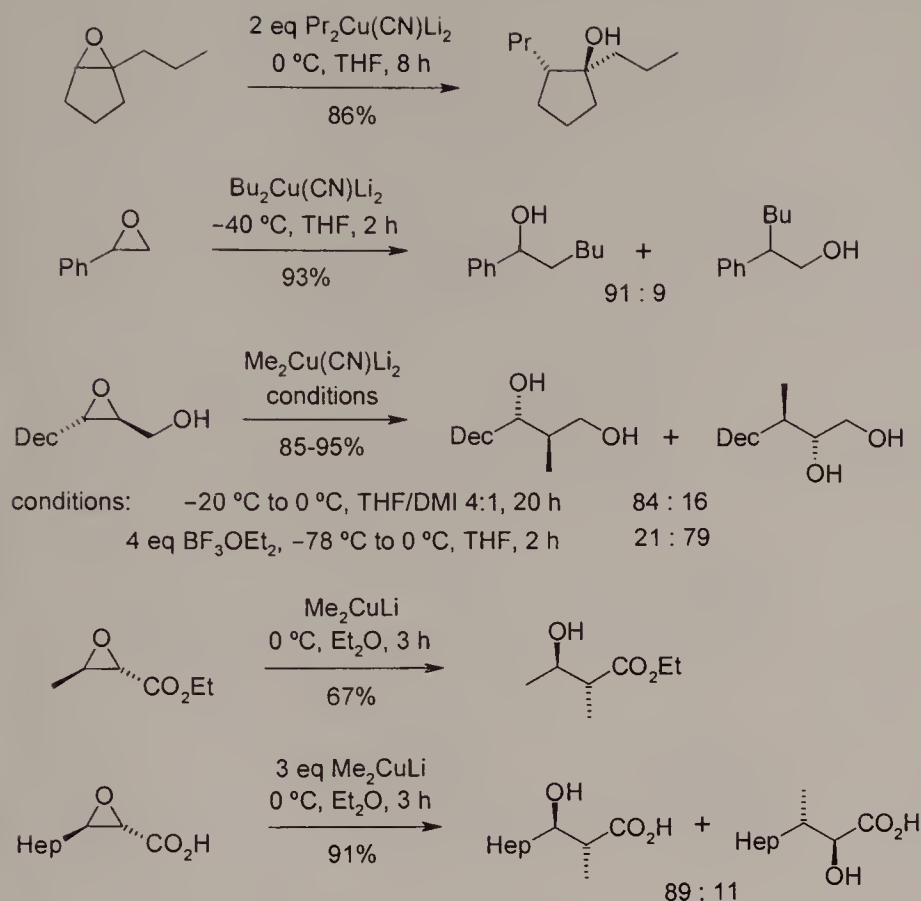
Scheme 4.67. Reaction of epoxides with organolithium and Grignard reagents [296, 310–313].

Consistently better results are obtained when organocopper reagents, rather than Grignard or organolithium reagents, are used for the ring opening of epoxides [314–317]. Cuprates are softer and less basic than the latter, and usually add to epoxides before rearrangement can occur. With vinyl epoxides conjugate addition of the organocopper reagent to the double bond is often (but not always) observed [227, 318]. Other organometallic reagents with a high tendency to yield 2-substituted ethanol on reaction with epoxides are organoaluminum [319], organozinc [320, 321], allyltitanium [322], and allylindium compounds [323]. To illustrate the reactivity of these reagents, the reactions of ethyl oxirane and styrene oxide with a selection of organometallic reagents are shown in Scheme 4.68.



Scheme 4.68. Reactions of ethyl oxirane and styrene oxide with a variety of organometallic reagents [293, 302, 320].

The regioselectivity of epoxide ring opening by organometallic reagents depends to a large extent on the type of metal chosen. If the organometallic reagent is soft (cuprates, allylic organometallic reagents, enolates) the regioselectivity is mainly controlled by steric effects. Hard organometallic compounds containing metals with a high affinity for oxygen or which are strongly Lewis-acidic will preferentially attack the most polarized C–O bond of an epoxide. As illustrated by the examples shown in Scheme 4.69, organocopper reagents usually attack epoxides at the sterically less demanding site, or at the position which would undergo S_N2 reaction most easily.

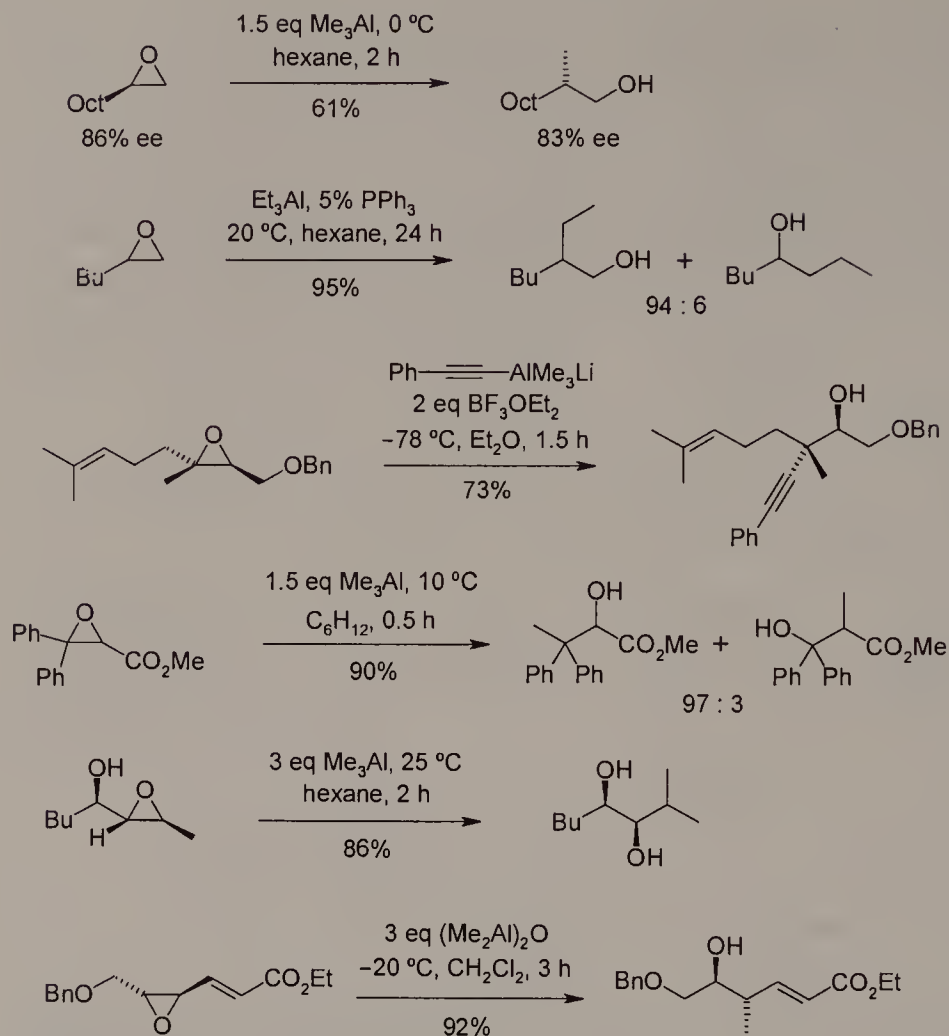


Scheme 4.69. Addition of organocupper reagents to epoxides [303, 314, 316, 317].

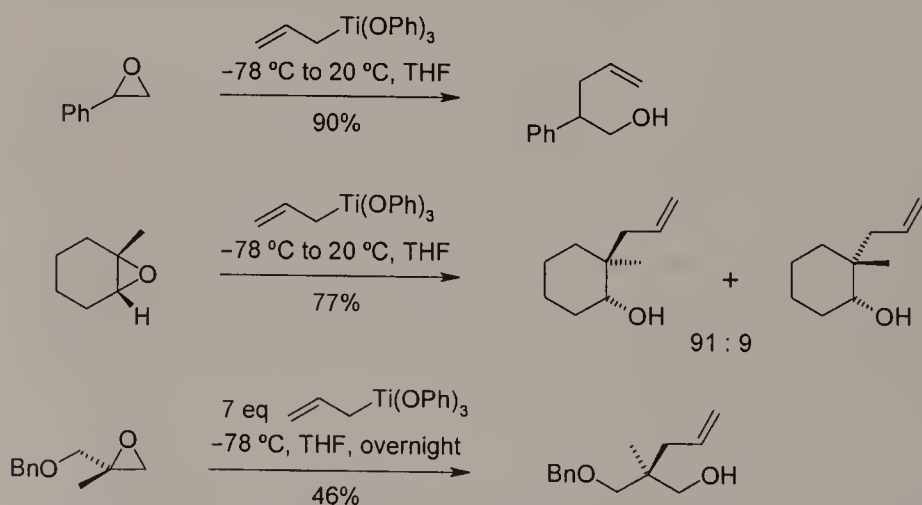
Treatment of epoxides with organoaluminum compounds[293] or other Lewis-acidic organometallic reagents can lead to nucleophilic attack at the most highly substituted carbon atom. Thus, as shown in Scheme 4.68, the regioselectivity of styrene oxide opening is reversed when using an organoaluminum reagent instead of a cuprate. Further examples are sketched in Scheme 4.70.

The reactivity of organotitanium compounds is similar to that of organoaluminum compounds, and attack at the most polarized C–O bond is usually observed (Scheme 4.71). The lack of stereoselectivity of the second example in Scheme 4.71 suggests the intermediate formation of carbocations or radicals.

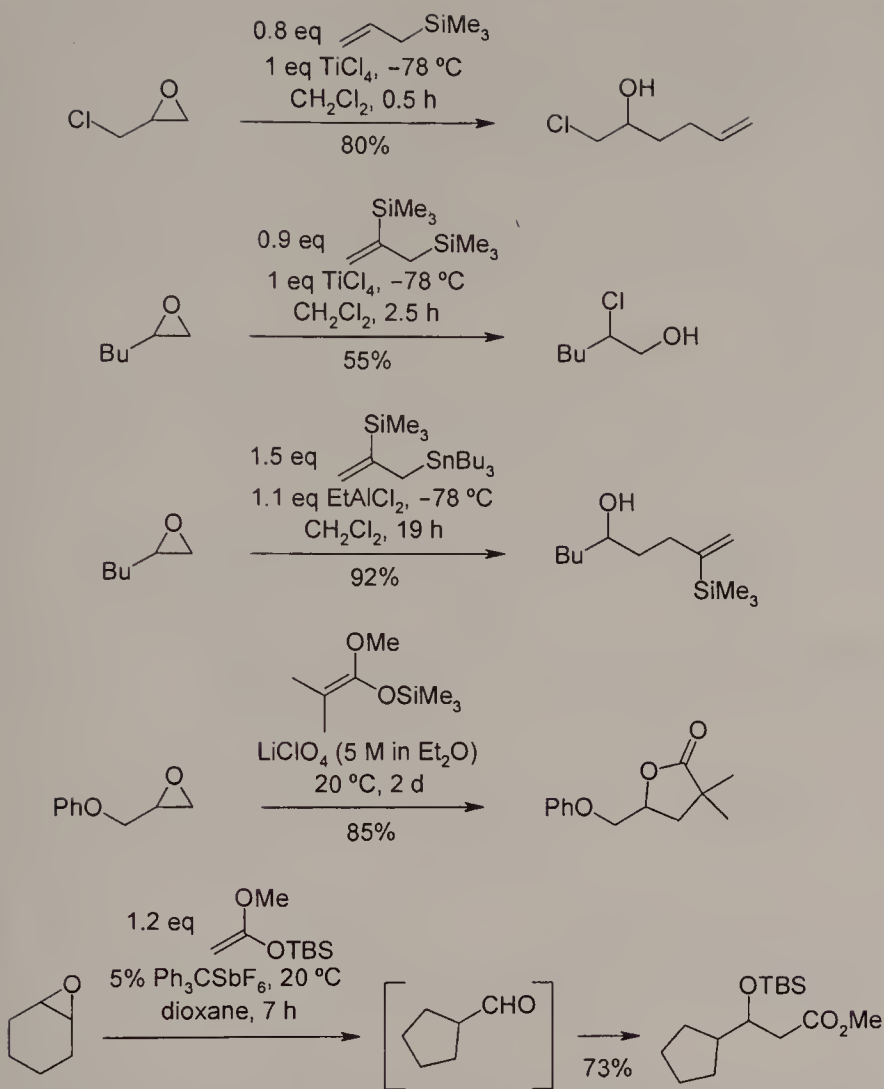
In the presence of Lewis acids allyl silanes and stannanes react with epoxides generally at the sterically less demanding carbon atom. Other electron-rich alkenes, such as ketene acetals, can also be used as nucleophiles. The strong Lewis acids required might, however, also lead to rearrangement of the epoxide before addition of the nucleophile can occur (last reaction, Scheme 4.72).



Scheme 4.70. Addition of organoaluminum reagents to epoxides [293, 319, 324–326].



Scheme 4.71. Addition of organotitanium reagents to epoxides [322, 327].

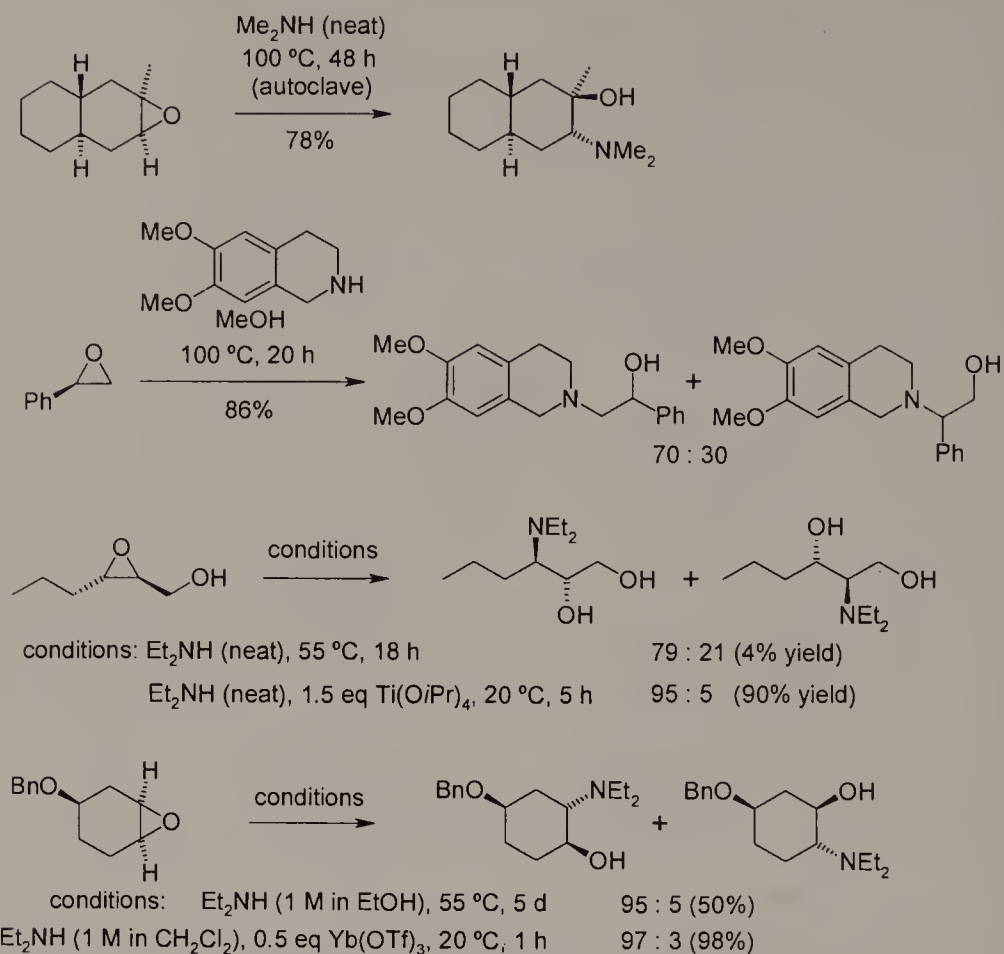


Scheme 4.72. Reaction of epoxides with allyl silanes, allyl stannanes, and silylenol ethers [297, 308, 309, 328].

4.3.8.3 Epoxide Opening by Amines

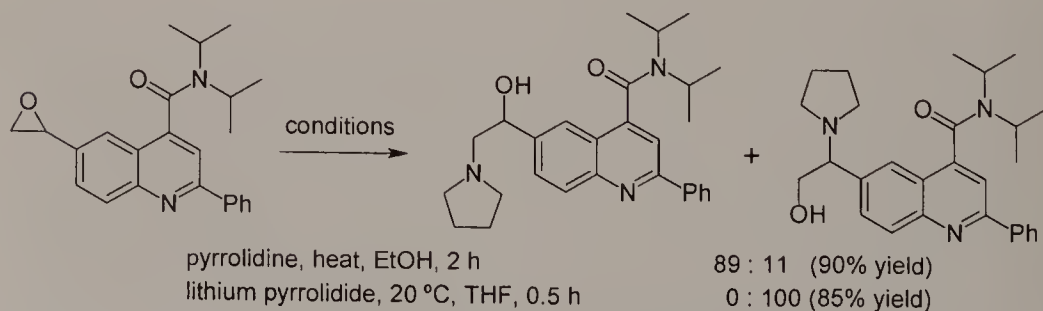
Amines usually react with epoxides at the less substituted carbon atom (Scheme 4.73) [329, 330]. With sterically demanding reaction partners these reactions will often proceed slowly or, as with tetraalkyl epoxides, not at all [252, 331]. Higher reaction rates can be achieved by increasing the concentration of the reactants, by using lithium amides as nucleophiles [332], or by catalysis with Lewis acids [252, 333] or Brønsted acids [334]. Ammonia can also be alkylated by 2,3-dialkyl epoxides (80°C , 15–60 h [335]). Hydroxymethyl epoxides (but not alkoxymethyl epoxides) can be activated toward nucleophilic attack by amines by use of stoichiometric amounts of $\text{Ti}(\text{OiPr})_4$ [336] (third example, Scheme 4.73).

The regioselectivity of epoxide ring opening by amines can occasionally be modified by using a lithium amide instead of the amine. In the example sketched in



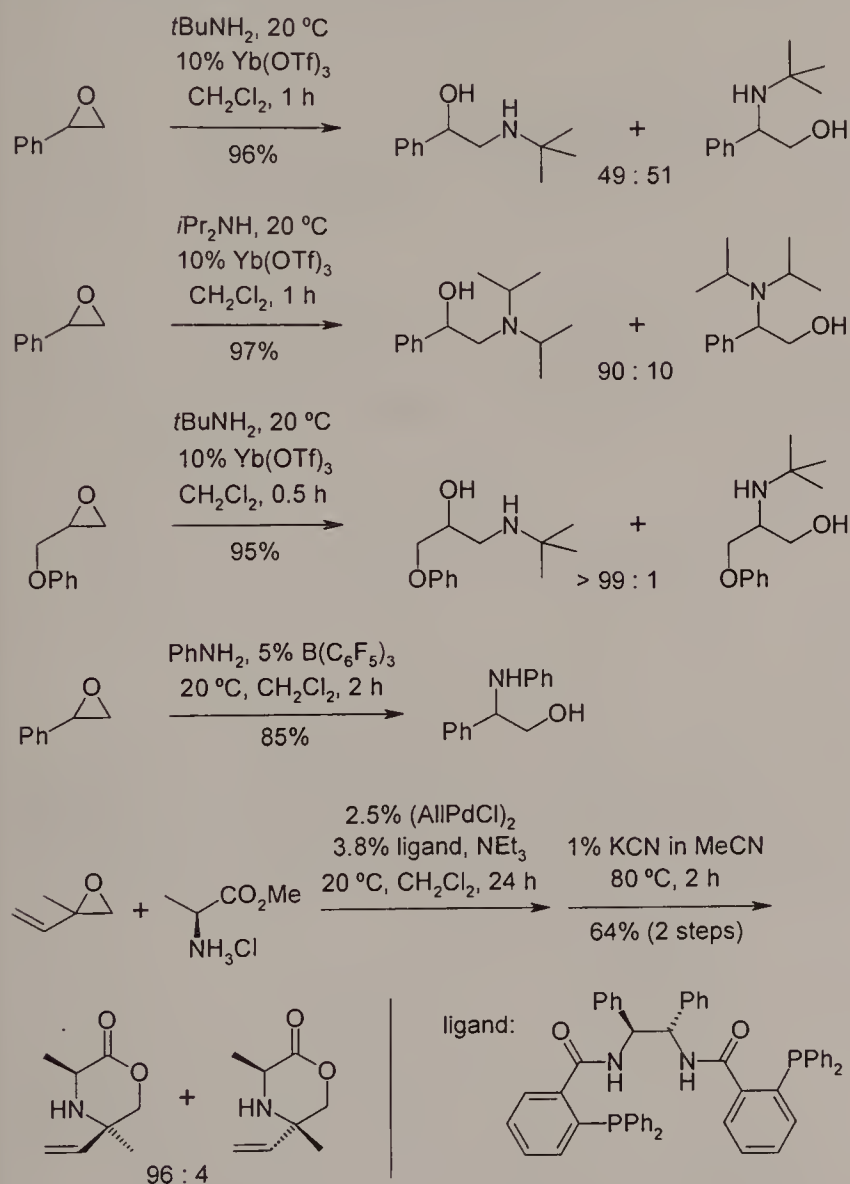
Scheme 4.73. Reactions of epoxides with amines [252, 336–338].

Scheme 4.74 complete reversal of regioselectivity is observed when highly basic lithium amides are used as nucleophiles. Activation of the benzylic C–O bond by chelate formation of Li^+ with the oxirane and the carbonyl group has been proposed as a possible reason for this unexpected reversal of regioselectivity [332].



Scheme 4.74. Reagent-controlled regioselectivity of epoxide ring opening with amines [332].

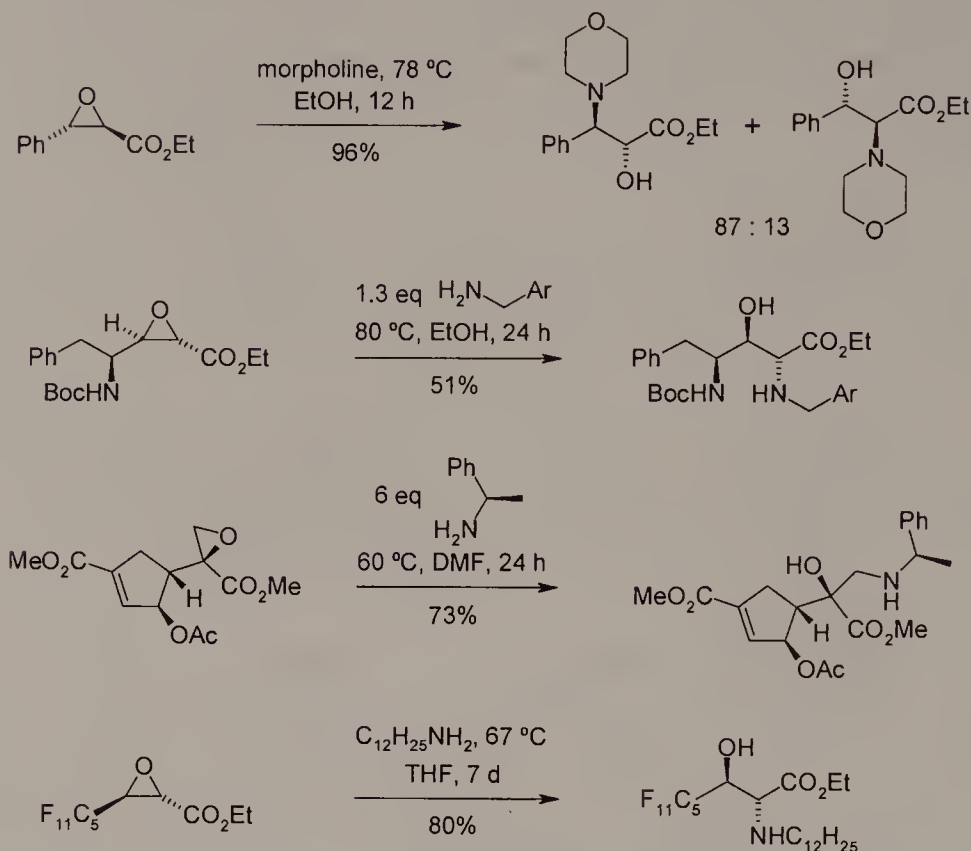
Catalysis by acids, which is only rarely effective for aliphatic amines but better suited to the less basic aromatic amines [334], can promote nucleophilic attack at the most strongly polarized C–O bond of the epoxide (Scheme 4.75) [333, 334, 339]. Vinyl epoxides react with amines in the presence of Pd(0) under mild conditions to yield allylamines [340]. If such reactions are performed in the presence of an enantiomerically pure ligand, racemic vinyl epoxides can be converted into enantiomerically enriched products of nucleophilic ring opening (last example, Scheme 4.75).



Scheme 4.75. Catalyzed reaction of epoxides with amines [252, 340, 341].

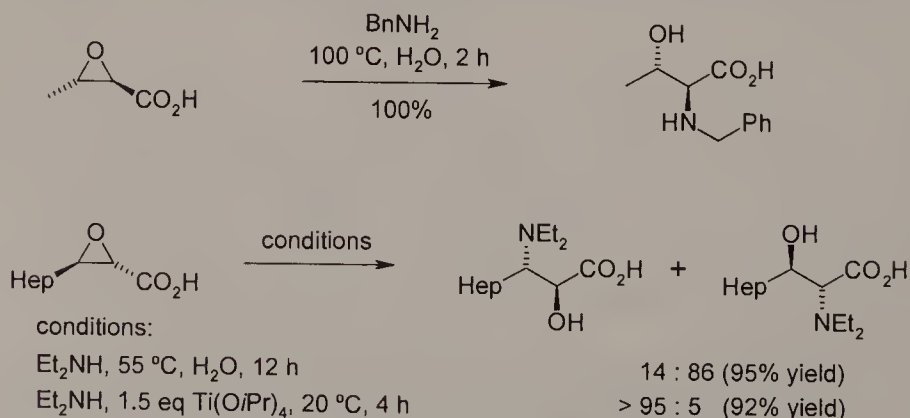
The alkoxycarbonyl group does not have a strong directing effect on the ring opening of epoxides by amines (Scheme 4.76), and steric or electronic effects of the other substituents can be more important to the outcome of these reactions. The

regioselectivity of the last reaction in Scheme 4.76 is dominated by the perfluoroalkyl group, which strongly inhibits nucleophilic attack at the carbon atom to which it is attached (see Section 4.3.5).



Scheme 4.76. Reactions of amines with alkoxy carbonyl-substituted epoxides [342–345].

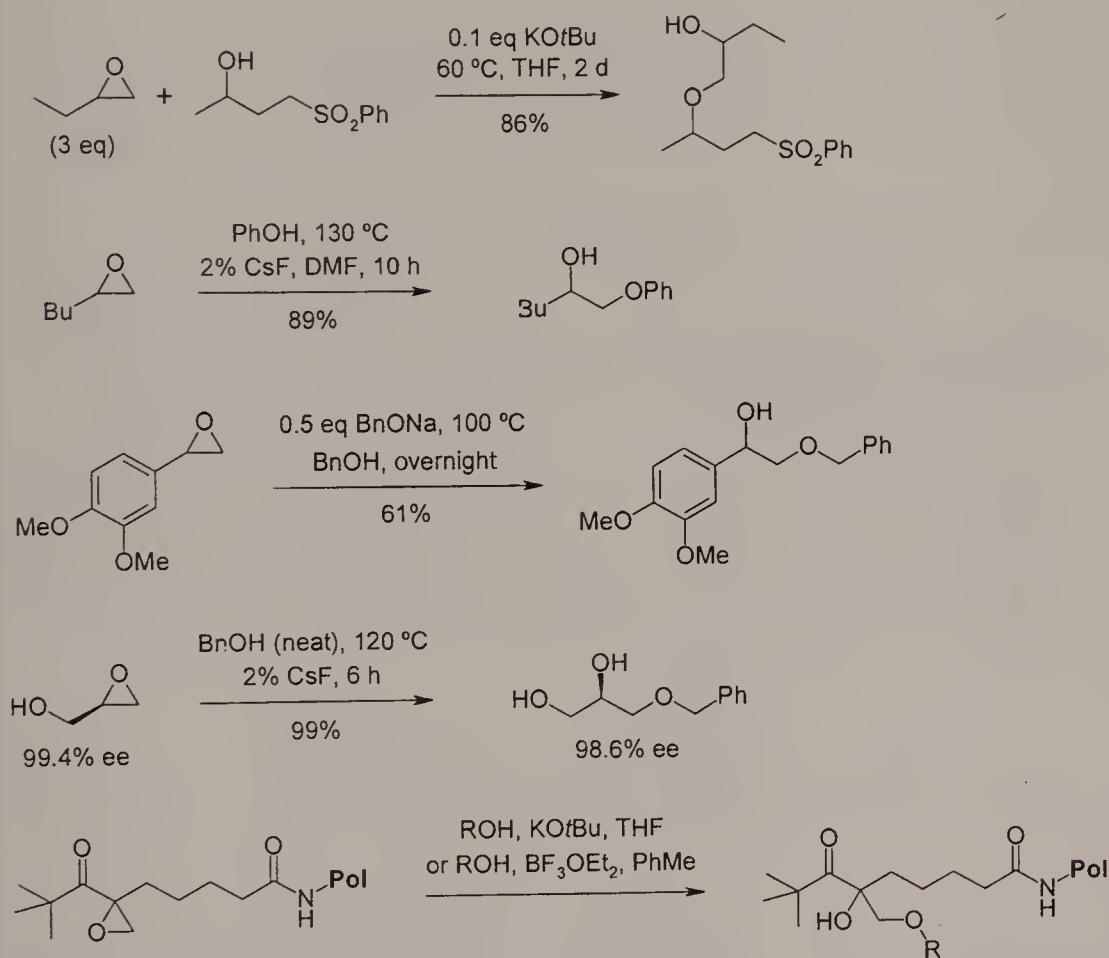
The carboxyl group seems to activate epoxides slightly toward nucleophilic attack by amines, and in the absence of catalysts most 2,3-epoxycarboxylic acids react with amines to yield 2-amino-3-hydroxycarboxylic acids [346–348]. This regioselectivity can, however, be overridden by complex formation with $\text{Ti}(\text{O}i\text{Pr})_4$ (Scheme 4.77).



Scheme 4.77. Reactions of amines with 2,3-epoxycarboxylic acids [349, 350].

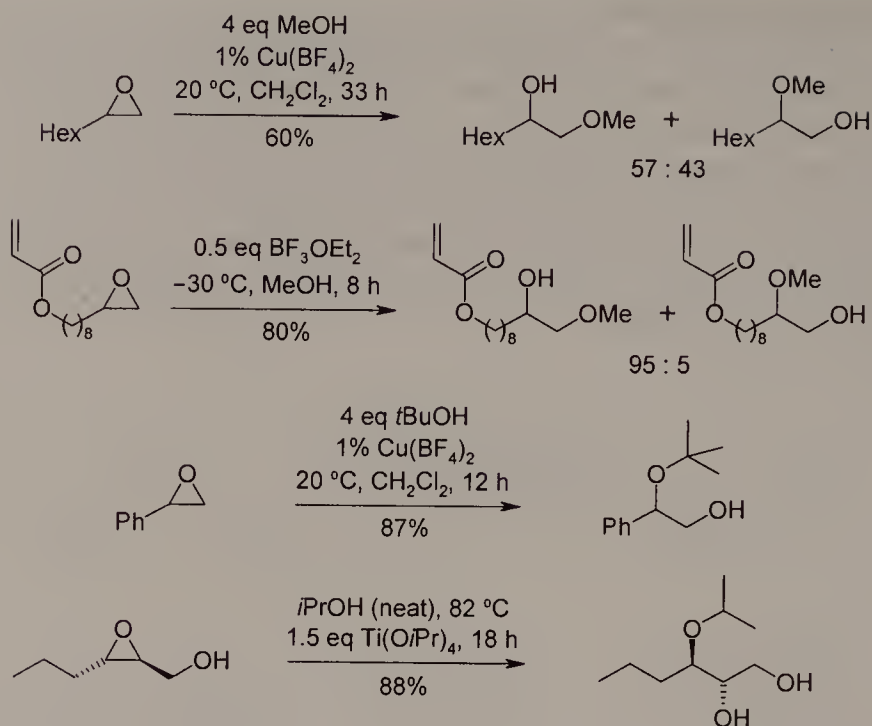
4.3.8.4 Epoxide Opening by Alcohols

Aliphatic or aromatic alcohols can be alkylated by epoxides under either basic or acidic reaction conditions. Reaction of aliphatic alcoholates with epoxides can be complicated by base-induced rearrangement or oligomerization of the epoxide, because alcoholates are strongly basic and because the product of epoxide ring opening is again an alcoholate. These side reactions can be suppressed by using only catalytic amounts of base (Scheme 4.78). The examples sketched in Scheme 4.78 show that under basic reaction conditions nucleophilic attack occurs preferentially at the sterically most accessible carbon atom.



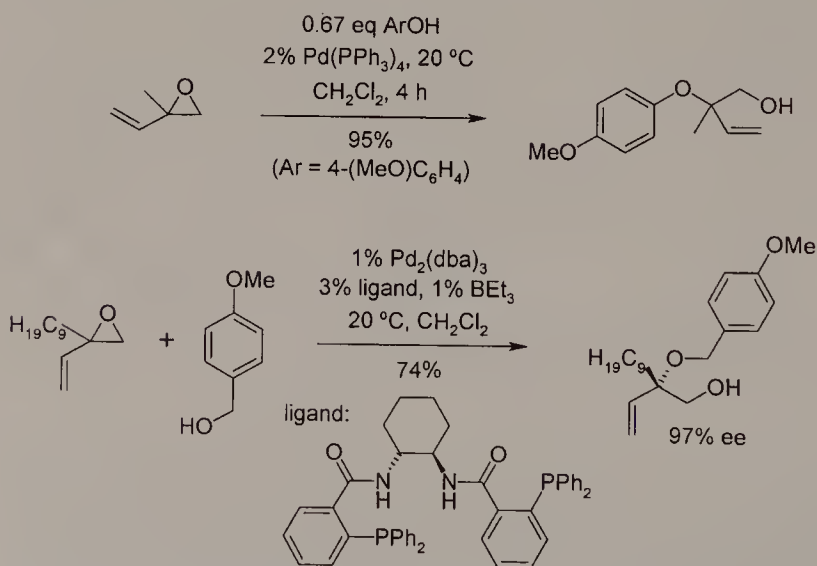
Scheme 4.78. Reactions of epoxides with alcohols under basic reaction conditions [329, 351–353]. Pol = polystyrene or TentaGel; R = alkyl.

Less problematic are etherifications with epoxides under acidic reaction conditions. Although we would expect the nucleophile to attack the position which most easily forms a carbocation, this does not always happen and steric effects also seem to be important (Scheme 4.79).



Scheme 4.79. Acid-mediated ring opening of epoxides by alcohols [336, 354, 355].

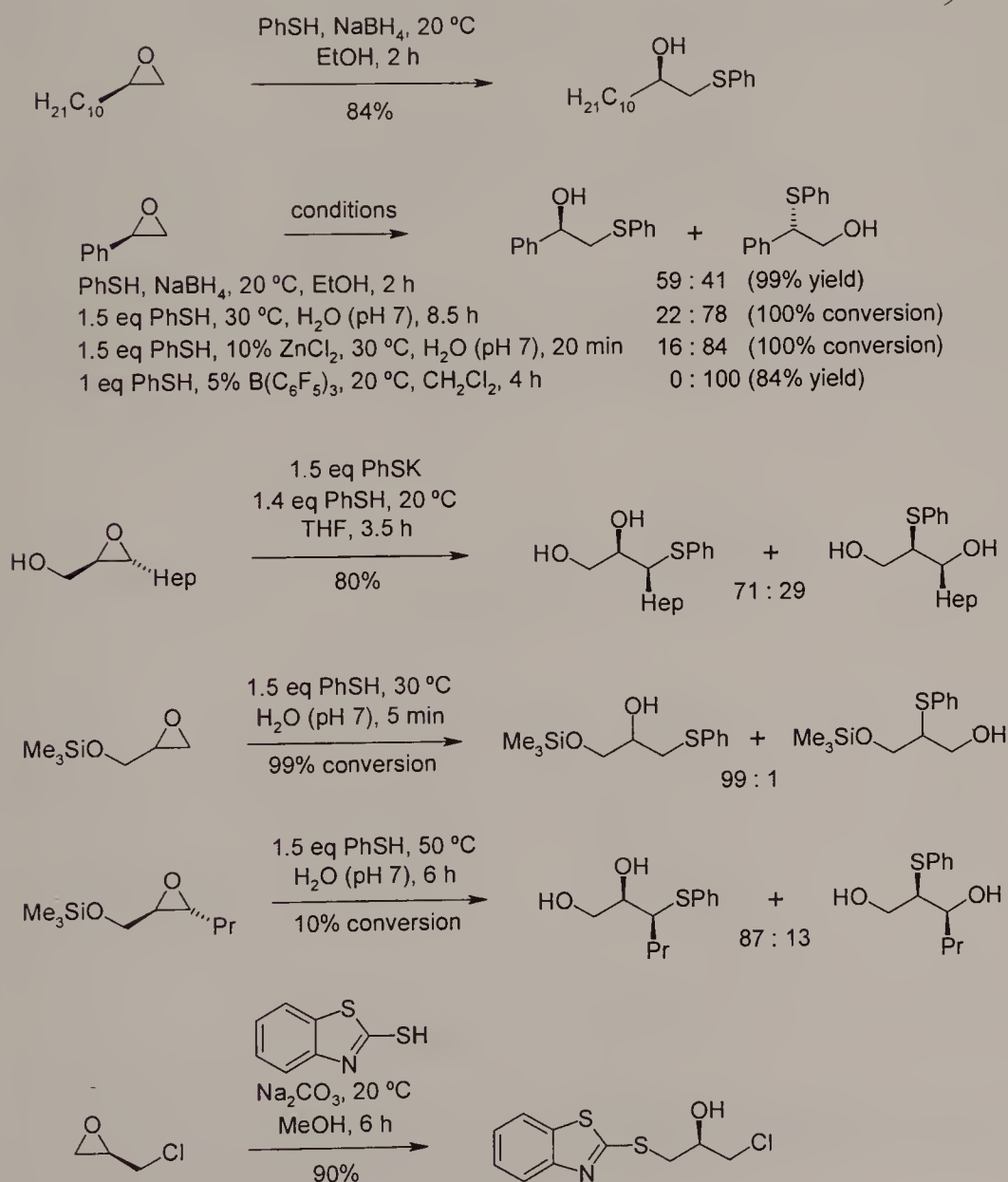
Vinyl epoxides react with Pd(0) to yield electrophilic allyl complexes which can convert alcohols and phenols into allyl ethers (Scheme 4.80). These alkylations usually yield 2-alkoxy-2-vinylethanols, and if the Pd-mediated etherification is performed in the presence of a chiral, enantiomerically pure diphosphine, enantiomerically enriched ethers may be obtained (Scheme 4.80) [356, 357].



Scheme 4.80. Pd(0)-catalyzed etherification with vinyl epoxides [259, 356].

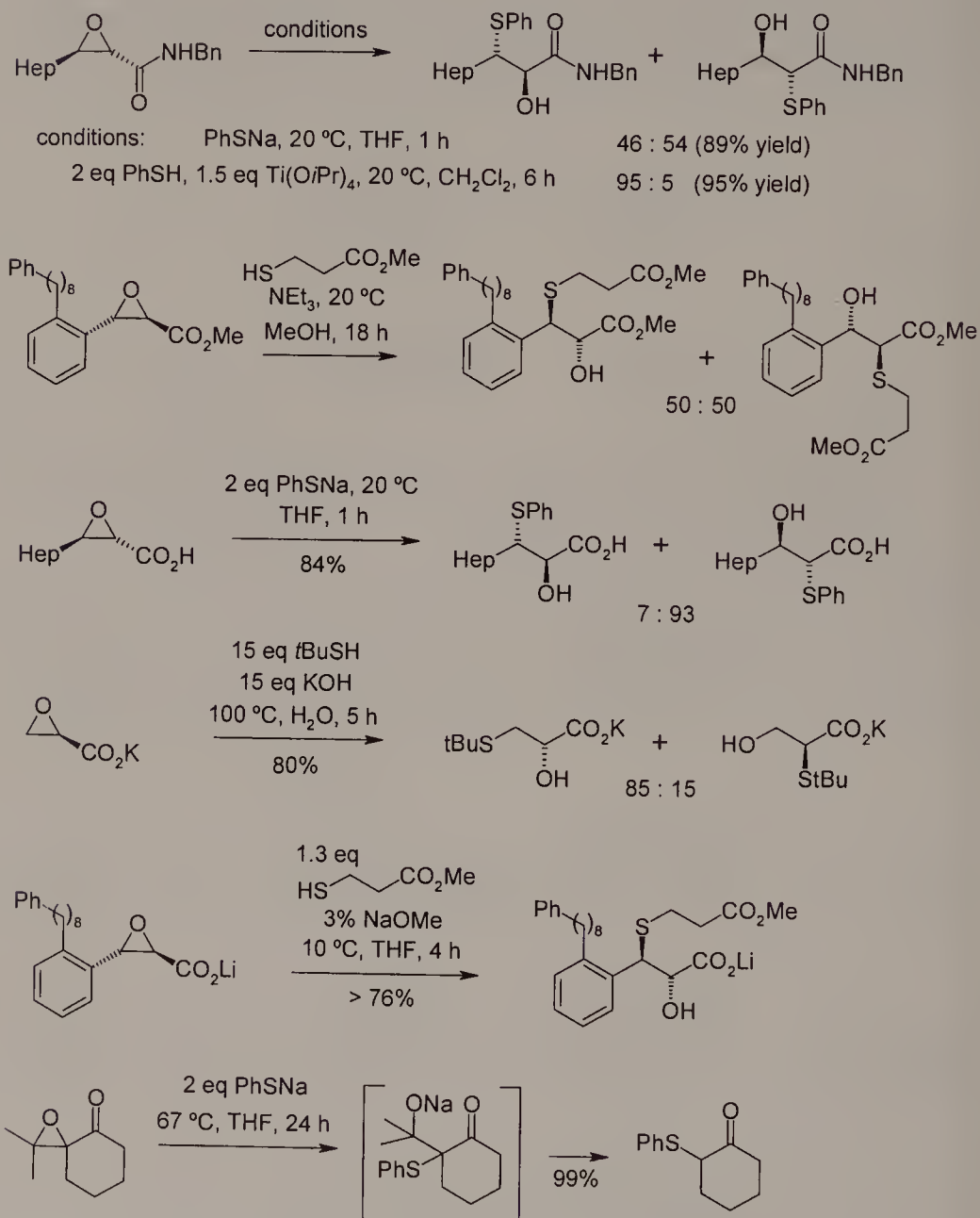
4.3.8.5 Epoxide Opening by Thiols

Thiols are highly reactive, soft nucleophiles which can be readily alkylated by epoxides under both acidic or basic reaction conditions. Even tetraalkyl epoxides yield the expected 2-mercapto ethanol[358], although these might be rather unstable and undergo fragmentation[359] (last reaction, Scheme 4.82). As with other nucleophiles, steric effects usually control the regioselectivity of epoxide opening under basic reactions, whereas in the presence of acids the stability of the two epoxide-derived carbocations can have a decisive effect on the resulting product ratio (Schemes 4.81 and 4.82). Thus, the regioselectivity of thiol alkylation by styrene oxide (second example, Scheme 4.81) changes significantly on addition of a Lewis acid.



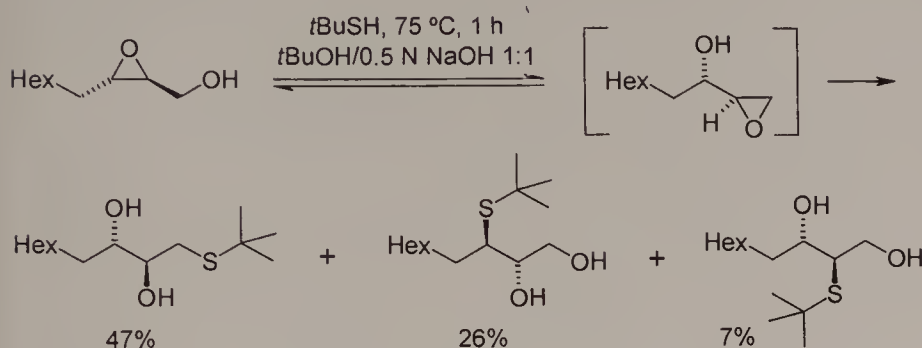
Scheme 4.81. Reactions of thiols with epoxides [247, 249, 341, 360, 361].

Similarly, the outcome of reactions of 2,3-epoxycarboxylic acid derivatives with thiols can be affected by addition of Lewis acids (first reaction, Scheme 4.82). As illustrated by the examples in Scheme 4.82, the regioselectivity of these reactions depends, however, to a large extent on the precise structure of the reacting partners, and can be difficult to predict.



Scheme 4.82. Reactions of 2,3-epoxycarboxylic acid derivatives and epoxy ketones with thiols [349, 359, 362–364].

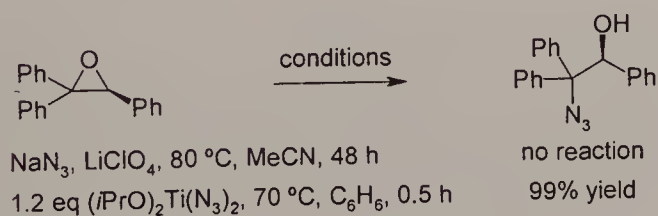
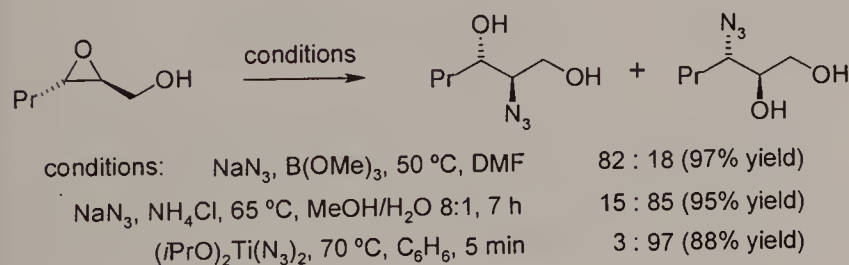
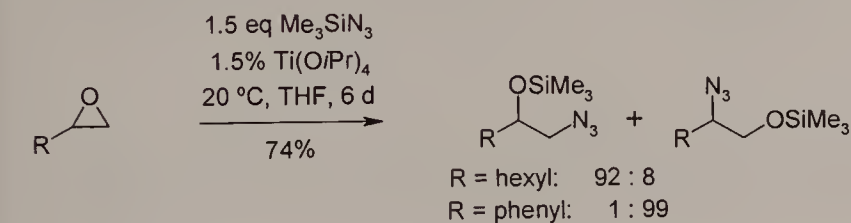
2,3-Epoxy-1-propanols with substituents at C-3 can rearrange on treatment with a base to give a terminal epoxide (Payne rearrangement; Scheme 4.83). Because the rearranged epoxide will react with nucleophiles such as amines or thiols more rapidly than the unrearranged epoxide, the main product can result from ring opening of the former (Scheme 4.83).



Scheme 4.83. Payne rearrangement followed by thiol-mediated ring opening of 3-substituted 2,3-epoxy-1-propanols [365].

4.3.8.6 Epoxide Opening by Azide

Either alkali metal azides or Me_3SiN_3 can be used for ring opening of epoxides by the azide ion to yield 2-azido ethanol. With the latter reagent the corresponding trimethylsilyl ethers can be obtained instead of the alcohols.

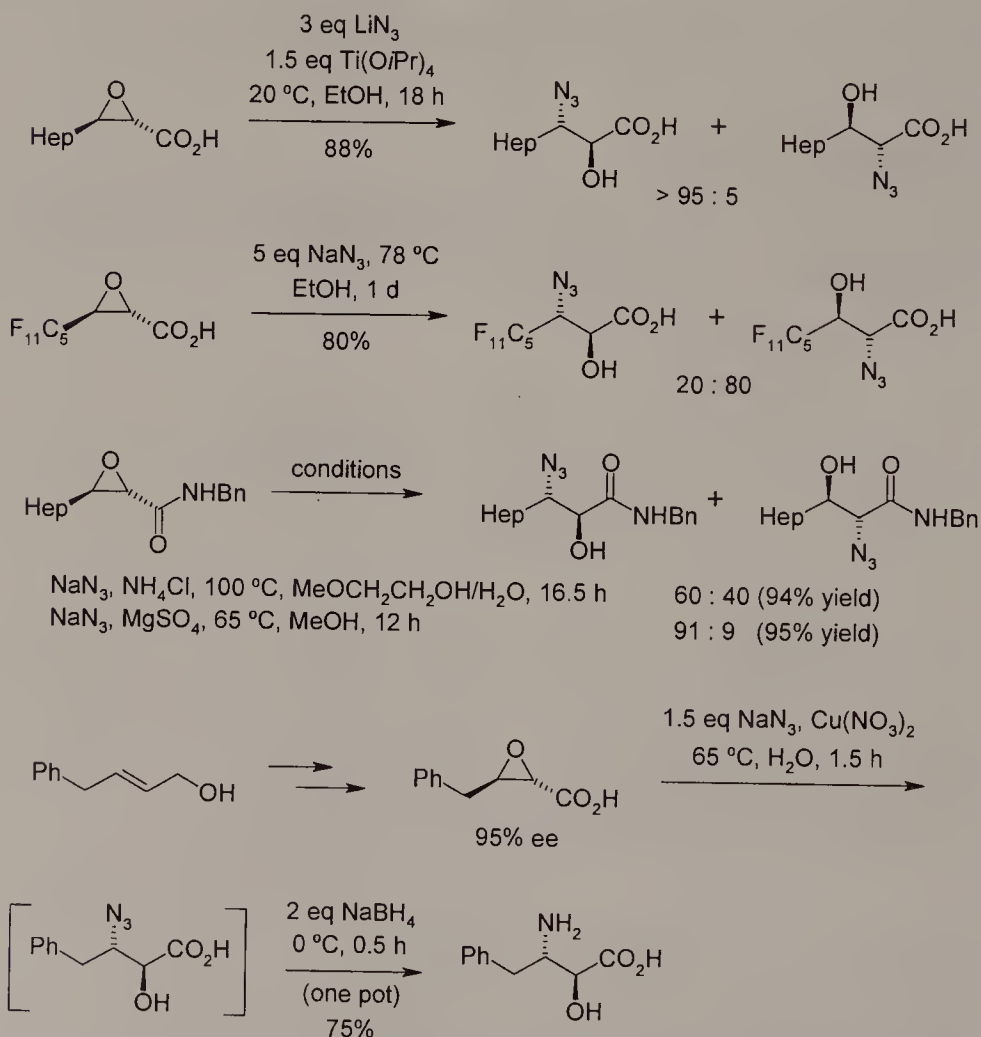


Scheme 4.84. Ring opening of epoxides by azide [253, 336, 369–371].

Most epoxides react with alkali metal azides or Me_3SiN_3 only sluggishly, and different catalysts have been recommended, for example quaternary ammonium salts [248, 366], AlCl_3 [367], and copper(II) salts [368]. Other reagents are given in Schemes 4.84 and 4.85.

The regioselectivity of epoxide ring opening by azide is similar to that of other nucleophiles. Monoalkyl epoxides are preferentially attacked at the methylene group whereas in styrene oxides the benzylic C–O bond is usually cleaved, in particular in the presence of acids (Scheme 4.84). By choosing the right reagents and additives, 2,3-epoxypropanols can be converted into either of both possible azido diols.

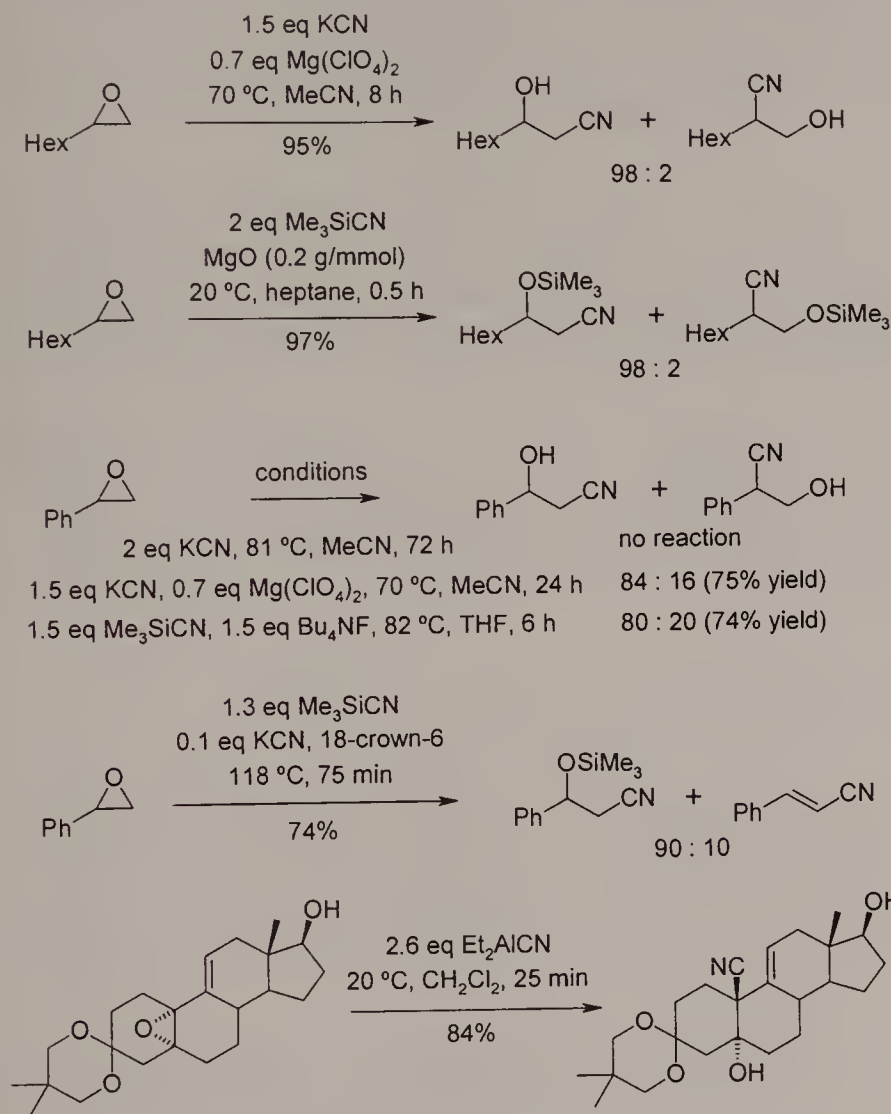
2,3-Epoxy-carboxylic acid derivatives react with azide to yield mainly 2-hydroxy-3-azidoalkanoic acid derivatives [367, 368] (Scheme 4.85). Addition of Lewis acids to the reaction mixture enhances this selectivity further and renders this reaction a valuable strategy for stereoselective preparation of α -hydroxy- β -amino acids from allyl alcohols [368] (last example, Scheme 4.85).



Scheme 4.85. Reactions of 2,3-epoxycarboxylic acid derivatives with azide [247, 345, 349, 368].

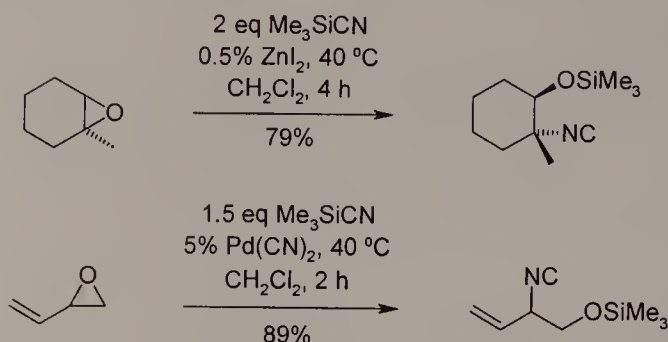
4.3.8.7 Epoxide Opening by Cyanide

Epoxides react with cyanide under basic reaction conditions to yield 3-hydroxypropionitriles by nucleophilic attack at the sterically less demanding carbon atom (Scheme 4.86). Me_3SiCN can also be used as reagent, but trimethylsilyl ethers will be the main products. With some types of epoxide (e.g. styrene oxide [372]) the products readily dehydrate to yield α,β -unsaturated nitriles [373] (Scheme 4.86).



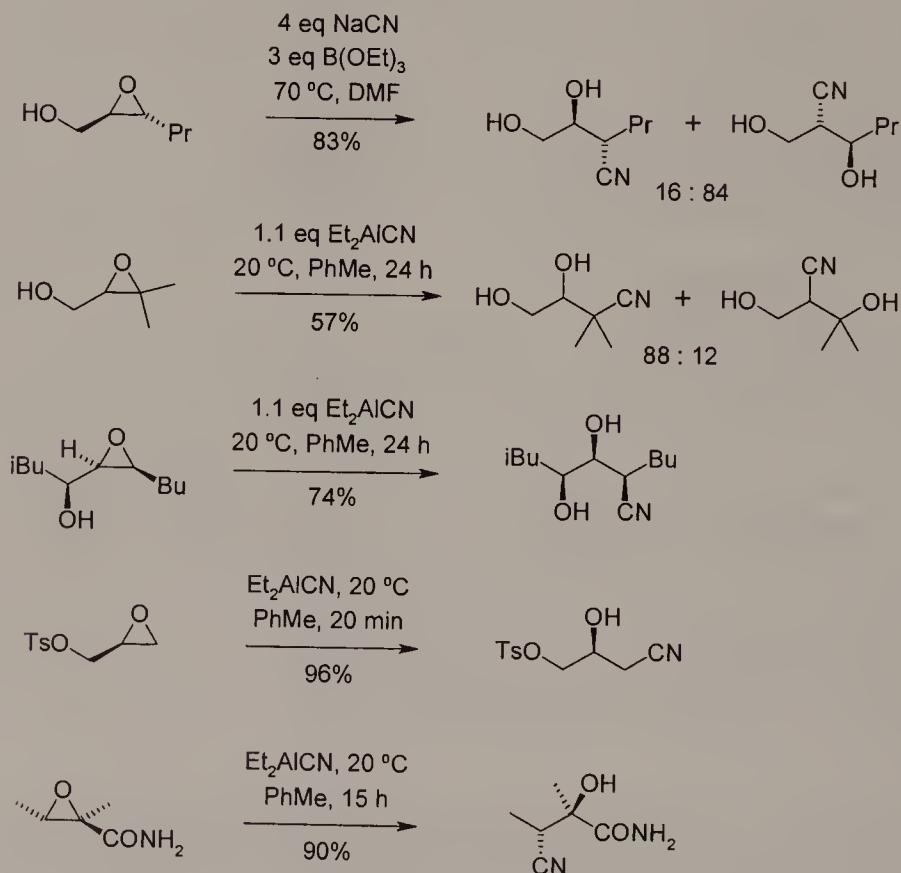
Scheme 4.86. Ring opening of epoxides by cyanide [248, 372, 374–376].

Under acidic reaction conditions the formation of isonitriles can compete efficiently with nitrile formation (Scheme 4.87) [377]. Particularly effective reagents for the formation of isonitriles are mixtures of Me_3SiCN with Lewis acids such as Zn(II) , Pd(II) , or Sn(II) salts. Aluminum-derived Lewis acids with Me_3SiCN , on the other hand, mediate the conversion of epoxides into nitriles [378, 379].



Scheme 4.87. Formation of isonitriles from epoxides and Me_3SiCN [378, 379].

Epoxides substituted with oxymethyl or other electron-withdrawing groups are usually attacked by cyanide in the presence of acids at the carbon which can form the better stabilized carbocation (Scheme 4.88). As with other nucleophiles, for 2,3-epoxypropanols this regioselectivity can be reversed by addition of boron-derived Lewis acids (first example, Scheme 4.88).

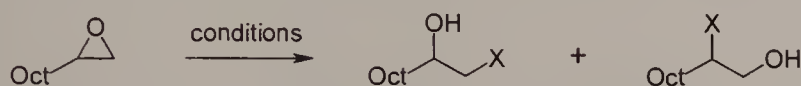


Scheme 4.88. Ring opening of oxymethyl epoxides and 2,3-epoxyamides by cyanide [243, 369, 380, 381].

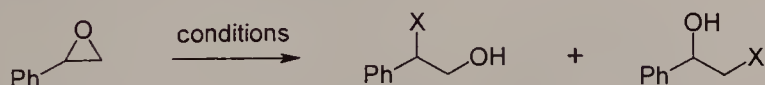
4.3.8.8 Epoxide Opening by Halides

Many different reagents and reaction conditions have been explored for ring opening of epoxides by halides to prepare 2-haloethanols. As illustrated by the selection of examples given in Scheme 4.89, the regioselectivity of this reaction can be controlled quite effectively.

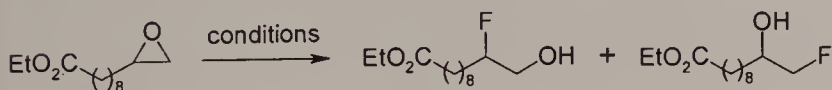
Styrene oxides are preferentially attacked by halides at the benzylic position, especially so under acidic reaction conditions. It has been claimed, however, that in water in the presence of cyclodextrins, styrene oxides react with halides to yield exclusively benzylic alcohols [382]. Benzylic alcohols can also be obtained from styrene oxides by treatment with halogens in the presence of pyridines [383].



HCl, 0 °C, Et ₂ O, 1 h	77 : 23 (X = Cl, 99% yield)
1.5 eq NH ₄ Cl, 1.5 eq LiClO ₄ , 65 °C, MeCN, 24 h	96 : 4 (X = Cl, 99% yield)
TiCl ₄ , -25 °C, heptane, 3 h	5 : 95 (X = Cl, 95% yield)
1.5 eq NH ₄ Br, 1.5 eq LiClO ₄ , 65 °C, MeCN, 24 h	66 : 34 (X = Br, 90% yield)
MgBr(TMP), 0 °C, THF, 2 h	100 : 0 (X = Br, 95% yield)
TiBr ₄ , -78 °C to 20 °C, heptane, 22 h	9 : 91 (X = Br, 95% yield)
1.5 eq NH ₄ I, 1.5 eq LiClO ₄ , 65 °C, MeCN, 24 h	88 : 12 (X = I, 92% yield)
AlI ₃ , 25 °C, heptane, 2 h	100 : 0 (X = I, 95% yield)



HX, 20 °C, H ₂ O, CHCl ₃ , 15 min (X = Cl, Br, I)	100 : 0 (> 94% yield)
1.5 eq NH ₄ Cl, 1.5 eq LiClO ₄ , 80 °C, MeCN, 4 h	60 : 40 (X = Cl, 50% yield)
1.1 eq SiCl ₄ , 10% HMPA, -78 °C, CH ₂ Cl ₂ , 20 min	94 : 6 (X = Cl, 94% yield)
1.5 eq NH ₄ Br, 1.5 eq LiClO ₄ , 80 °C, MeCN, 4 h	45 : 55 (X = Br, 96% yield)
1.5 eq NH ₄ I, 1.5 eq LiClO ₄ , 20 °C, MeCN, 3 h	67 : 33 (X = I, 96% yield)

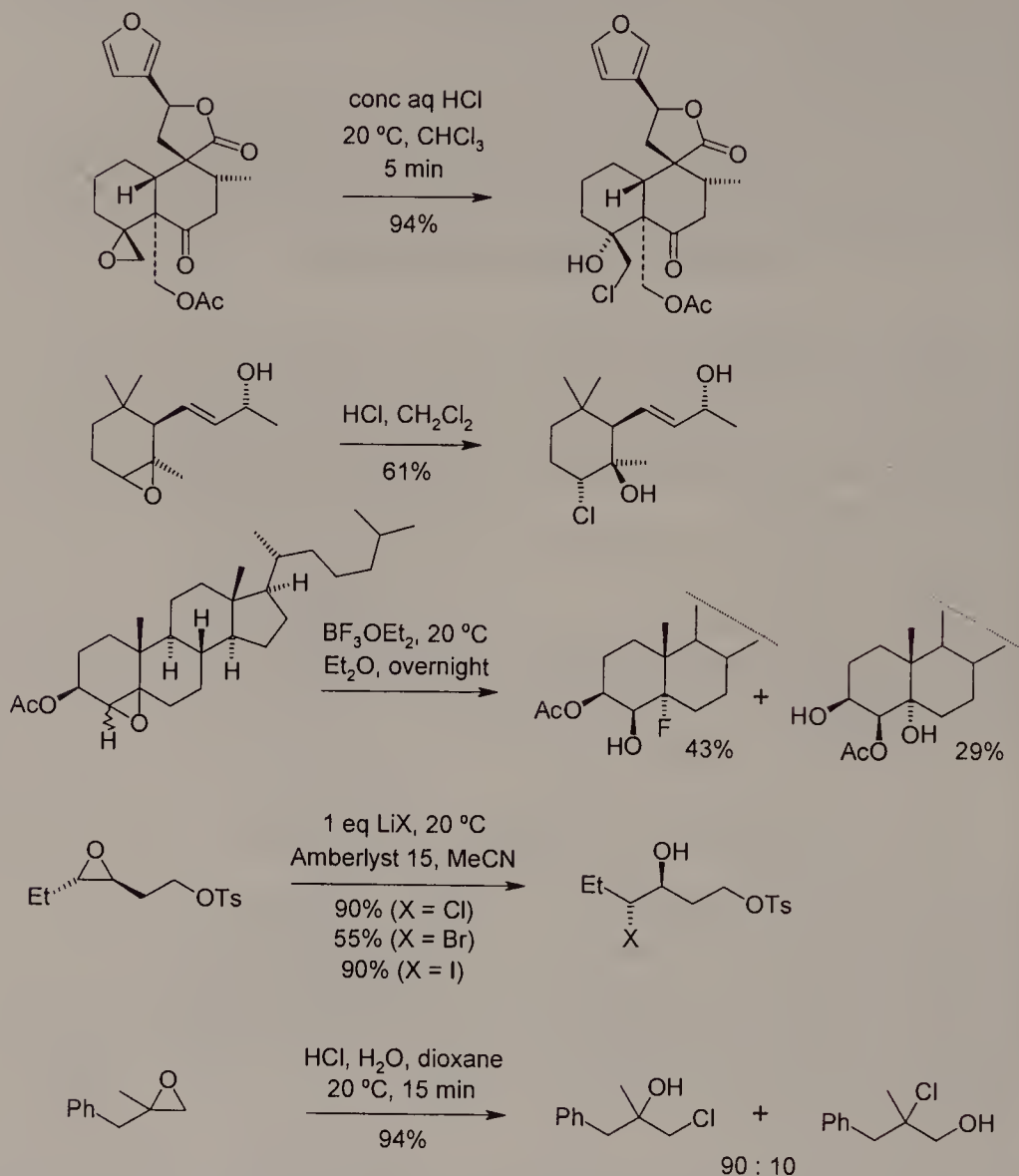


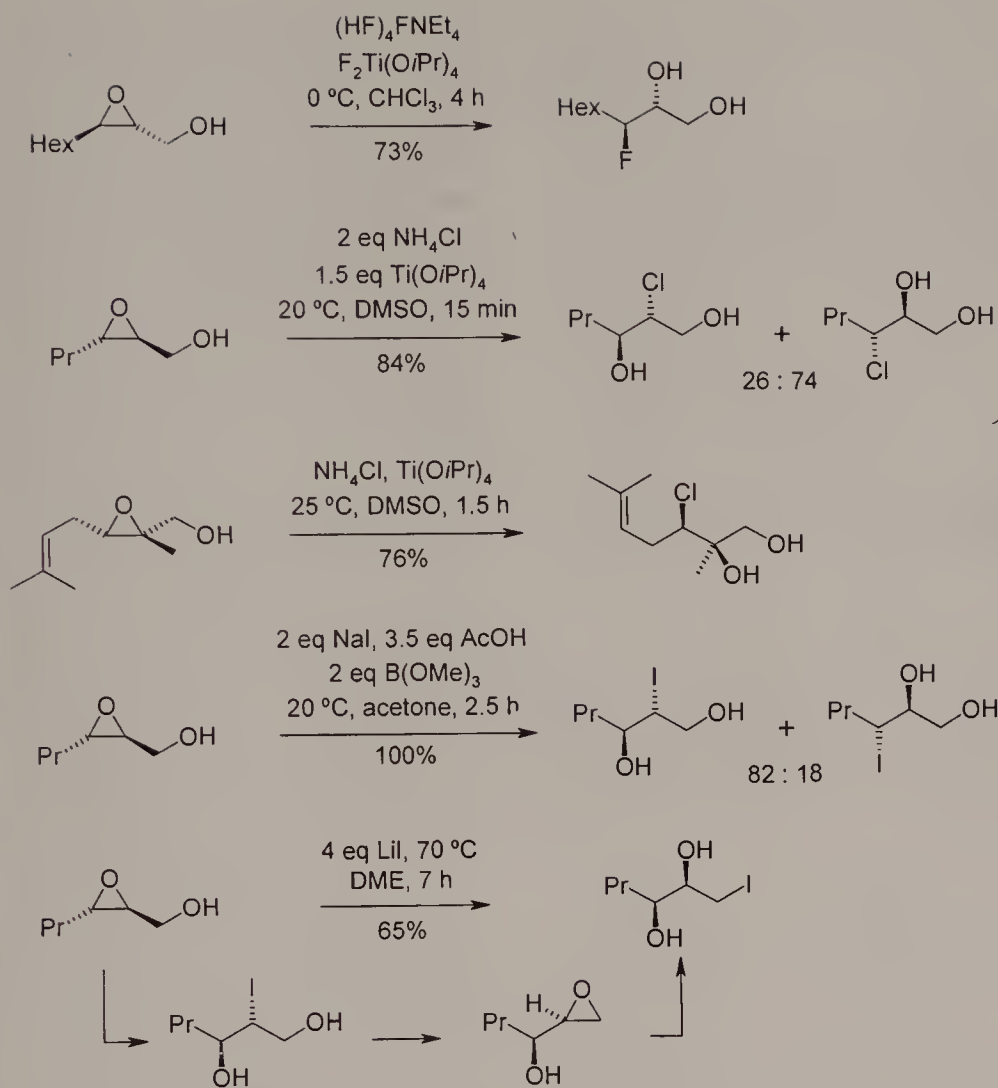
(HF) ₉ Py, 20 °C, CH ₂ Cl ₂ , 6 h	92 : 8 (83% yield)
(HF) ₃ NEt ₃ , 100 °C, PhMe, 36 h	45 : 55 (77% yield)
KHF ₂ , 18-crown-6, 153 °C, DMF, 36 h	26 : 74 (88% yield)

Scheme 4.89. Reaction of epoxides with halides [291, 384–386].

Treatment of epoxides with halides under acidic reaction conditions does not always lead to attack of the halide at the most highly substituted carbon atom. The examples in Schemes 4.89 and 4.90 show that often the opposite regioselectivity is

observed, an outcome that is neither readily explained nor predicted. Enantioselective versions of this reaction have been reported [384].

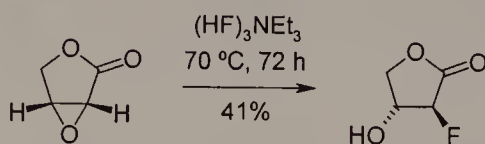
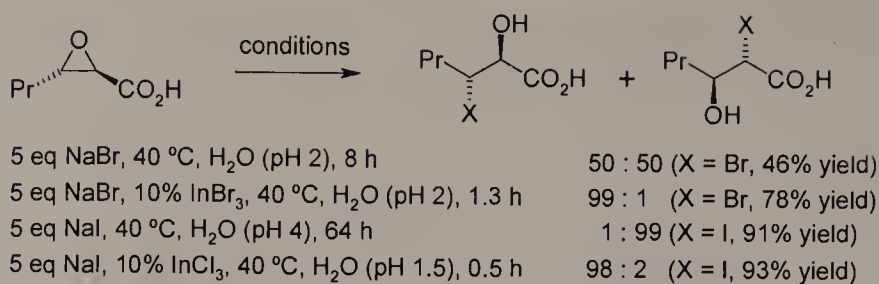




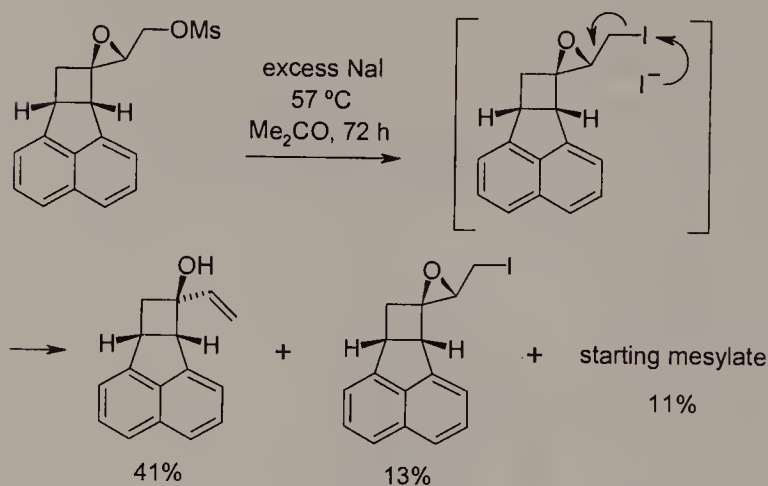
Scheme 4.91. Reaction of 2,3-epoxypropanols with halides [246, 336, 390–392].

2,3-Epoxy-carboxylic acids and derivatives thereof can yield, on reaction with halides, both possible regioisomers (Scheme 4.92). Strongly acidic reaction conditions or Lewis acids can promote the formation of 2-hydroxy-carboxylic acids.

Mesyloxymethyl epoxides and related compounds may lead to unexpected products on reaction with iodide, which occasionally acts as reducing agent. As illustrated in Scheme 4.93, halogen-free products can result from such reactions.



Scheme 4.92. Reaction of 2,3-epoxycarboxylic acids and lactones with halides [393, 394].



Scheme 4.93. Reductive ring opening of mesyloxy epoxides with iodide [395].

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5

The Alkylation of Carbanions

5.1

Introduction

The deprotonation of organic compounds by strong, non-nucleophilic bases followed by C-alkylation with a suitable electrophile has become one of the most predictable and straightforward methods for formation of C–C bonds. The popularity of this chemistry is also a consequence of the often-seen close resemblance of feasible structural modifications by a deprotonation/alkylation strategy to an unsophisticated retrosynthetic analysis of a given target compound. Other reactions, which involve, for instance, substantial rearrangement of the carbon framework (e.g. Cope rearrangement, fragmentations, ring contractions or enlargements) are usually more difficult to take into account during retrosynthetic analysis.

LDA and related, sterically hindered, lithium dialkylamides, first investigated by Levine [1], have completely replaced the more nucleophilic sodium amide, which had been the base of choice for many years [2]. Because the reactivity of an organometallic compound depends to a large extent on its state of aggregation (i.e. on the solvent and on additives) and on the metal, transmetalation of the lithiated intermediates and the choice of different solvents and additives emerged as powerful strategies for fine-tuning the reactivity of these valuable nucleophiles.

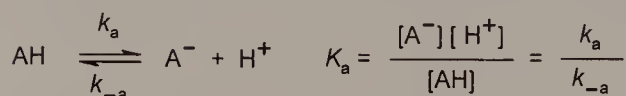
In this chapter the alkylation of carbanions with simple carbon electrophiles will be discussed, with special emphasis on the structure–reactivity relationship of the carbanion and on side reactions. In this context the term “carbanion” refers to an intermediate prepared by in-situ deprotonation of an organic compound, followed by optional cation exchange (transmetalation), which tends to be alkylated at carbon by soft electrophiles such as MeI or PhCHO. This type of reactivity is characteristic of enolates with an ionic M–O bond or for organometallic compounds with a strongly polarized or ionic M–C bond, M typically being an alkali metal, Mg, Cu, or Zn. Carbanions can, alternatively, also be prepared by halogen–metal exchange [3–8], sulfoxide– or sulfone–metal exchange [9–13], or by transmetalation of stannanes. The most suitable reagents for performing such metalating exchange reactions are organometallic compounds with a metal-bound secondary or tertiary alkyl group, such as *t*BuLi, *s*BuLi, *i*Pr₂Zn [14, 15], or *i*PrMgHal [6]. These reagents are thermodynamically less stable than organometallic compounds with primary alkyl

groups, and will not be readily regenerated from other organometallic reagents under the conditions of reversible transmetalation. Formally metal-free carbanions can be generated by treatment of silanes [16, 17] or silylenol ethers [18] with TBAF. For studies on the mechanism of enolate formation, see Refs [19–23].

5.2

The Kinetics of Deprotonations

For discussion of deprotonations of organic compounds both the rate of deprotonation and the equilibrium acidity must be considered. Equilibrium acidities are expressed by the pK_a value, which is defined as follows for an acid AH:



$$pK_a = -\lg K_a$$

where $[X]$ = concentration of X, K = equilibrium constant, and k = rate constant.

Equilibrium acidities of representative organic compounds have been determined [24–26], and depend both on the temperature and on the solvent (Table 5.1) [27–29]. Solvents which, because of their high dielectric constant or by hydrogen bonding, can stabilize ions will generally promote ionization, as will higher temperatures. The effect of the solvent on pK_a is particularly strong for acids which, on deprotonation, give anions of high charge density, but becomes smaller for highly delocalized anions of low charge density (Table 5.1).

Table 5.1. Equilibrium acidities in water and in DMSO at 25 °C [24, 30–33].

Acid	pK_a (H ₂ O)	pK_a (DMSO)	ΔpK_a
H ₂ O	15.75	32	16.25
MeOH	15.5	29.0	13.5
HF	3.2	15	11.8
PhC≡CH	20.0	28.7	8.7
PhOH	10.0	18.0	8.0
Me ₂ CO	19.3	26.5	7.2
MeNO ₂	10.0	17.2	7.2
PhCO ₂ H	4.25	11.1	6.85
MeCOPh	18.3	24.7	6.4
MeCONMe ₂	29.4	35	5.6
AcOEt	25.6	30	4.4
Ac–CH ₂ –Ac	8.9	13.3	4.4
HN ₃	4.7	7.9	3.2
MeCN	28.9	31.3	2.4
NC–CH ₂ –CN	11.0	11.0	0.0
Picric acid	0	0	0

From the discussion above follows that the weaker an acid, the larger its pK_a . Acids and bases with a pK_a outside the range given by the pK_a values of OH^- ($pK_a = 15.8$) and H_3O^+ ($pK_a = -1.75$) [24] cannot be deprotonated/protonated to a large extent in water. This does not mean, however, that acids with a $pK_a > 15.8$ cannot be deprotonated at all in water [32, 34]. Propionitrile ($pK_a = 30.9$ in water) and *N,N*-dimethylacetamide ($pK_a = 29.4$ in water) undergo KOD-catalyzed H–D exchange in water at substantial rates ($t_{1/2}$ [EtCN in 0.5 M KOD or MeCONMe₂ in 0.25 M KOD] = 138 h [30, 31]); this shows that the corresponding carbanions are indeed formed, although to a small extent only.

The degree of dissociation of an acid in water can be easily estimated with the Henderson–Hasselbach equation. When the pH of the solution equals the pK_a of an acid, then the acid is 50% dissociated ($[\text{AH}] = [\text{A}^-]$); for each integer by which the pH differs from the pK_a the ratio $[\text{A}^-]/[\text{AH}]$ will increase or decrease by a factor of 10:

$$pK_a = -\lg K_a = -\lg \frac{[\text{A}^-]}{[\text{AH}]} + \text{pH}$$

$$pK_a - \text{pH} = -\lg \frac{[\text{A}^-]}{[\text{AH}]}$$

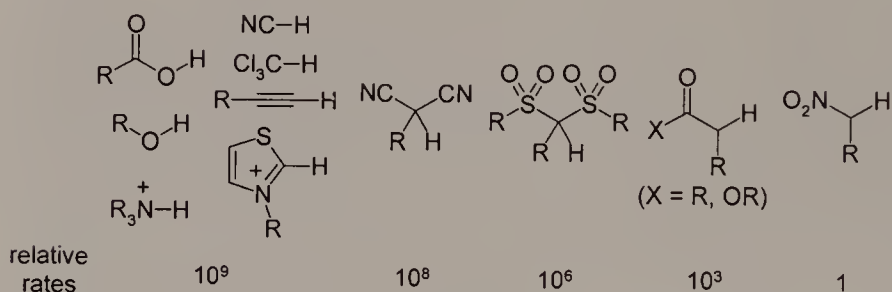
Equilibrium acidities are usually determined by titration, either with indicators of known pK_a [24] or by following the extent of dissociation spectroscopically (e.g. by UV-spectroscopy [35]). Kinetic acidities, i.e. the rates of deprotonation of acids, can be determined by measuring rates of racemization [36] or rates of H–D or H–T exchange [37, 38], by chemical relaxation experiments (e.g. T-jump method [35, 39]), or by ^1H NMR (line broadening and saturation recovery [40]).

The rate of deprotonation of an acid by a base depends on their structures [41], on the solvent and temperature, and on the difference (ΔpK_a) between the pK_a of the acid and that of the base. When acid and base have the same pK_a ($\Delta pK_a = 0$) the change of free energy for proton transfer becomes zero and the reaction becomes thermoneutral. Under these conditions the rate of proton transfer is limited only by the so-called intrinsic barrier [34], which is particularly sensitive to structural changes in the reaction partners [39]. When ΔpK_a increases, the rate of proton transfer also increases and approaches a limiting value, which depends on the structures of the acid and base and on the experimental conditions. For normal acids (O–H, N–H) in water the rate of proton transfer becomes diffusion-controlled ($k_a \approx 10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$) when $\Delta pK_a > 2$, but in aprotic solvents the limiting proton transfer rate can be substantially lower [42].

The equilibrium acidities of organic acids do not necessarily correlate with their kinetic acidities [39, 43–46]. Deprotonations of sparsely polarized X–H groups which are accompanied by a large change in hybridization and geometry proceed more slowly than deprotonations with little rehybridization (“principle of least nuclear motion” [45]). In Scheme 5.1 the approximate relative rates of proton transfer to a base from some classes of acid are given, assuming that $\Delta pK_a = 0$ (thermoneutral conditions). Proton transfer from carboxylic acids, phenols, or ammonium salts to bases are usually very fast ($k_a \approx 10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$), the main rate-determining factors

under thermodynamically favorable conditions ($\Delta pK_a > 2$) being diffusion and solvent reorganization. Under thermoneutral conditions proton transfer constants of these acids are approximately $5 \times 10^8 \text{ L mol}^{-1} \text{ s}^{-1}$ [35]. The fact that carboxylic acids and phenols are deprotonated at similar rates as ammonium salts shows that the stabilization of carboxylates or phenolates by charge delocalization and resonance is *small*, and that their high equilibrium acidity is mainly because of the sp^2 -hybridization of the oxygen-bound carbon atom and to electrostatic stabilization of O^- by the carbonyl group (in carboxylic acids) [47, 48].

Carbon acids which do not undergo significant rehybridization or structural reorganization upon proton loss, for example HCN [40], alkynes [33], chloroform [33], or thiazolium salts [49], also undergo fast deprotonation [50]. Much slower is, though, the deprotonation of sulfones, ketones, and nitroalkanes (Scheme 5.1). For most C,H-acidic compounds, rates of deprotonation *decrease* with increasing delocalization of the negative charge on to oxygen atoms. The stronger the stabilization of a carbanion by resonance and solvation, the more will this stabilization lag behind proton transfer in the transition state, leading to a lower deprotonation rate [51]. In non-aqueous solvents, where the energy gain by solvation is lower, the rate of deprotonation of, for instance, nitroalkanes is, therefore, larger than in water [52].



Scheme 5.1. Approximate relative rates of proton transfer in water at thermoneutrality ($\Delta pK_a = 0$) [35, 39, 51].

5.3

Regioselectivity of Deprotonations and Alkylations

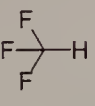
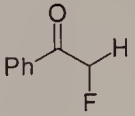
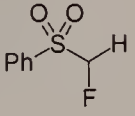
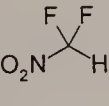
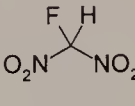
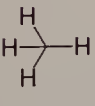
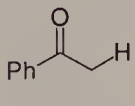
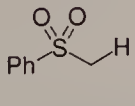
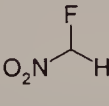
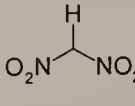
5.3.1

Introduction

On treatment with strong bases ($\Delta pK_a \text{ acid-base} \gg 2$), compounds containing more than one acidic C,H group are usually deprotonated first at the most acidic position and then at the less acidic sites if the difference between the equilibrium acidities of these C,H groups is large. The equilibrium acidity of C,H-acidic compounds usually (but not always) increases strongly with the number of carbanion stabilizing groups attached to the acidic C,H group ($\text{CH}_3\text{Z} < \text{CH}_2\text{Z}_2 < \text{CHZ}_3$; Z = carbanion stabilizing group; see, however, Scheme 5.2). Functional groups which stabilize carbanions do this either by charge delocalization to more electronegative atoms (carbonyl com-

pounds, nitroalkanes), by polar effects (nitriles, sulfones [29]), by field effects (ammonium salts), or by chelation of the metal ("dipole stabilization"; e.g. MC-CCONR₂, MC-NCO₂R, MC-OCONR₂ [53–59]). An approximate ranking of functional groups according to their ability to increase the equilibrium acidity of an aliphatic C,H group would be: NO₂ > SOME₂⁺ ≈ SME₂⁺ ≈ SO₂CF₃ > C₆H₄-4-NO₂ > PPh₃⁺ > CPh > COR > CN > SO₂Ph ≈ CO₂R > CONR₂ ≈ SPh > 2-pyridyl > SPh ≈ SePh ≈ NMe₃⁺ ≈ PPh₂ > Ph ≈ C≡CPh ≈ CH=CH₂ > OPh ≈ F > H > CH₃.

The effect on acidity of carbanion-stabilizing functional groups is not necessarily additive. Certain groups may have a carbanion-stabilizing effect in one compound, but reduce the acidity of another compound. Fluorine, for instance, can increase the acidity of alkanes by electron-withdrawal through σ bonds, but can destabilize a carbanion by electron-donation from its lone pairs into π -type orbitals. Thus, when bound to an sp^3 -hybridized carbon atom fluorine will generally enhance acidity, but when bound to an sp^2 carbon it can have a carbanion-destabilizing effect. Fluoroform which, on deprotonation, gives a pyramidalized carbanion with sp^3 -hybridized carbon [60], is much more acidic than methane (Scheme 5.2). Fluoroacetophenone or fluoromethyl phenyl sulfone, on the other hand, in which stabilization of the carbanion by delocalization of the negative charge to oxygen is important, are only slightly more acidic than acetophenone and methyl phenyl sulfone, respectively. 9-Fluorofluorene [61] or fluorodinitromethane, which yield on deprotonation planar, sp^2 -hybridized carbanions, are even less acidic than the corresponding non-fluorinated compounds (Scheme 5.2).

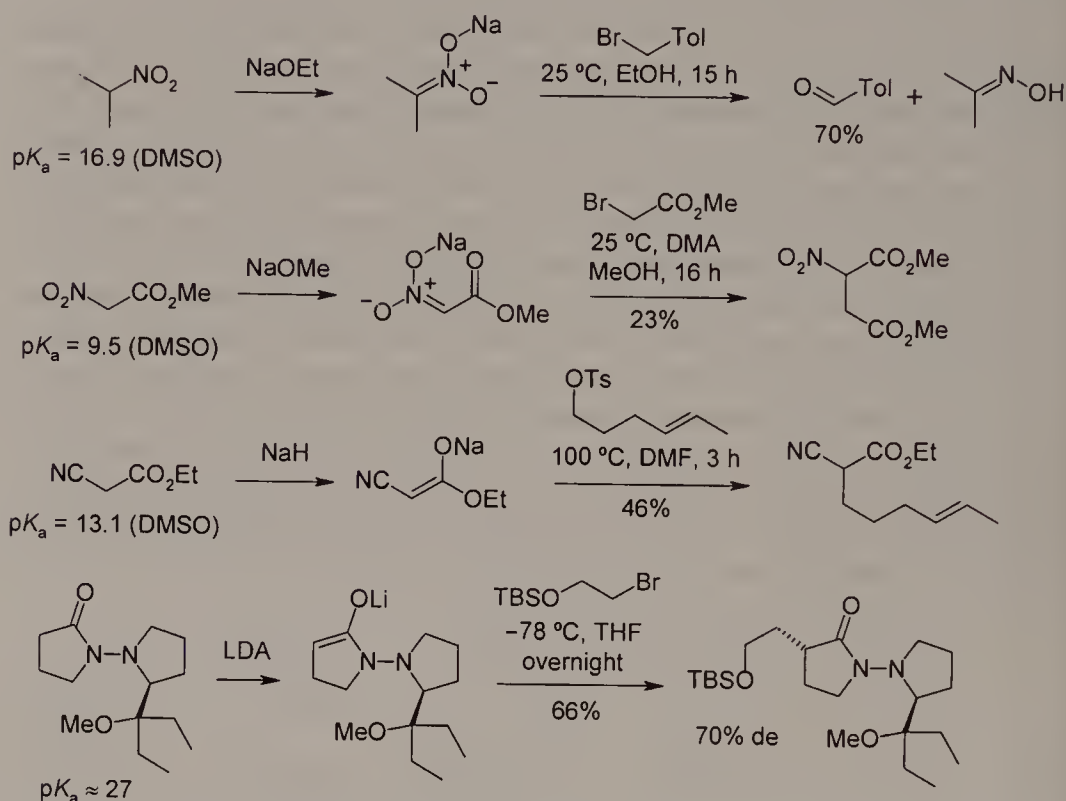
				
pK _a 27 (H ₂ O)	21.6 (DMSO)	28.5 (DMSO)	12.4 (H ₂ O)	7.70 (H ₂ O)
				
pK _a 48 (H ₂ O)	24.7 (DMSO)	29.0 (DMSO)	9.55 (H ₂ O)	3.57 (H ₂ O)

Scheme 5.2. The effect of fluorine on the acidity of organic compounds [24, 62–65].

There is no perfectly linear correlation between the basicity and nucleophilicity of carbanions [66], but higher basicity usually also implies higher nucleophilicity. Carbanions in which the negative charge is highly delocalized (e.g. diethylmalonate) will usually react more slowly with electrophiles than less extensively delocalized carbanions of similar basicity (e.g. malodinitrile) [66].

The more acidic a C,H group, the less basic and nucleophilic will the corresponding carbanion usually be. Consequently, carbanions generated by deprotonation of strongly acidic C,H groups will react slowly with electrophiles, and are usually difficult to alkylate, as illustrated by the examples in Scheme 5.3. Monodeprotonated

nitroalkanes (first reaction, Scheme 5.3) are difficult to alkylate at carbon, and are preferentially *O*-alkylated (unless a path via SET is accessible; see Section 4.1). The resulting *O*-benzylated nitroalkanes can decompose during work-up to yield benzaldehydes and oximes [67–69]. The dianions of nitroalkanes, on the other hand, can be readily alkylated at carbon [70, 71].



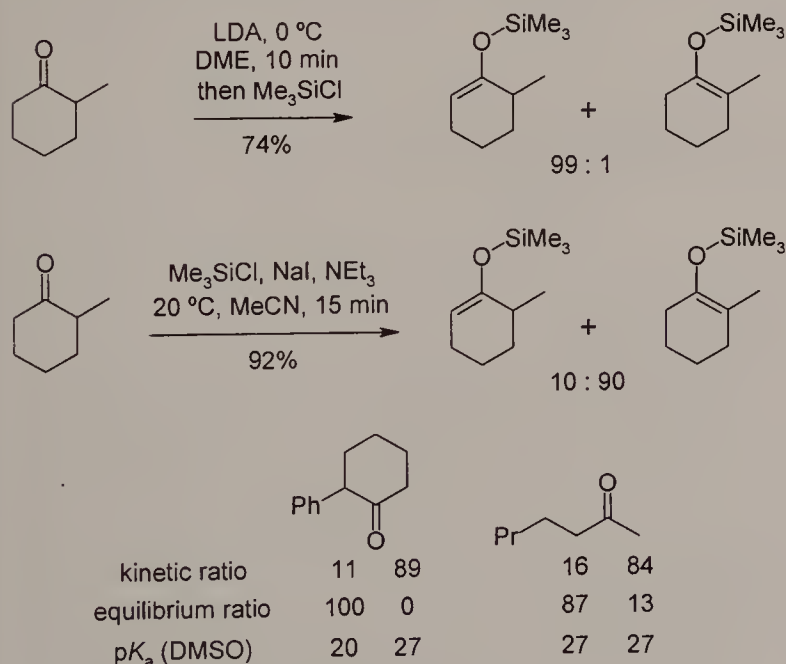
Scheme 5.3. Dependence of the reactivity of carbanions on their basicity [68, 72–74].

5.3.2

Kinetic/Thermodynamic Enolate Formation

Stoichiometric, irreversible formation of enolates from ketones or aldehydes is usually performed by addition of the carbonyl compound to a cold solution of LDA. Additives and the solvent can strongly influence the rate of enolate formation [23]. The use of organolithium compounds as bases for enolate formation is usually not a good idea, because these reagents will add to ketones quickly, even at low temperatures. Slightly less electrophilic carbonyl compounds, for example some methyl esters [75], can, however, be deprotonated by BuLi if the reactants are mixed at low temperatures (typically -78°C), at which more metalation than addition is usually observed. A powerful lithiating reagent, which can sometimes be used to deprotonate ketones at low temperatures, is *t*BuLi [76].

The organic chemist is occasionally confronted with the problem that a compound has several different X–H groups of similar pK_a . If only one of these is to be alkylated, one option would be to perform a regioselective deprotonation. This can sometimes be achieved by exploiting small differences between the kinetic or equilibrium acidities of the acidic sites. If strong bases such as LDA ($pK_a = 35.7$) or LiTMP ($pK_a = 37.3$) [77] are used deprotonation of many classes of compound can be conducted irreversibly and at low temperatures, at which interconversion of the possible, different carbanions is slow. If the carbanion formed by deprotonation of the C,H group of highest kinetic acidity (i.e. the initially formed carbanion) is not the thermodynamically most stable carbanion, equilibration of these carbanions at low temperatures might be sufficiently slow to enable the generation of the essentially pure, less stable carbanion ("kinetic control"). As shown in Scheme 5.4, 2-methylcyclohexanone ($pK_a \approx 26.4$) will be deprotonated by LDA more rapidly at the α -methylene group, because this group is sterically more accessible and because this position is statistically twice as likely as the methine group to be deprotonated. The enolate resulting from deprotonation of the sterically more demanding methine group is, however, more stable, because it is the more highly substituted alkene. Thus, if the products can equilibrate under the reaction conditions chosen the main product will usually result from the most highly substituted enolate [78, 79]. Acidic reaction conditions are also conducive to the formation of the most highly substituted enol derivative [80, 81]. As shown in Scheme 5.4, positions at which the equilibrium acidity is significantly lower than for other C,H groups might be kinetically sufficiently more acidic to enable their selective deprotonation.

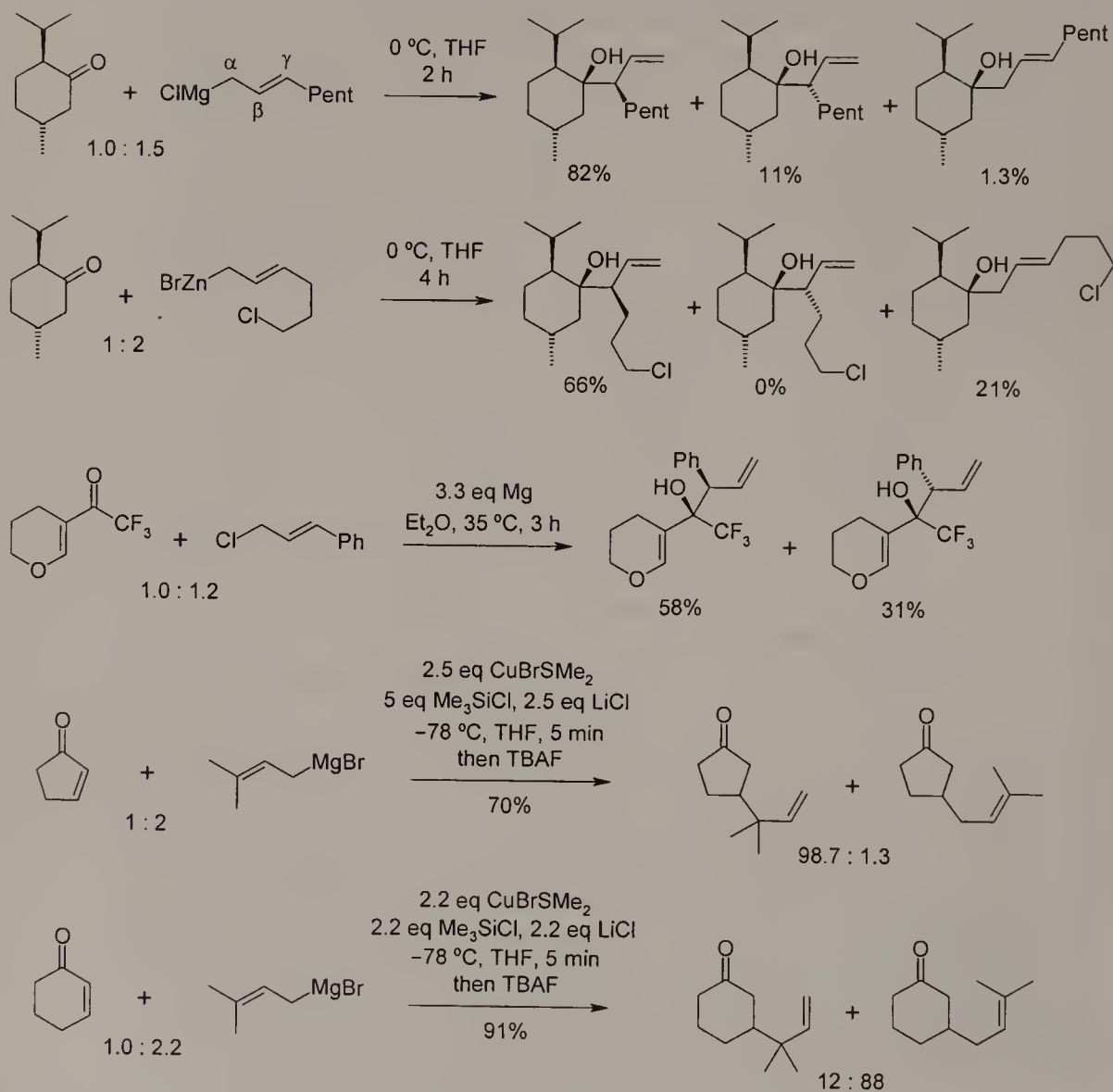


Scheme 5.4. Enolate formation under kinetic and thermodynamic control [79, 82–84].

5.3.3

Allylic and Propargylic Carbanions

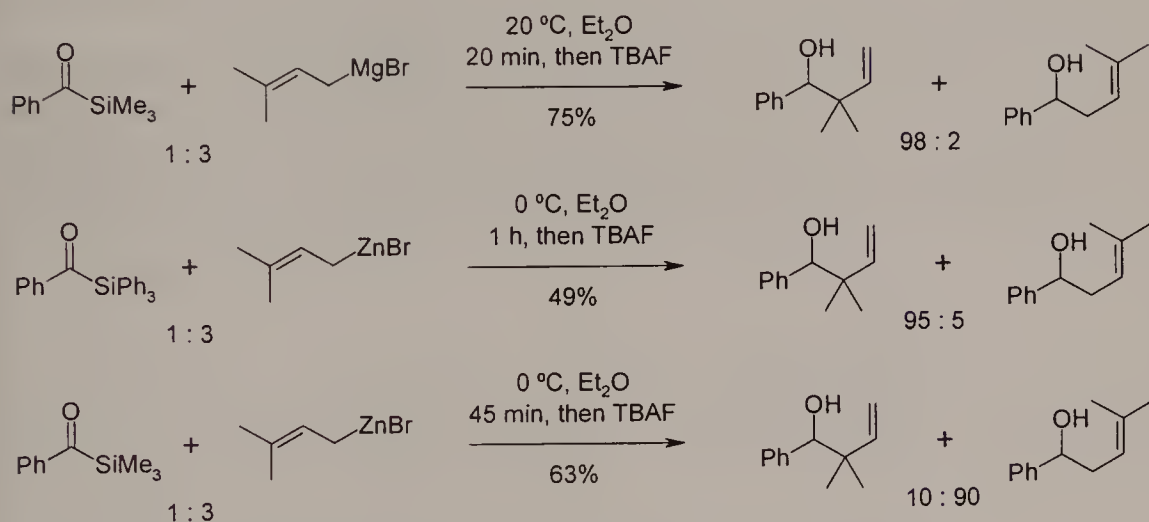
Allylic and propargylic carbanions are ambident nucleophiles which can in principle yield unrearranged or rearranged products when treated with an electrophile. Most nucleophilic allyl metals react with electrophiles at the γ position, and only occasionally (in particular with organopotassium and organosodium compounds [85, 86]) are mixtures of γ - and α -alkylated products obtained. Thus, 2-butenyllithium [87], magnesium [88, 89], titanium [90], zinc [91, 92], or copper reagents attack alkyl halides, aldehydes, ketones, imines, or electron-deficient alkenes mainly at the γ carbon to yield 1-methylallyl derivatives (Scheme 5.5). Some of these reactions can be conducted in the presence of enantiomerically pure catalysts with high diastereo-



Scheme 5.5. Reaction of allylic organometallic reagents with different electrophiles [94–96].

and enantioselectivity [93]. As shown by the two last reactions in Scheme 5.5, the α/γ -selectivity of prenyl copper reagents depends on the precise structure of the electrophile.

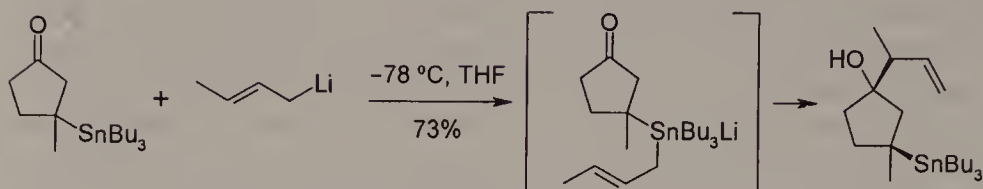
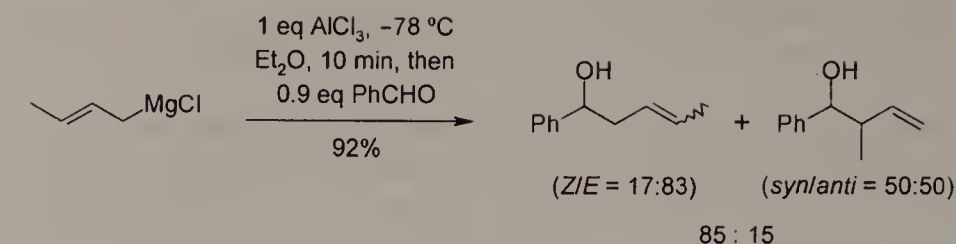
Substrates in which γ attack implies significant steric congestion can, however, predominantly yield products of α attack. A trick for enhancing the steric demand of aldehydes consists in using bulky acylsilanes instead. These react with organomagnesium or -zinc reagents to yield α -silyl alcoholates which undergo Brook rearrangement to silylethers. The latter can be readily desilylated to the corresponding secondary alcohols [86]. As illustrated by the examples in Scheme 5.6, the triphenylsilyl group is not well suited to enhance the α selectivity, but acyltrimethylsilanes combined with organozinc reagents yield mainly products of α attack. Bulkier electrophiles, such as acyltriisopropylsilanes, for instance, yield almost exclusively products of α attack on treatment with crotyl or prenyl zinc reagents. The corresponding Grignard reagents, however, still react mainly with the γ carbon, even with these sterically demanding silanes [86].



Scheme 5.6. Reaction of acylsilanes with prenylmagnesium and zinc bromide [86].

Selective α attack with crotyl metals can be achieved by transmetalation, i.e. by a sequence of two sequential γ derivatizations of the allylic carbanion (Scheme 5.7). This can, for instance, be achieved by treating crotyl magnesium chloride with AlCl_3 , followed by treatment with the electrophile. Not all transmetalations do, however, lead to an allylic rearrangement. Crotyllithium, for instance, reacts with stannanes with its α carbon to yield pentavalent stannates. In the example shown in Scheme 5.7 (last reaction) after allylation of tin (α attack) a highly diastereoselective intramolecular transfer of the crotyl group from tin to the carbonyl group occurs with allylic rearrangement [97].

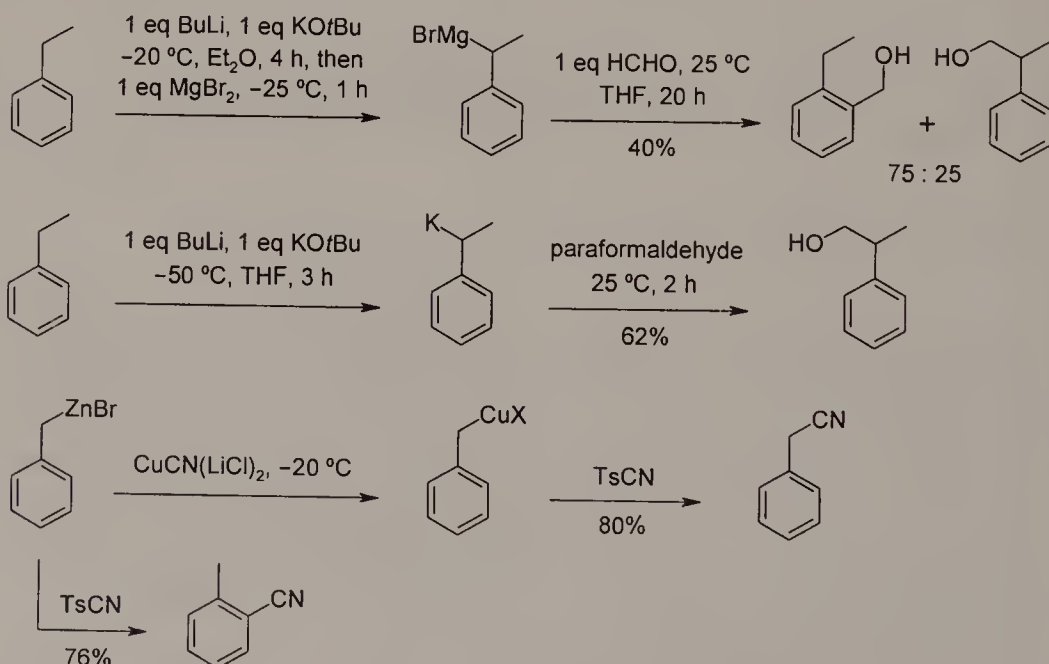
Benzylic organometallic compounds may react with electrophiles at either the benzylic or *ortho* position. Benzylic Grignard or organozinc reagents react with elec-



Scheme 5.7. Transmetalation of crotylmagnesium and crotyllithium compounds [97, 98].

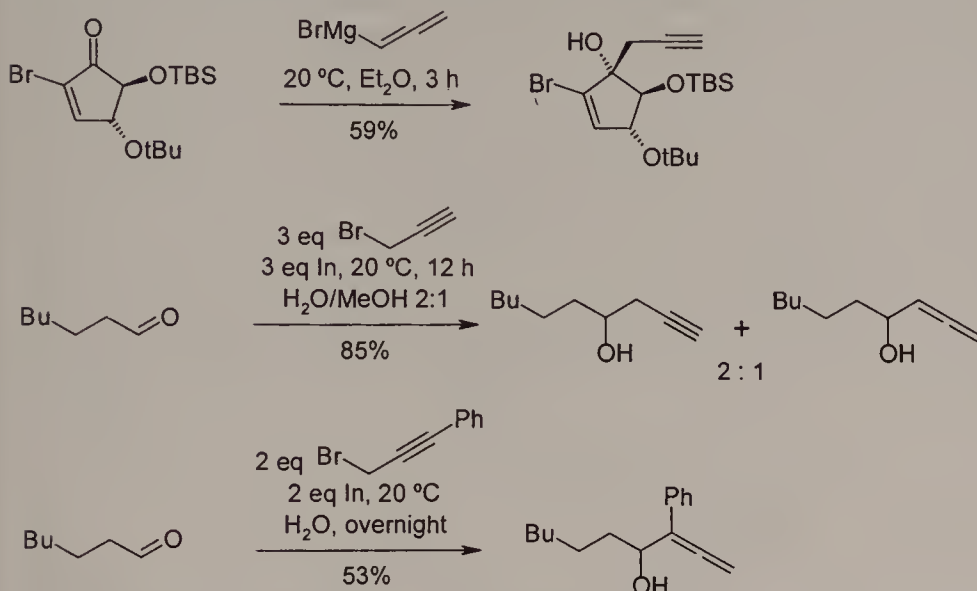
trophiles preferentially at the *ortho* position, whereas α attack is observed with the corresponding benzylpotassium or copper derivatives (Scheme 5.8).

Non-stabilized propargylic carbanions can react either without rearrangement to yield alkynes or rearrange to yield allenes. Propargyl bromide reacts with magnesium to yield allenylmagnesium bromide [100], which reacts with ketones [101], aldehydes [102, 103], benzyl halides [104], or tin halides [105] in Et_2O to yield alkynes (Scheme 5.9). Similarly, treatment of aldehydes with propargyl bromide and tin,

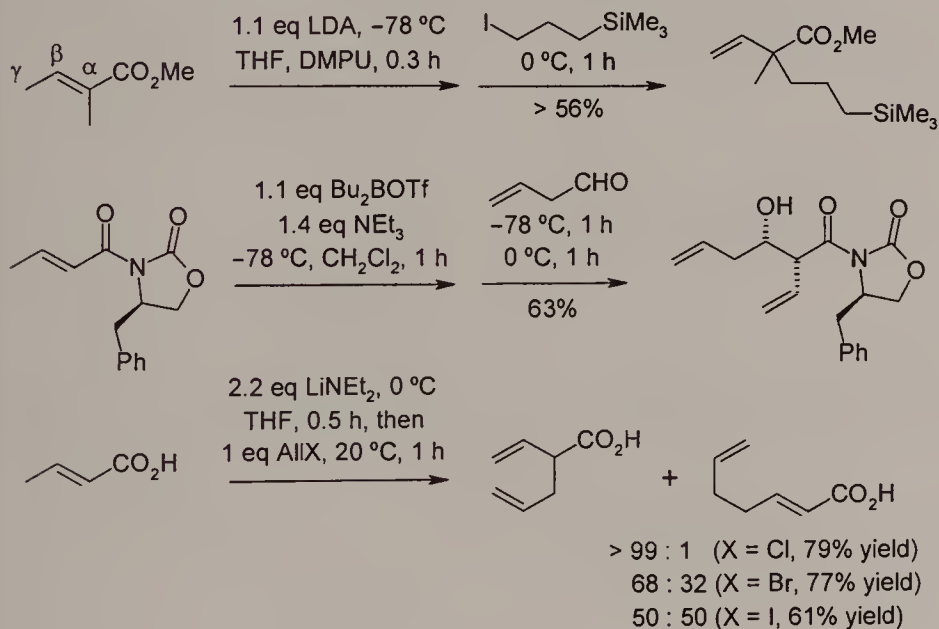


Scheme 5.8. Metal-dependent regioselectivity of the hydroxymethylation and cyanation of benzylic carbanions [85, 99].

zinc, indium, or bismuth in water leads mainly to alkynes[106]. In CH_2Cl_2 under acidic reaction conditions mixtures of allenes and alkynes often result[107, 108]. Propargyl derivatives of the type $\text{RC}\equiv\text{CCH}_2\text{X}$ ($\text{R}\neq\text{H}$) mainly yield allenes on halogen-metal exchange followed by reaction with an electrophile[105–108].



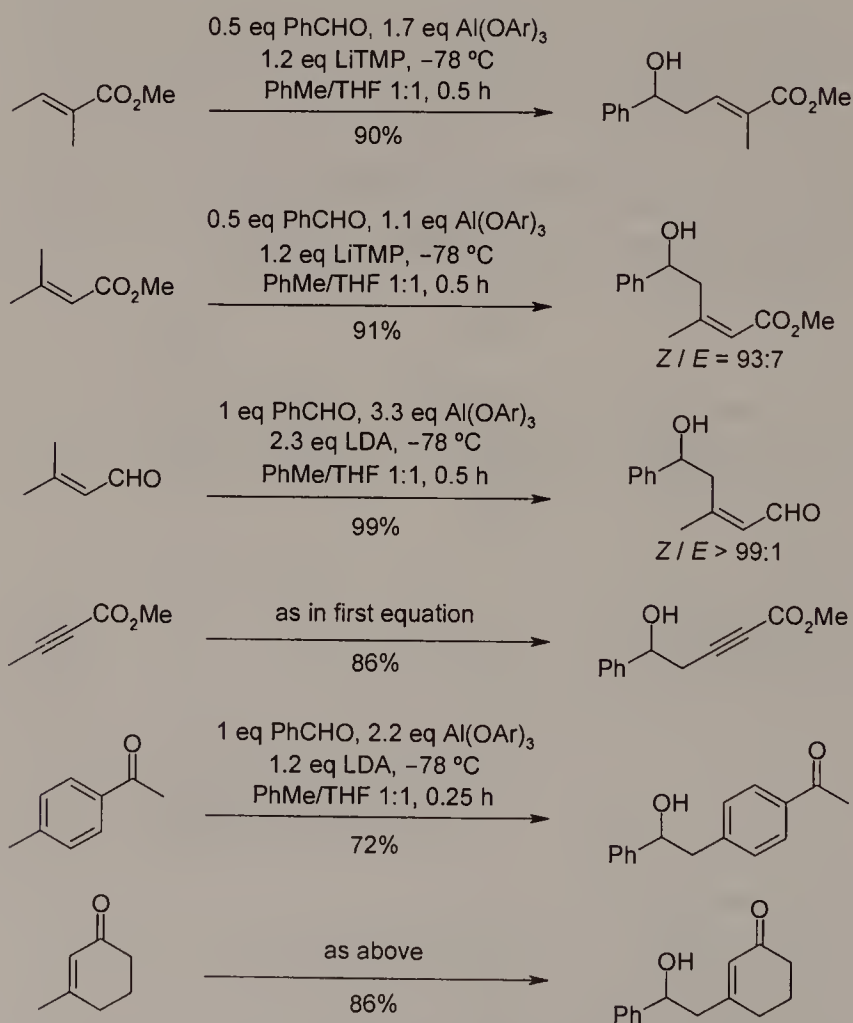
Scheme 5.9. Reactions of propargylic carbanions with electrophiles [101, 106].



Scheme 5.10. Alkylations of allylic carbanions [109, 111, 122–124].

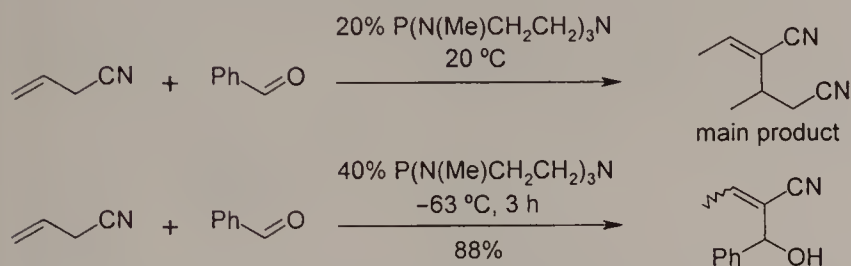
Metalated enones and related compounds are usually alkylated at the position α to the electron-withdrawing group [109–113], but the precise structure of the electrophile can also have an impact on regioselectivity (Scheme 5.10). Certain substrates, such as crotonic acid dianions [111], crotonamide dianions [114, 115], or certain enones [116] can also give mixtures of α - and γ -alkylated products, whereas metalated β -oxy [117–119] or β -amino [120, 121] acrylic acid derivatives often yield pure products of γ -alkylation.

Selective alkylation of the γ position of α,β -unsaturated esters, aldehydes, or ketones can be achieved if a sterically demanding Lewis acid is used to coordinate to the carbonyl group and inhibit α -alkylation by steric shielding [123, 125, 126] (Scheme 5.11). This method not only results in high regioselectivity but also enables highly stereoselective aldol-type additions to be performed in good yields, even with sensitive substrates, such as α,β -unsaturated aldehydes [126]. Thus, when two diastereotopic γ positions are available, the addition of a bulky aluminum phenolate leads to the clean formation of the *Z*-alkene (second and third examples, Scheme 5.11).



Scheme 5.11. γ -Alkylations of allylic and propargylic carbanions [123, 125, 126].
Ar = 2,6-Ph₂C₆H₃.

One potential problem in the reactions of stabilized allylic or propargylic carbanions is the dimerization of the starting material if the carbanions are not formed stoichiometrically. Alkenes substituted with electron-withdrawing groups are good Michael acceptors, to which nucleophiles will undergo conjugate addition. For instance, the Baylis–Hillman reaction of allyl cyanide with benzaldehyde requires careful optimization of the reaction conditions to avoid dimerization of the nitrile (Scheme 5.12). This problem is related to a common side reaction of Michael additions: reaction of the product with the Michael acceptor (Scheme 10.21).



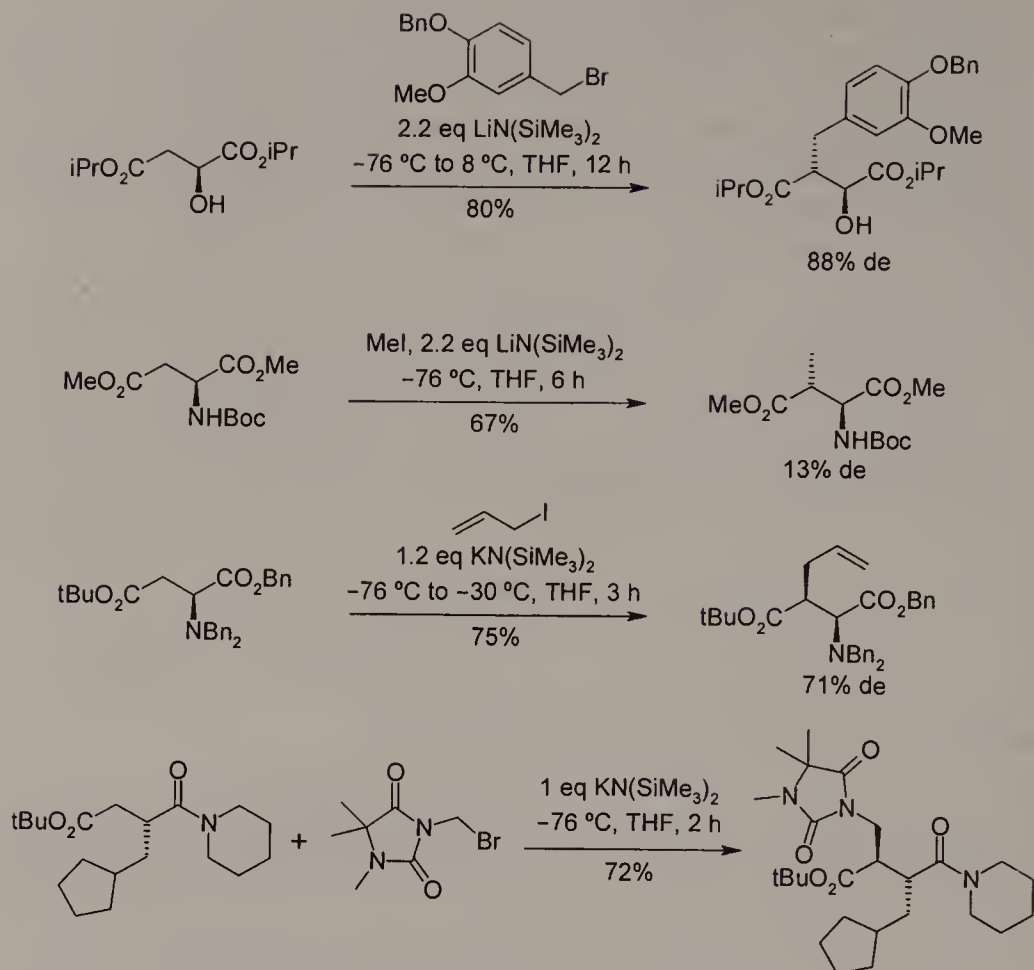
Scheme 5.12. Baylis–Hillman reaction of allyl cyanide [110].

5.3.4

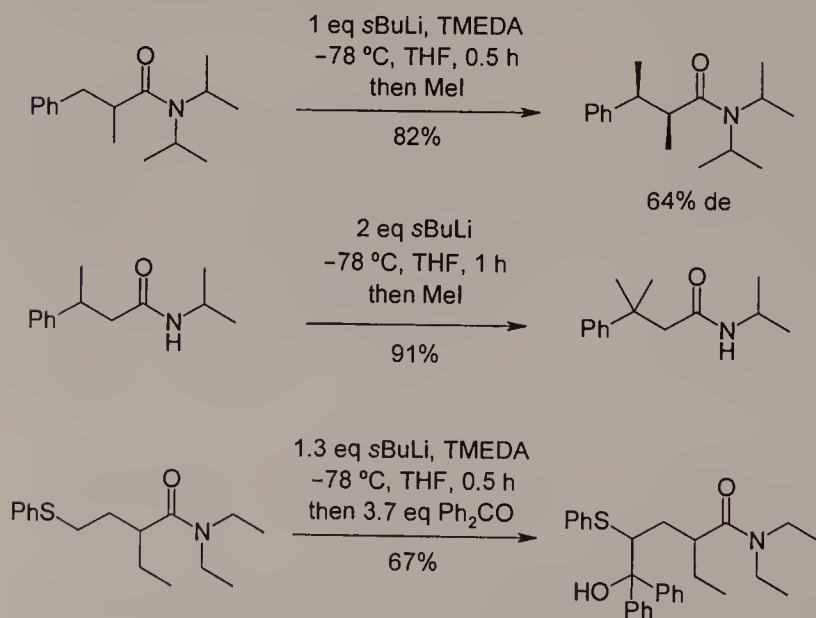
Succinic Acid Derivatives and Amide-derived Carbanions

The regioselective deprotonation of heteroatom-substituted succinic acid derivatives has been thoroughly investigated. The choice of protective group for the heteroatom is critical to avoid β -elimination. Because negatively charged atoms or groups destabilize a vicinal carbanion, derivatives of 2-hydroxy or 2-aminosuccinic acid (malic and aspartic acid) can be selectively converted to dianions and alkylated at the methylene group [127] (Scheme 5.13). Succinic acid derivatives in which the two carboxyl groups have been differentiated (e.g. amide/ester or ester/acid) can also be alkylated regioselectively [128–130] (Scheme 5.13).

The regioselectivity of the last reaction in Scheme 5.13 is not only because of the greater acidity of the methylene group, but also because some secondary and tertiary amides (e.g. β -arylamides, β -vinylamides, or β -(phenylthio)amides, or borane complexes of β -phosphino propionamides [132, 133]) are deprotonated at the β position under kinetic control to yield chelate-stabilized carbanions [58, 134]. Illustrative examples of such remarkable metalations are shown in Scheme 5.14.



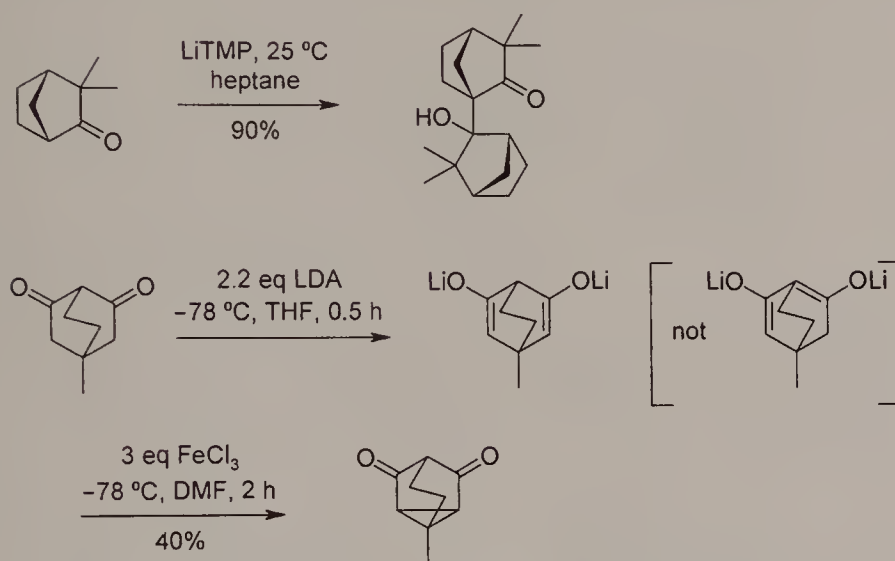
Scheme 5.13. Alkylation of substituted succinic acid derivatives [128–131].

Scheme 5.14. Alkylation of amides at the β and γ positions [53, 58, 134].

5.3.5

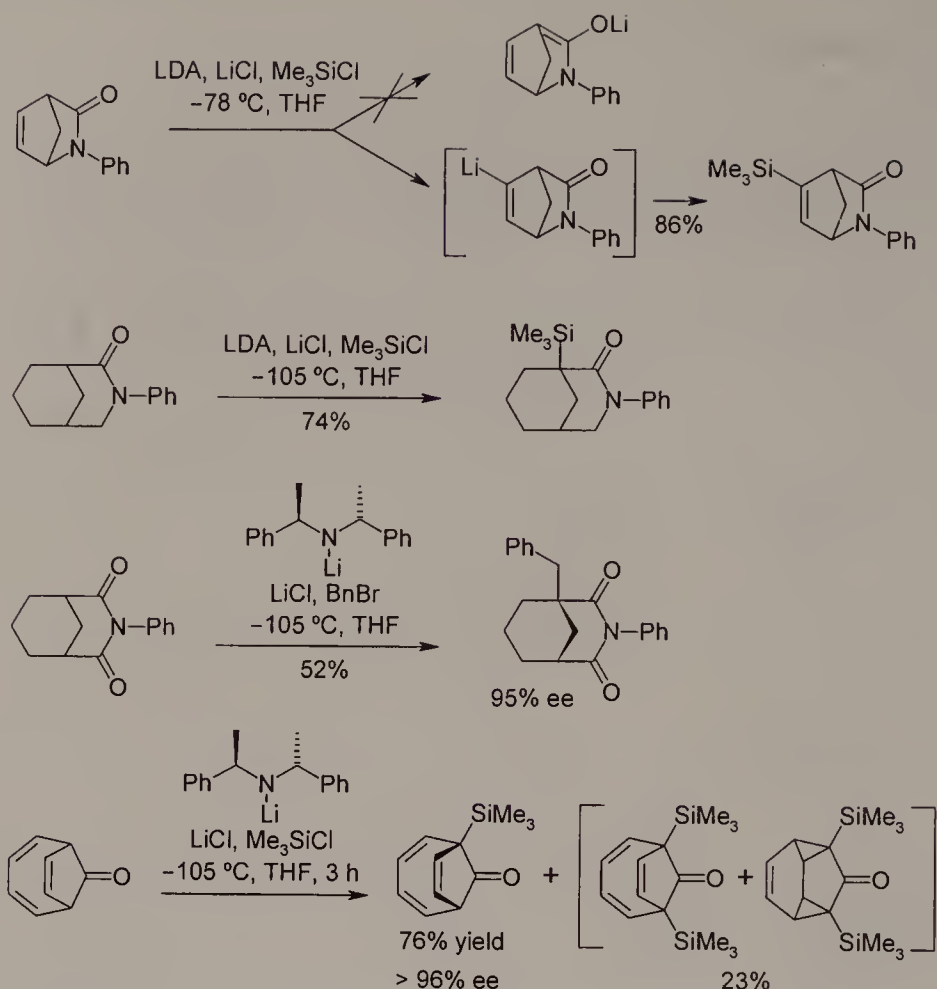
Bridgehead Carbanions

Small bicyclic ketones or lactams with a bridgehead C,H group are much less acidic than comparable acyclic compounds, because delocalization of the negative charge to the carbonyl oxygen atom would imply the formation of a highly strained bridgehead alkene. Such bridgehead enolates usually oligomerize quickly by intermolecular addition of the carbanion to the non-enolized carbonyl groups, sometimes even in the presence of other trapping reagents [135]. Even cyclic 1,3-diketones are no longer C,H-acidic if C-2 is located at a bridgehead position (second example, Scheme 5.15).



Scheme 5.15. Deprotonation and reactions of bicyclic ketones [135, 136].

If bridgehead enolates are, however, generated in the presence of a strong, base-resistant electrophile, under optimized conditions no oligomers but the expected, bridgehead-derivatized products can sometimes be isolated (Scheme 5.16). In the examples in Scheme 5.16 interestingly no *ortho*-metalation of the phenyl group is observed.



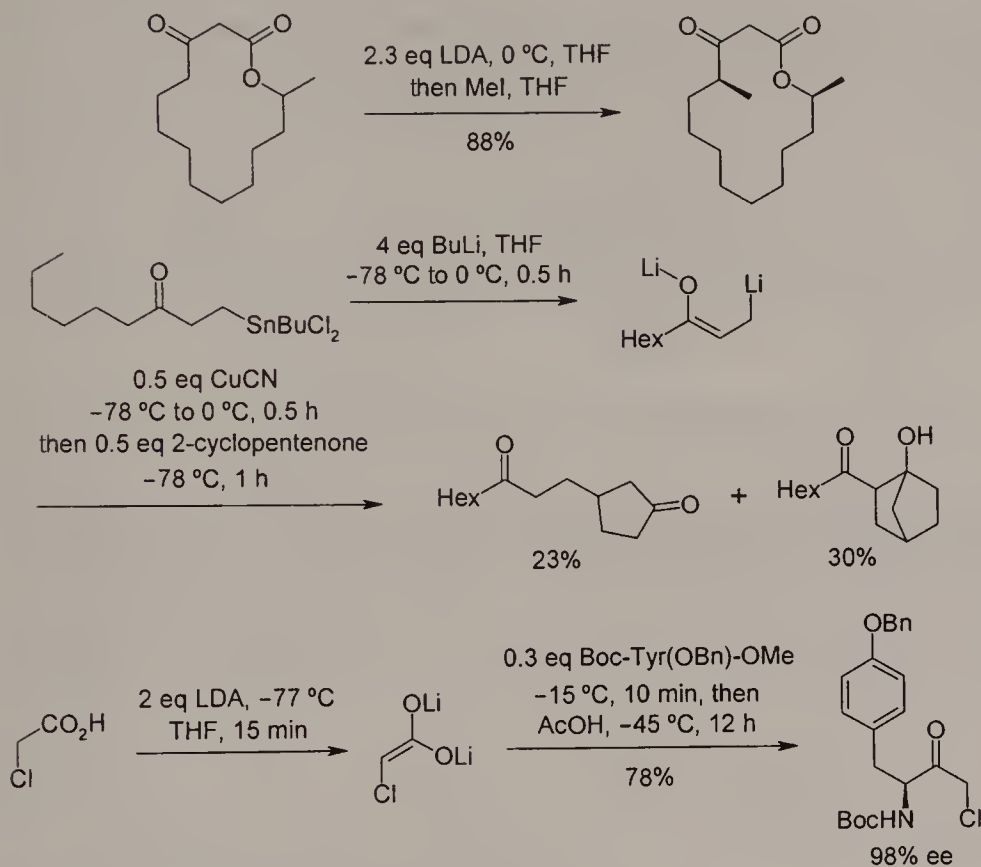
Scheme 5.16. Generation and derivatization of bridgehead enolates [135, 137].

5.3.6

Dianions

A valuable alternative to regioselective deprotonations of substrates with more than one acidic group is the formation of a di- or polyanion by addition of an excess of a strong base. If the nucleophilic sites in the polyanion have different chemical hardness, regioselective alkylation can be achieved by selecting a soft or a hard electrophile (second reaction, Scheme 5.13). If two or more C,H groups are deprotonated, and if the resulting nucleophilic sites are similarly hard, the most nucleophilic site (often that formed last) will be the most reactive, and will be alkylated first. This strategy has been extensively used to alkylate 3-oxobutyrate or related 1,3-dicarbonyl compounds at C-4 (first reaction, Scheme 5.17). Further useful dianions can be generated from ketones ($\text{C}=\text{C}(\text{OM})\text{CM}$ or $\text{C}=\text{C}(\text{OM})\text{CCM}$) [138–142], carboxylic acids ($\text{C}=\text{C}(\text{OM})_2$) [143–145], succinic acid derivatives ($((\text{C}=\text{C}(\text{OM})\text{OR})_2)$ [146], alkynes ($\text{MC}\equiv\text{CCM}$, $\text{MC}\equiv\text{CC}-\text{OM}$) [147–155], imidazoles [156], thiophenes [157, 158], β -alanine derivatives ($\text{MN}-\text{CC}=\text{C}(\text{OM})\text{X}$) [159], 3-nitropropanoates [160, 161],

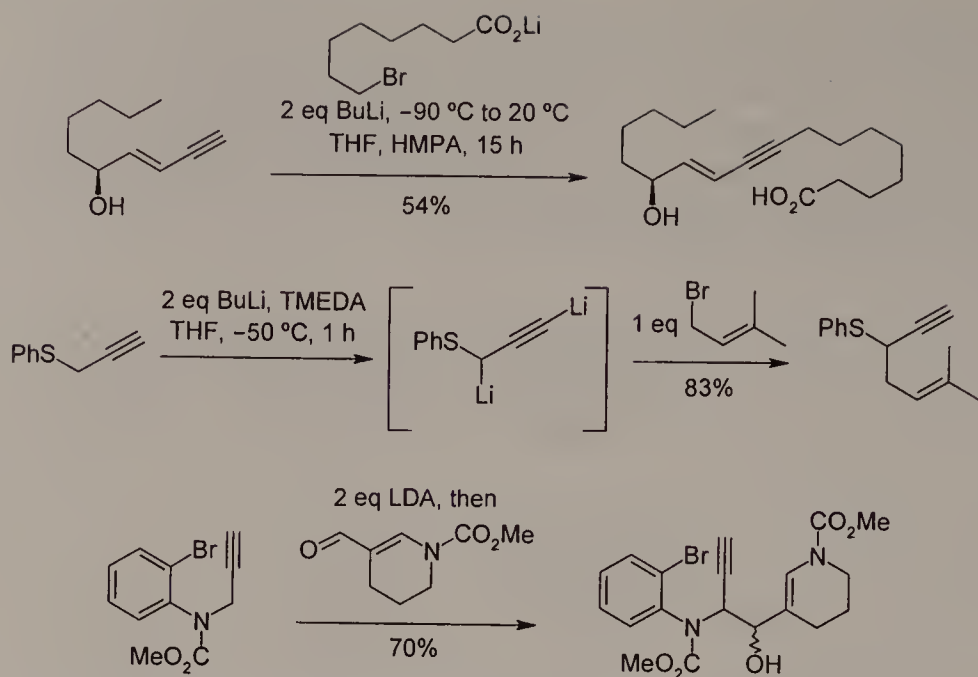
3-hydroxypropanoates [162, 163], 2-hydroxyethylsulfones [164, 165], arenes [166–168], allenes [169], thioamides [170], and sulfonamides (MC-SO₂NM [171]; R₂NSO₂-CM₂ [172]). Twofold metalation of nitroalkanes leads to intermediates which undergo clean C-alkylation [70, 71], in contrast to monodeprotonated nitroalkanes, which are quite unreactive and are mainly alkylated at oxygen [67–69, 173] (Scheme 5.3). Illustrative examples of the regioselective alkylation of dianions are illustrated in Schemes 5.17 and 5.18.



Scheme 5.17. Alkylation of dianions [141, 144, 174].

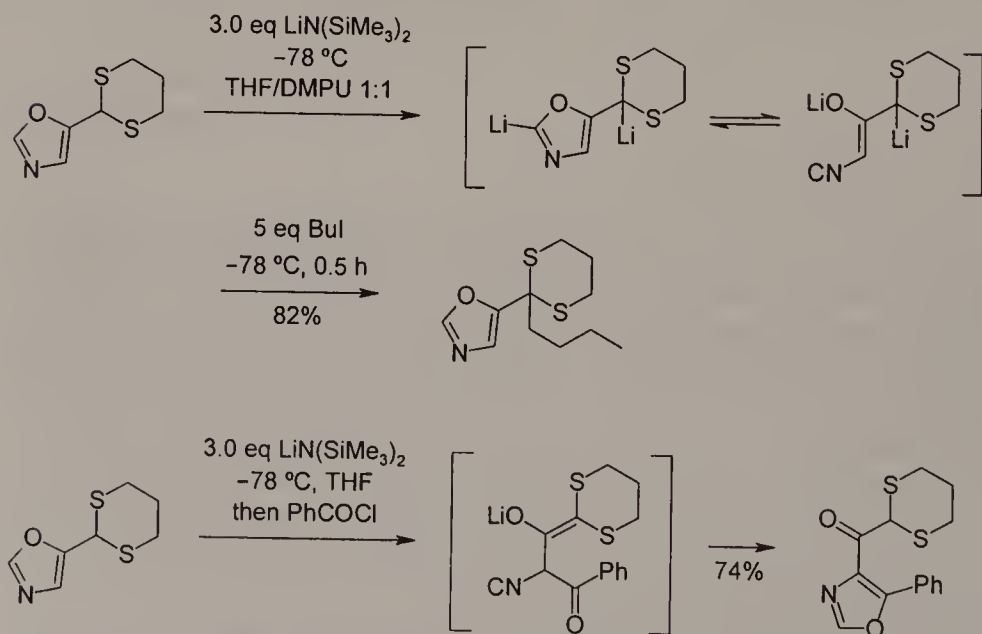
Some dianions, in particular Grignard dianions, can be poorly soluble [151], and addition of HMPA or DMPU [175] to enhance their solubility might be advisable. Propargyl derivatives usually yield, on treatment with a base, the acetylide first, because the acetylenic C–H bond is usually more acidic and leads to less rehybridization on deprotonation. Phenyl propargyl sulfide, for instance, can be lithiated and alkylated selectively at the alkynyl group by using one equivalent of BuLi as base [176]. Alkylation of the propargylic position requires either protection of the alkyne (e.g. as trimethylsilane [177]) or the formation of a dianion (Scheme 5.18). The dianions from phenyl propargyl sulfoxide or sulfone have been reported to be significantly less reactive than that derived from phenyl propargyl sulfide [147].

1,3-Oxazoles can be readily deprotonated at C-2, but the resulting carbanions are unstable and can undergo reversible ring opening [179]. An interesting example of



Scheme 5.18. Alkylation of alkyne-derived dianions [147, 148, 178].

electrophile- and solvent-dependent regioselectivity in the derivatization of an oxazole-based dianion is illustrated in Scheme 5.19. When alkylating reagents are used as electrophiles, the dianion undergoes rearrangement-free alkylation at the dithiane. Acylating reagents, however, react faster with the ring-opened dianion to yield an intermediate α,α -diacylisonitrile which, on ring closure, leads to the formation of 4-acyloxazoles.



Scheme 5.19. Regioselective derivatization of an oxazole-derived dianion [180].

5.3.7

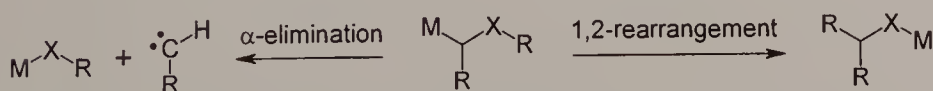
 α -Heteroatom Carbanions

Carbanions in which delocalization of the negative charge to a more electronegative atom than carbon is not possible usually require strong bases for their formation. Typical pK_a values of hydrocarbons and some compounds with carbon–heteroatom single bonds are given in Table 5.2. Because of their high basicity, formation of such “non-stabilized” carbanions rarely competes with the formation of, e.g., enolates or other, better stabilized carbanions. Instead of forming a bond with an electrophile, these strongly basic carbanions can also just deprotonate it if the electrophile can act as an acid. This happens frequently when highly enolized aldehydes or ketones (e.g. acetophenones or tetralones) are chosen as electrophiles, but can also occur with allyl or alkyl halides if the carbanion is very basic [181]. In these circumstances transmetalation (e.g. Li, Na, K to Mg, Mn, Cu, Zn, Cd, Ce, In, Ti, or Zr) will be required to reduce the basicity of the carbanion [171, 182–188]. Organozirconium reagents can even add to ketones containing a CH-NO_2 group without being protonated [183].

Table 5.2. Equilibrium acidities of hydrocarbons in DMSO (H_2O) at 25 °C [24, 25, 33, 189].

Acid	pK_a	Acid	pK_a
Cyclopentadiene	18.0 (16)	Propene	44 (43)
Indene	20.1 (20)	$\text{H}_2\text{C}=\text{CH}_2$	(44)
Fluorene	22.6 (23)	Cyclopropane	(46)
$\text{PhC}\equiv\text{CH}$	28.7 (20.0)	CH_4	56 (48)
Ph_3CH	30.6	Me_4N^+	42
Ph_2CH_2	32.2	MePPh_3^+	22
PhCH_3	43 (40)	MeOPh	49
PhH	(43)	Me_2S	45

Carbanions generated by deprotonation of compounds of type $\text{R}'\text{CH}_2\text{X}$ ($\text{X} = \text{SiR}_3$, NR_3^+ , NR_2 , PR_2 , OR , SR , Hal) cannot be stabilized by conjugative charge delocalization, but only by inductive effects, field effects, negative hyperconjugation, or chelate formation [59]. If no possibility of chelation of the metal is available these carbanions will tend to be highly reactive and undergo “forbidden” (i.e. non-concerted) rearrangements via homolytic bond cleavage (e.g. [1,2]-Wittig ($\text{X} = \text{O}$) [190–192], Stevens ($\text{X} = \text{NR}_2^+$) [193–195], or related rearrangements [195, 196]) or α -elimination to yield carbenes (Scheme 5.20).

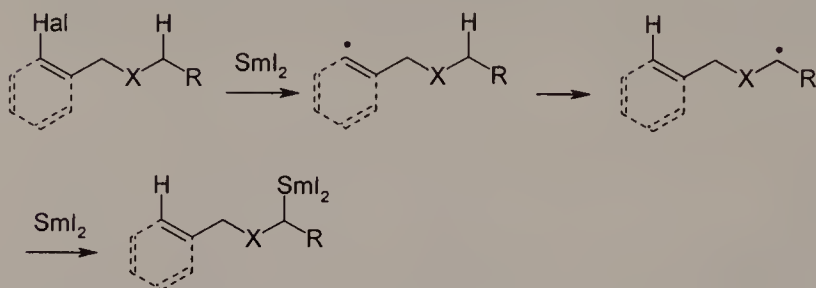


Scheme 5.20. Possible decomposition reactions of α -heteroatom substituted carbanions. $\text{X} = \text{O}$, NR , NR_2^+ .

Such reactive carbanions can also act as reducing agents or as strong bases, and can lead to numerous unexpected reactions [197]. Few solvents are sufficiently inert to withstand them [198]. Chelate-stabilized, α -heteroatom-substituted carbanions can, on the other hand, be quite stable, and in recent years numerous useful transformations involving these intermediates have been developed.

Allylic and propargylic heteroatom-substituted carbanions can yield rearranged or unrearranged products on treatment with an electrophile. The regio- and stereo-selectivity of these reactions depends on the precise structure of the carbanion, on the metal and solvent chosen [199], and on the structure of the electrophile [150, 200–203], and can be difficult to predict.

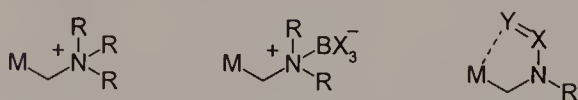
In addition to deprotonation with strong bases, halogen–metal exchange, or trans-metalation, α -heteroatom-substituted carbanions can also be prepared by 1,5-hydrogen transfer to vinyl radicals, followed by reduction [204, 205] (Scheme 5.21) or by a related intramolecular 1,4-proton transfer [206].



Scheme 5.21. Generation of carbanions by 1,5-hydrogen transfer.
X = NR [205], O [204].

5.3.7.1 α -Nitrogen Carbanions

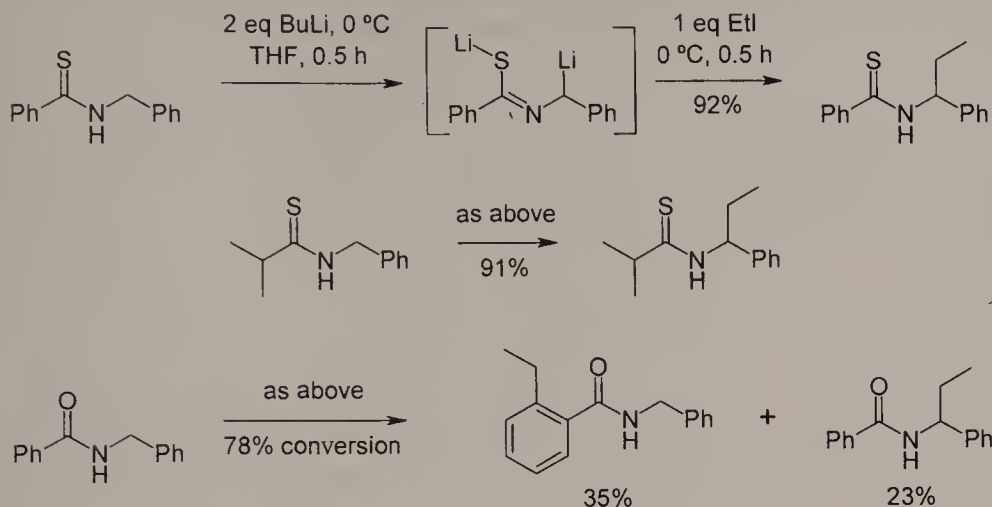
Simple tertiary amines are difficult to deprotonate selectively [195, 196, 200]. To increase the acidity of the α -C,H-groups the amine can be quaternized [207], treated with a Lewis acid [208–211], oxidized to an amine N-oxide [161], or, for secondary amines, derivatized with a functional group capable of forming a chelate with the metal (Scheme 5.22).



Scheme 5.22. Strategies for the enhancement of the α -acidity of amines.

Non-enolizable amides, for example *N,N*-dialkyl pivalamides [212], benzamides, thiobenzamides [213], or phosphinamides ($\text{Ph}_2\text{P}(\text{O})\text{NR}_2$ [214]), can be lithiated α to the amino group by treatment with *s*BuLi [54, 213, 215] or *t*BuLi [216], without further additives, in THF at -78°C . *N,N*-Dimethylbenzamides can be attacked at the carbonyl group by these organolithium reagents to yield ketones [217] or alcohols, but with sterically more demanding amides metalation is usually faster than addition.

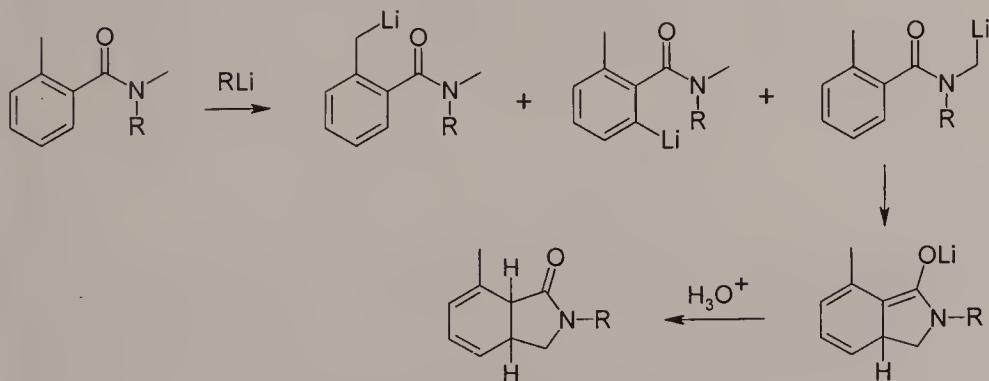
N-Benzyl thioamides can be readily lithiated twice with BuLi, to yield benzylic organolithium derivatives. As illustrated by the examples (Scheme 5.23), the regioselectivity of this metalation is quite different than that of comparable amides.



Scheme 5.23. Alkylation of thioamide-derived dianions [170].

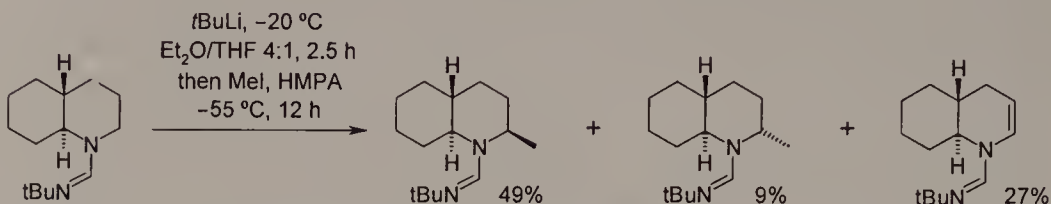
As shown by the last reaction in Scheme 5.23, the metalation of benzamides is complicated by several potential side reactions (Scheme 5.24). Thus, benzamides can also undergo *ortho*-metalation [181, 217–222] or metalation at benzylic positions [223–225]. *Ortho*-metalation seems to be promoted by additives such as TMEDA, and benzylic metalation can be performed selectively with lithium amide bases [217, 224], which are often not sufficiently basic to mediate *ortho*- or α -amino metalation. If deprotonation of the CH–N group succeeds, the resulting product might also undergo cyclization by intramolecular attack at the arene [214, 216] (see also Ref. [226] and Scheme 5.27) instead of reacting intermolecularly with an electrophile. That this cyclization occurs, despite the loss of aromaticity, shows how reactive these intermediates are.

Because amides are often difficult to hydrolyze, their utility as transient activating groups for amines is limited. For this reason more readily hydrolyzable groups were



Scheme 5.24. Potential products of the lithiation of benzamides.

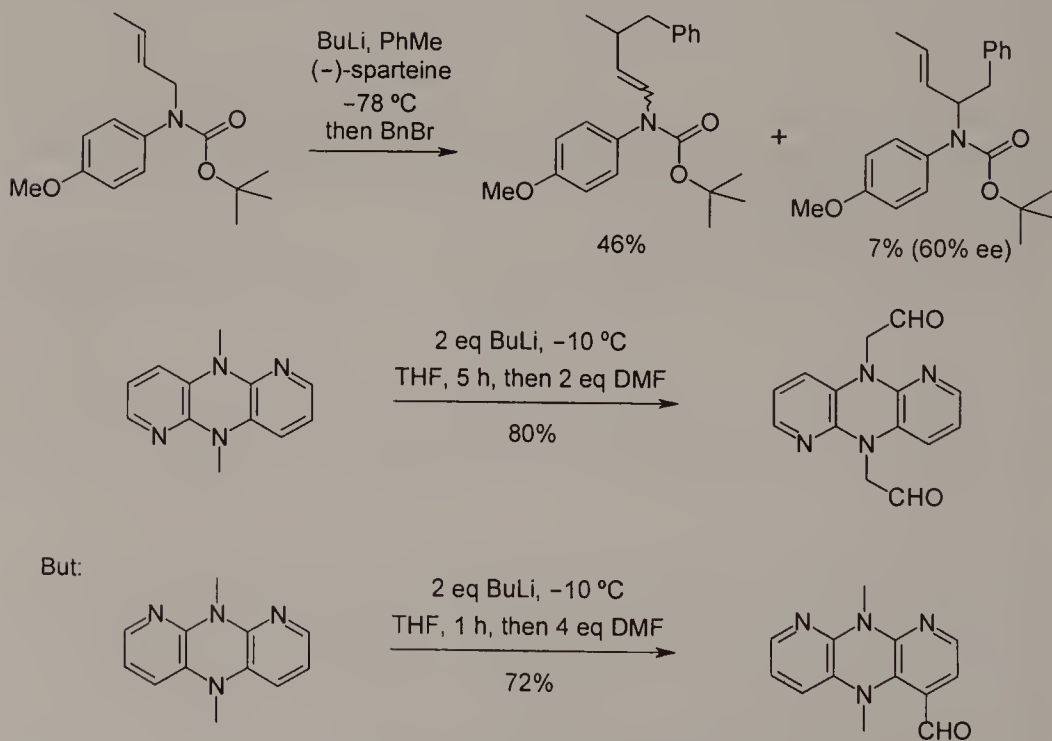
evaluated. Formamides and thioformamides are usually not deprotonated α to nitrogen but at the formyl group [59, 227–231] (Section 5.3.9). Formamidines ($R_2N-CH=NR$), however, have proven to be suitable activating groups for α -metalation of amines [232–237] (Scheme 5.25). The corresponding carbanions are highly reactive, and can act either as nucleophiles or as reducing agents [233, 235].



Scheme 5.25. Metalation and alkylation of formamidines [235].

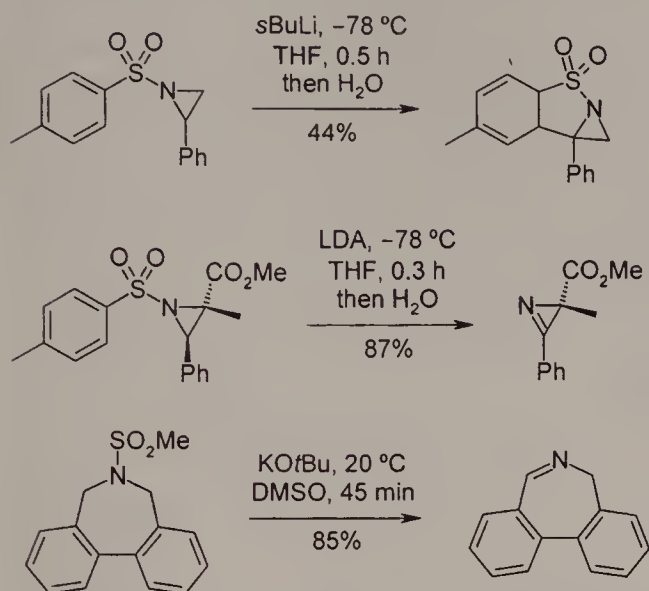
Further derivatives of amines in which the α -C,H groups are sufficiently acidic to enable metalation are carbamates [235, 238–240] (Scheme 5.26), imides [241], *N*-nitroso amines [59, 242], ureas [201, 243], some *N*-phosphorus derivatives [212, 214, 226, 244, 245], *N*-(2-pyridyl)amines (Scheme 5.26), and isonitriles [59]. A potential side reaction in the examples in Scheme 5.26 is the lithiation of the arene; this is, in fact, observed with an isomeric dipyridopyrazine (last reaction, Scheme 5.26).

Sulfonamides also can be metalated at the nitrogen-bound carbon [247] (Scheme 5.27). The sulfonyl group is, however, usually not well suited for the stabilization of α -metalated amines because sulfinate is a good leaving group, and imines



Scheme 5.26. Lithiation and alkylation of carbamates [56] and pyridylamines [246].

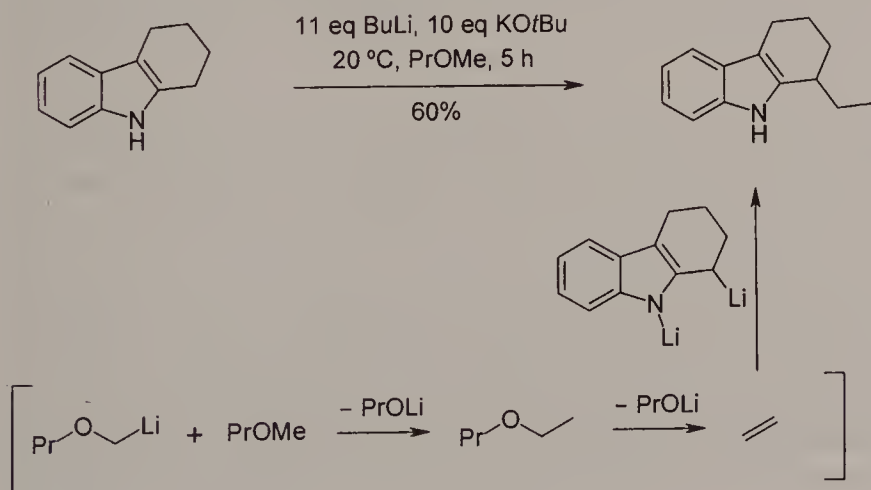
usually result when sulfonamides of secondary amines are treated with strong bases [248] (Scheme 5.27). Similarly, some *N*-phosphorus derivatives undergo elimination to yield imines when treated with a strong base [244]. A further side reaction of chelate-stabilized α -amino carbanions is the intramolecular migration of the chelating group to the carbanion (Section 5.4.5).



Scheme 5.27. The sulfonyl group as carbanion-stabilizing or leaving group [247, 249–251].

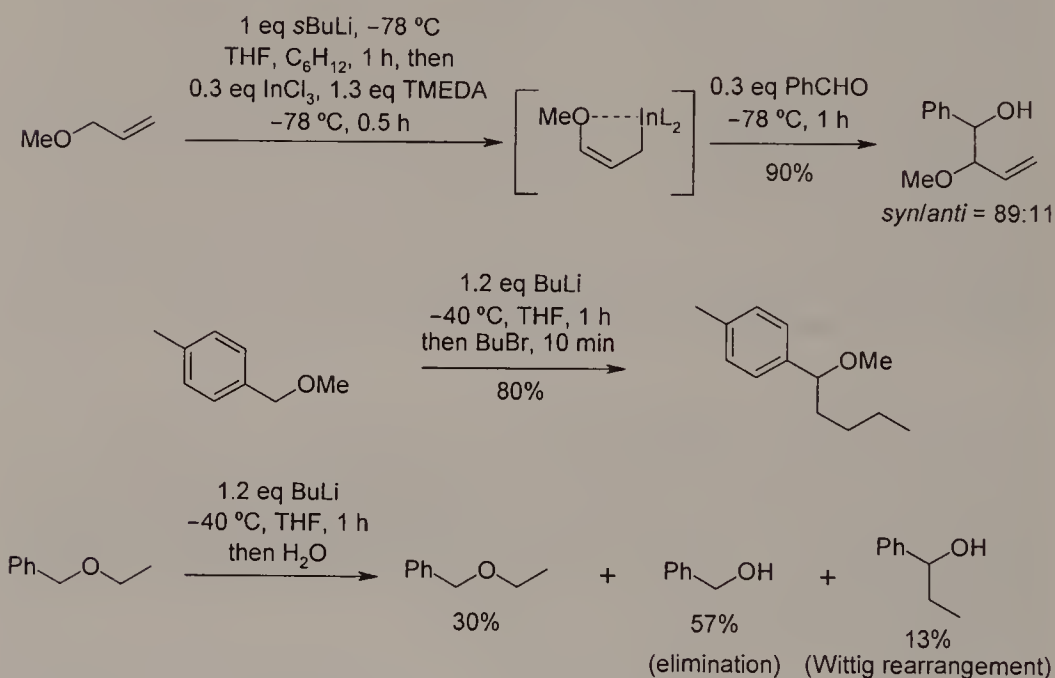
5.3.7.2 α -Oxygen and α -Sulfur Carbanions

α -Metalated, non-chelate stabilized ethers are highly reactive intermediates which tend to rearrange (Wittig rearrangement) or undergo other decomposition reactions such as eliminations or intermolecular nucleophilic displacement of alkoxide (Scheme 5.28). Because of their high energy, the reaction of metalated ethers with electrophiles can readily lead to product mixtures.



Scheme 5.28. Cleavage of ethers by strong bases [197].

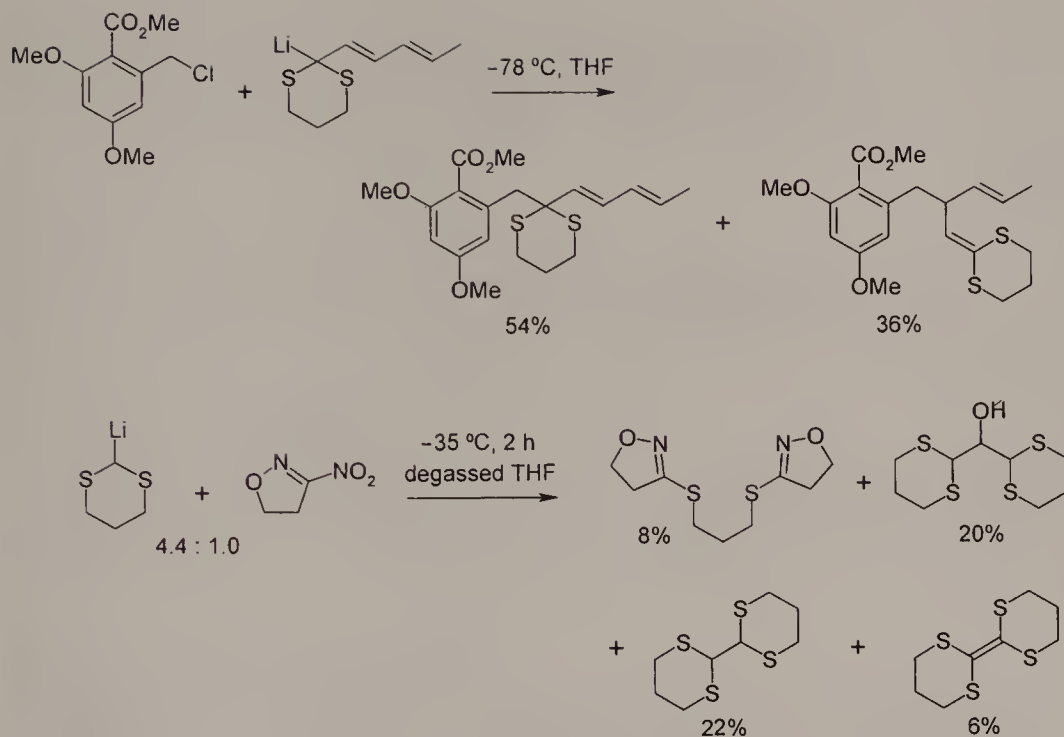
Benzyl methyl ether or allyl methyl ethers can be selectively metalated at the benzylic/allylic position by treatment with BuLi or *s*BuLi in THF at -40°C to -80°C , and the resulting organolithium compounds react with primary and secondary alkyl halides, epoxides, aldehydes, or other electrophiles to yield the expected products [187, 252, 253]. With allyl ethers mixtures of α - and γ -alkylated products can result [254], but transmetalation of the lithiated allyl ethers with indium yields γ -metalated enol ethers, which are attacked by electrophiles at the α position (Scheme 5.29). Ethers with β hydrogen usually undergo rapid elimination when treated with strong bases, and cannot be readily C-alkylated (last reaction, Scheme 5.29). Metalation of benzyl ethers at room temperature can also lead to metalation of the arene [255] (Section 5.3.11) or to Wittig rearrangement [256]. Epoxides have been lithiated and silylated by treatment with *s*BuLi at -90°C in the presence of a diamine and a silyl chloride [257].



Scheme 5.29. Reactions of metalated ethers [187, 252].

Convenient alternatives to direct deprotonation of ethers are tin–lithium exchange [199, 258–261], halogen–magnesium exchange [262], or reductive cleavage of O,Se-acetals [263, 264]. Another synthetic equivalent of α -metalated ethers are (alkoxymethyl)phosphonium salts [265].

α -Sulfur carbanions are usually more stable than metalated ethers, and lithiated 1,3-dithianes, in particular, have found widespread application in organic synthesis as synthetic equivalents of acyl anions (Scheme 5.30). Lithiated dithianes are, however, in the same way as most other organolithium reagents, highly oxygen- and oxidant-sensitive, and numerous byproducts can be formed if oxygen is not rigorously excluded from the reaction or if the electrophile can act as an oxidant. Oxidation by

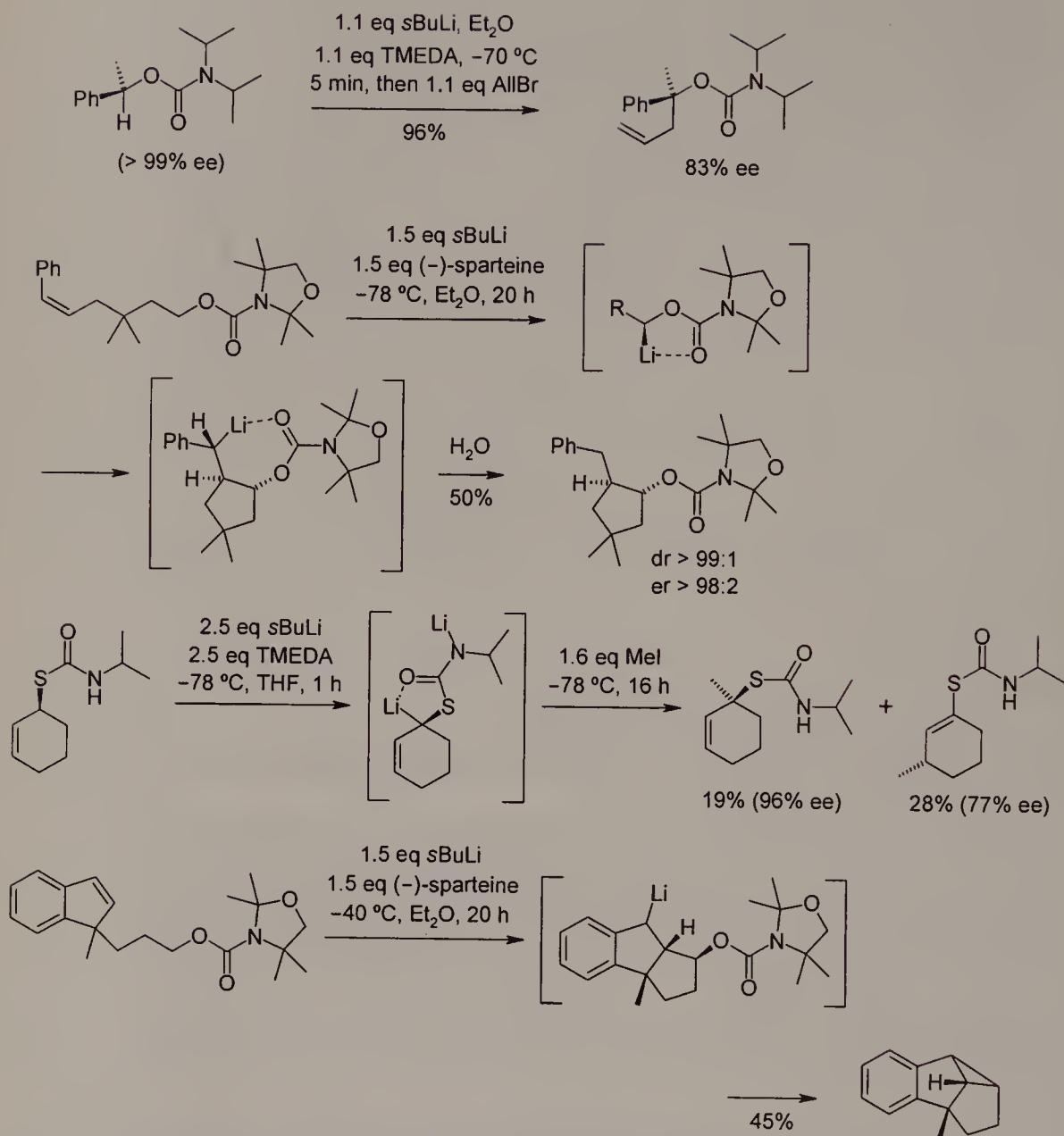


Scheme 5.30. Reactions of lithiated 1,3-dithianes [266, 267].

SET to the nitro group is probably the reason for the product mixture formed in the second example in Scheme 5.30.

α -Oxygen or α -sulfur carbanions can be stabilized by intramolecular chelation. Thus, carbamates such as those developed by Hoppe (Scheme 5.31) yield, on deprotonation, stable carbanions, which undergo clean, highly regio- and stereoselective, and often high-yielding reactions with a variety of electrophiles [202, 203, 254, 268–271]. In the presence of stoichiometric amounts of enantiomerically pure diamines enantioselective deprotonations can be performed (Scheme 5.31). Because the carbamate group can be displaced by nucleophiles, addition of α -metalated carbamates to alkenes can lead to the formation of cyclopropanes (last reaction, Scheme 5.31) [272, 273].

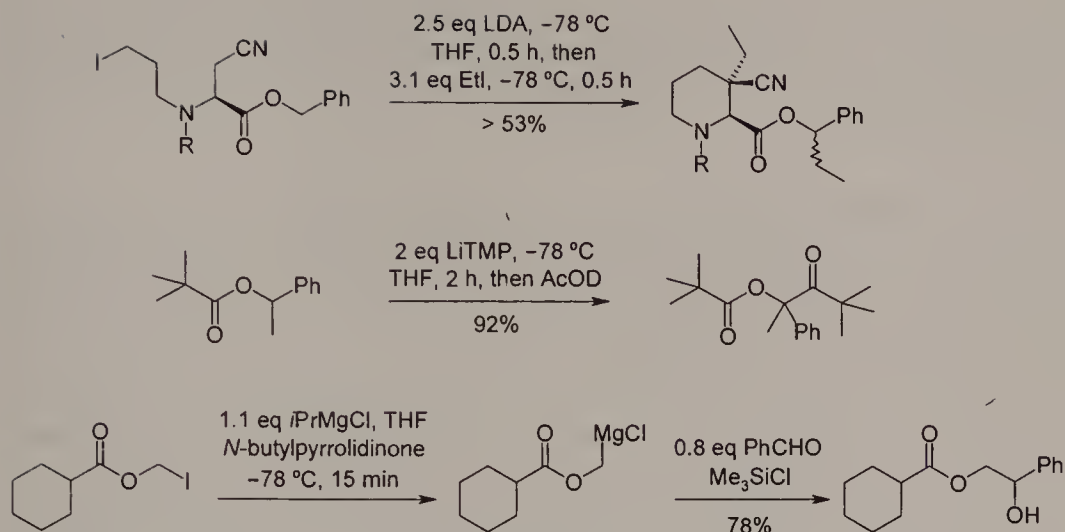
Other compounds which can be deprotonated to yield chelate-stabilized α -oxygen carbanions include non-enolizable esters, for example 2,6-dialkylbenzoates [59, 275–277], 2-alkoxybenzimidazoles [188], and some oxazolines [278]. Pivalates can also be lithiated α to oxygen, but the resulting carbanions are quickly transformed into ketones either by reaction with the starting ester (Scheme 5.32) or by intramolecular rearrangement [276]. Similarly, phosphates, on metalation, undergo rapid rearrangement to α -hydroxyphosphonates [279, 280]. Ester-derived Grignard reagents of the type $\text{RC}(=\text{O})\text{OCR}_2\text{MgX}$ can be prepared by halogen–magnesium or sulfoxide–magnesium exchange, and do not rearrange to ketones at $-78\text{ }^{\circ}\text{C}$ (at least within 15 min; Scheme 5.32) [281]. An exceptionally facile deprotonation reported by Christie and



Scheme 5.31. Formation and alkylation of chelate-stabilized α -oxygen and α -sulfur carbanions [55, 272–274].

Rapoport is the lithiation and alkylation of the enolizable α -amino ester shown in Scheme 5.32 (first example).

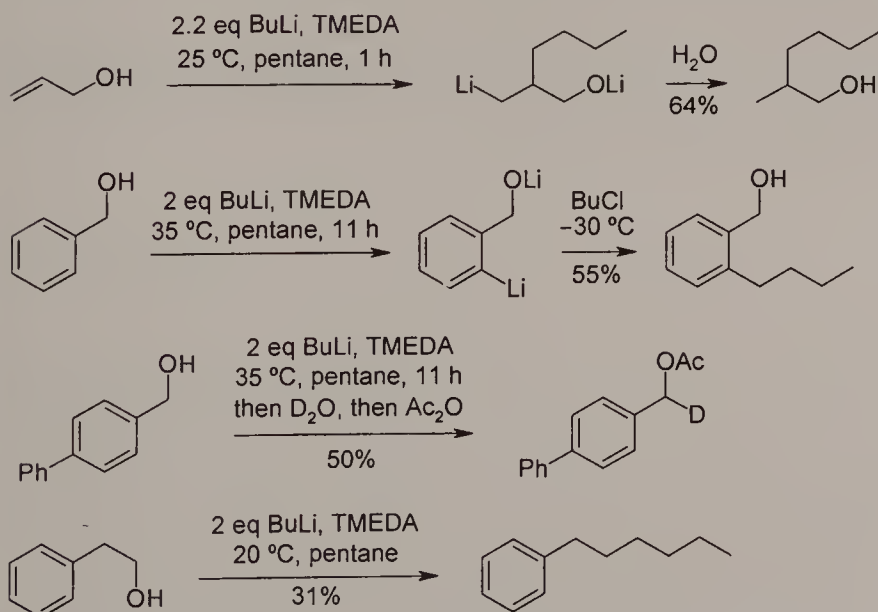
α -Sulfur chelate-stabilized carbanions have been prepared by metalation of 2-(alkylthio)thiazolines, 2-(alkylthio)oxazolines, 2-(alkylthio)pyridines [283], thiocarbonates, dithiocarbamates [284–286], thiol esters, and related compounds [59] (see also Schemes 5.31 and 5.76). Reaction of ketones or aldehydes with these nucleophiles can yield thiiranes, presumably via intramolecular transfer of the sulfur-



Scheme 5.32. Metalation and reaction of esters [276, 281, 282]. R = 9-phenylfluoren-9-yl.

bound carbanion-stabilizing group to the newly formed alcoholate followed by intramolecular nucleophilic displacement by sulfur.

Unsubstituted aliphatic alcohols cannot usually be α -metalated by treatment with strong bases (to yield a dianion). Dilithiated methanol has been prepared by treatment of $\text{Bu}_3\text{SnCH}_2\text{OH}$ with two equivalents of BuLi, and can be alkylated at carbon [287]. Treatment of allyl alcohol with excess BuLi/TMEDA in pentane at room temperature does not lead to formation of the dianion of allyl alcohol but to addition of BuLi to the C–C double bond [288] (Scheme 5.33). Benzylic alcohols, on the other hand, can be deprotonated twice and, depending on the substitution pattern at the



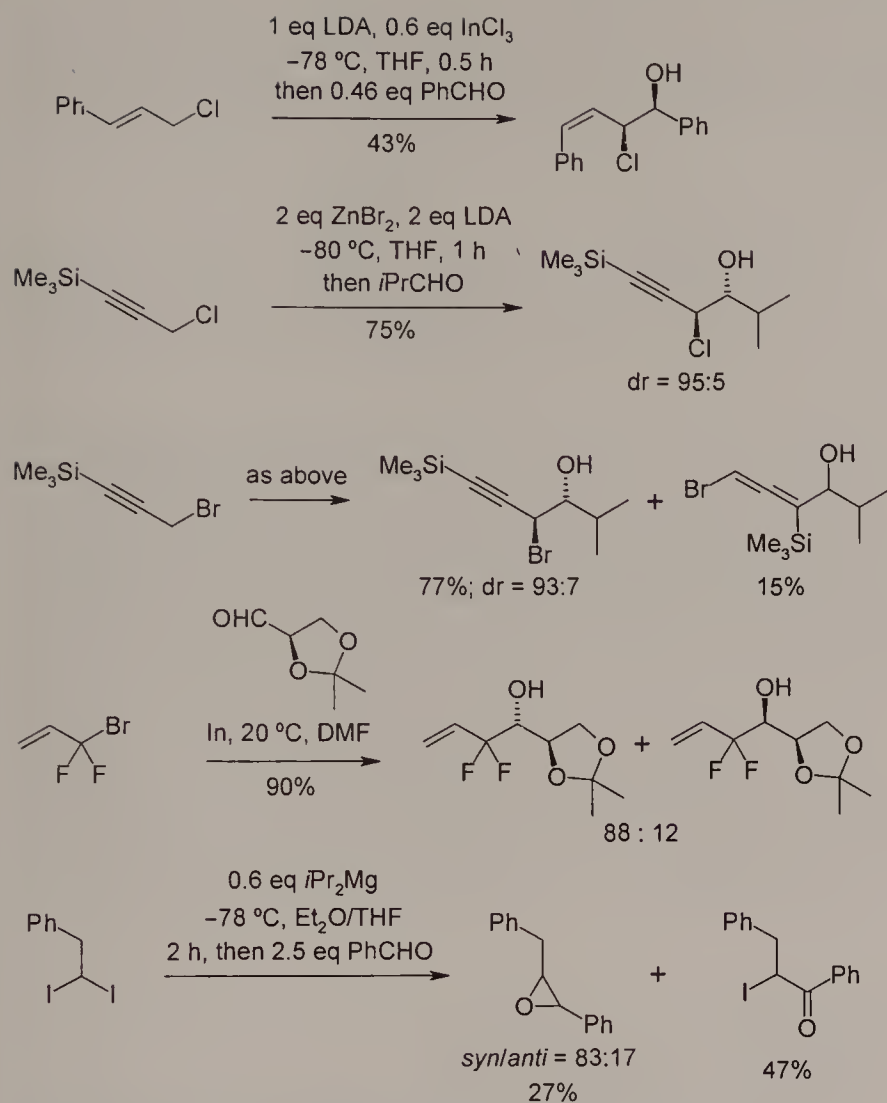
Scheme 5.33. Formation and reactions of dimetalated alcohols [256, 288, 289].

arene, metalation can occur either at the benzylic methylene group [256] or at the arene [289, 290] (Scheme 5.33). Attempts to dilithiate 2-phenylethanol at room temperature led to immediate formation of polymers and hexylbenzene, presumably via elimination of lithium oxide to yield styrene, followed by addition of BuLi (Scheme 5.33) [289].

5.3.7.3 α -Halogen Carbanions

The main competing pathways available to metalated alkyl halides are α - and β -elimination [291] and alkylation of the base or carbanion by the starting halide [292]. Metalation and alkylation of alkyl halides at the α position can, therefore, usually only be performed when this position is activated by an additional electron-withdrawing group, and β -elimination is either not possible or difficult. Non-nucleophilic bases must, furthermore, be used to avoid alkylation of the base by the halide. 2-Haloacetic esters [293, 294], 2-haloacetic thioesters [295], 4-halocrotonic acid esters [123], 2-(1-haloalkyl)oxazolidines [292, 296–298], α -halo ketones [299], α -halo sulfoxides [300, 301], and α -halo imines [302, 303] can all be metalated and alkylated at low temperatures without loss of halide from the nucleophile. Examples of the α -alkylation of less acidic alkyl halides have also been reported (Scheme 5.34). The metalation of allylic [187, 304–308] or propargylic [309] chlorides or bromides can be performed at low temperatures, and addition of Lewis acids can enable highly stereoselective alkylations with these carbanions (Scheme 5.34). Transmetalation may lead to improved yields or to a modified stereochemical outcome [304, 310]. Non-stabilized α -halocarbanions have also been prepared by exchange of a sulfinyl group by lithium or magnesium [300, 311, 312] and by partial halogen–metal exchange of 1,1-dihaloalkanes [310, 313–315] (Scheme 5.34).

The addition of α -deprotonated alkyl halides to alkenes or carbonyl compounds can, because of the good leaving-group properties of halides, also lead to formation of cyclopropanes [292] or epoxides [187, 304, 306, 310], respectively. Because of the inherent instability of α -halo organometallic compounds, these intermediates should be handled carefully and on a small scale only. The ketone produced by the last reaction in Scheme 5.34 is probably formed by Oppenauer oxidation of the intermediate alcohol by the excess benzaldehyde [310].



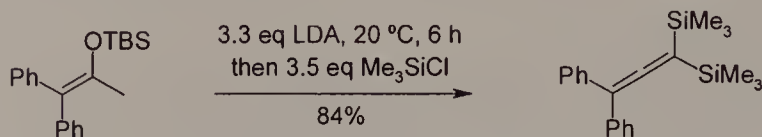
Scheme 5.34. Generation and alkylation of α -halo organometallic compounds [187, 309, 310, 316].

5.3.8

Vinylic Carbanions

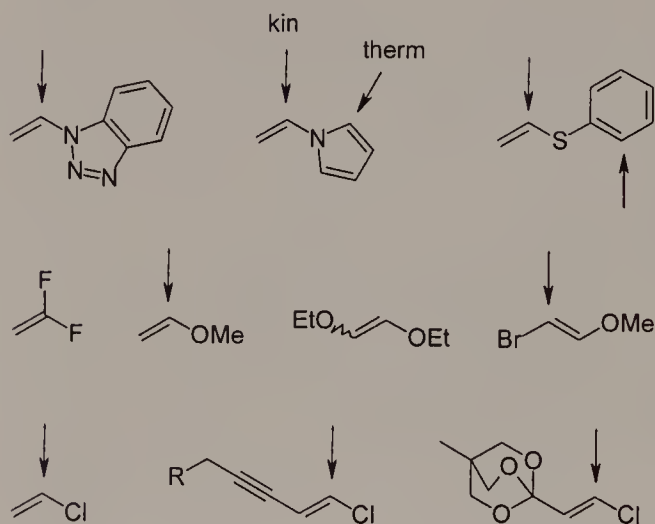
Vinylic carbanions are closely related to metalated arenes or heteroarenes, the main difference being that the formation of alkynes from vinylic carbanions with a vicinal leaving group proceeds more readily than the formation of arynes [317, 318]. The most straightforward methods for regioselective preparation of vinylolithium or related organometallic compounds are halogen- or tin-metal exchange [319] and treatment of tosylhydrazones with organolithium compounds (Shapiro reaction) or cuprates [320]. Direct vinylic deprotonations will usually proceed regioselectively only when the substrate contains functional groups which exert a strong directing or carbanion-stabilizing effect and when no allylic protons are available (these are

usually removed more rapidly [321, 322]; benzylic protons are, however, often removed more slowly than aromatic protons). Cyclopropenes and allenes are particularly acidic alkenes [323, 324]; the latter occasionally even enable twofold deprotonation (Scheme 5.35).



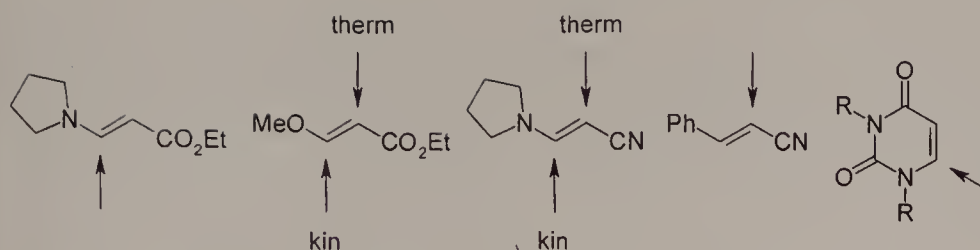
Scheme 5.35. Formation and silylation of an allene-derived dianion [169].

Vinyl halides containing vinylic protons can undergo either halogen–metal exchange or hydrogen–metal exchange when treated with an alkyllithium compound [317, 325–327]. Scheme 5.36 shows some substrates which can be selectively deprotonated at a vinylic position (arrow) by BuLi or a related base. The anion resulting from 1,1-difluoroethene can be generated and alkylated only at temperatures below -100°C , because it undergoes rapid β -elimination at higher temperatures [328] (Scheme 5.59).



Scheme 5.36. Alkenes which can be metalated and trapped with electrophiles, and preferred sites of vinylic deprotonation [317, 326, 328–332]. kin: kinetically favored; therm: thermodynamically favored.

Acrylic acid derivatives with a heteroatom (N, O, S, Hal) at C-3 can be cleanly deprotonated at this position with BuLi or LDA at low temperatures [329, 333–338] (Scheme 5.37). Some of these anions rearrange to the α -metalated acrylates on warming [329], but can also decompose (see Section 5.4.7). Non-heteroatom-substituted lithium β -lithioacrylate [329] or β -magnesioacrylic acid derivatives [339, 340] have been prepared by bromine–lithium or halogen–magnesium exchange.

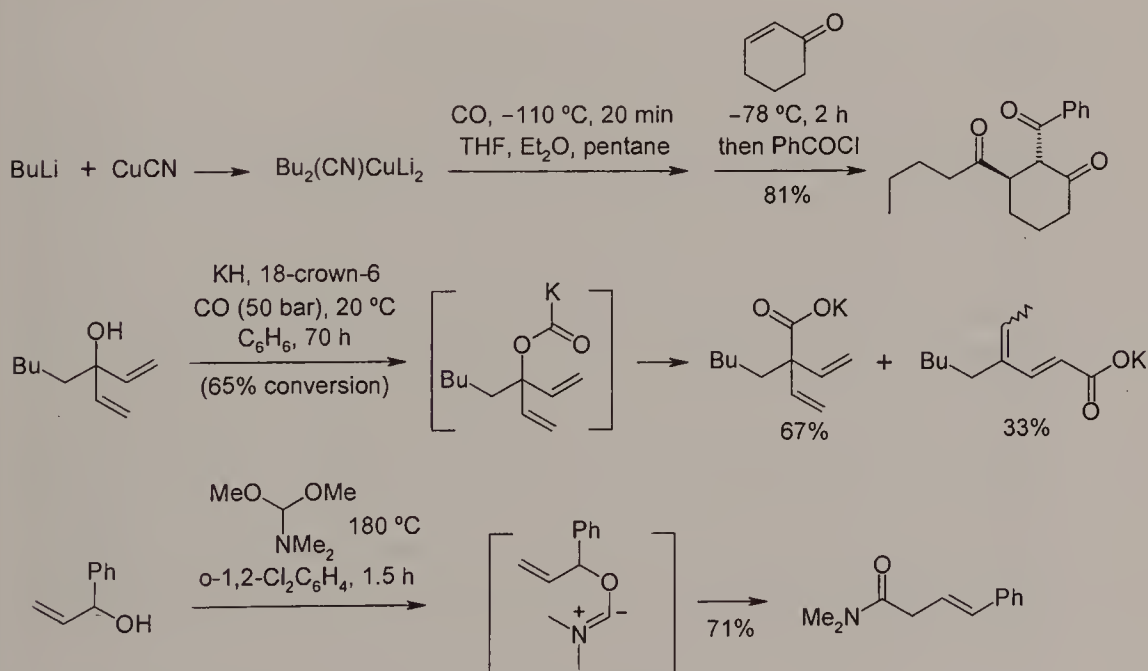


Scheme 5.37. Preferred sites of vinylic deprotonation of acrylic acid derivatives [329, 337] and pyrimidinediones [341–343]. kin: kinetically favored; therm: thermodynamically favored.

5.3.9

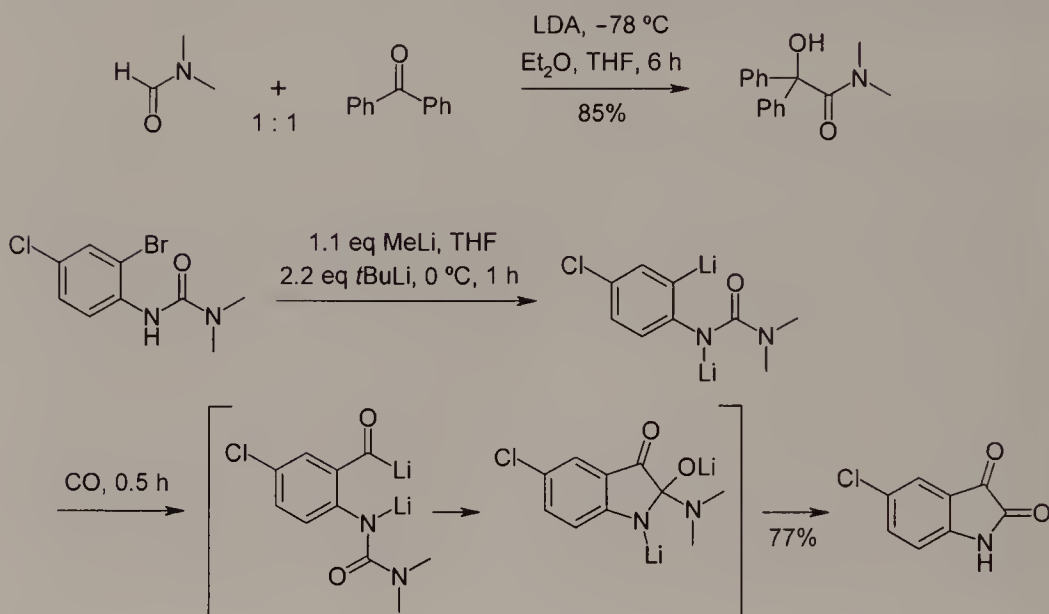
Acyl, Imido, and Related Carbanions

Acyl anions ($\text{RC}(=\text{O})\text{M}$) are unstable, and quickly dimerize at temperatures $> -100^\circ\text{C}$ (Section 5.4.7). These intermediates are best generated by reaction of organolithium compounds or cuprates with carbon monoxide at -110°C and should be trapped immediately by an electrophile [344–347]. Metalated formic acid esters ($\text{ROC}(=\text{O})\text{M}$) have been generated as intermediates by treatment of alcoholates with carbon monoxide, and can either be protonated to yield formic acid esters, or left to rearrange to carboxylates ($\text{ROC}(=\text{O})\text{M} \rightarrow \text{RCO}_2\text{M}$) (Scheme 5.38) [348]. Related intermediates are presumably also formed by treatment of alcohols with formamide acetals (Scheme 5.38) [349]. More stable than acyl lithium compounds are acyl silanes or transition metal acyl complexes, which can also be used to perform nucleophilic acylations [350].



Scheme 5.38. Generation and reactions of acyl anions and related intermediates [347–349].

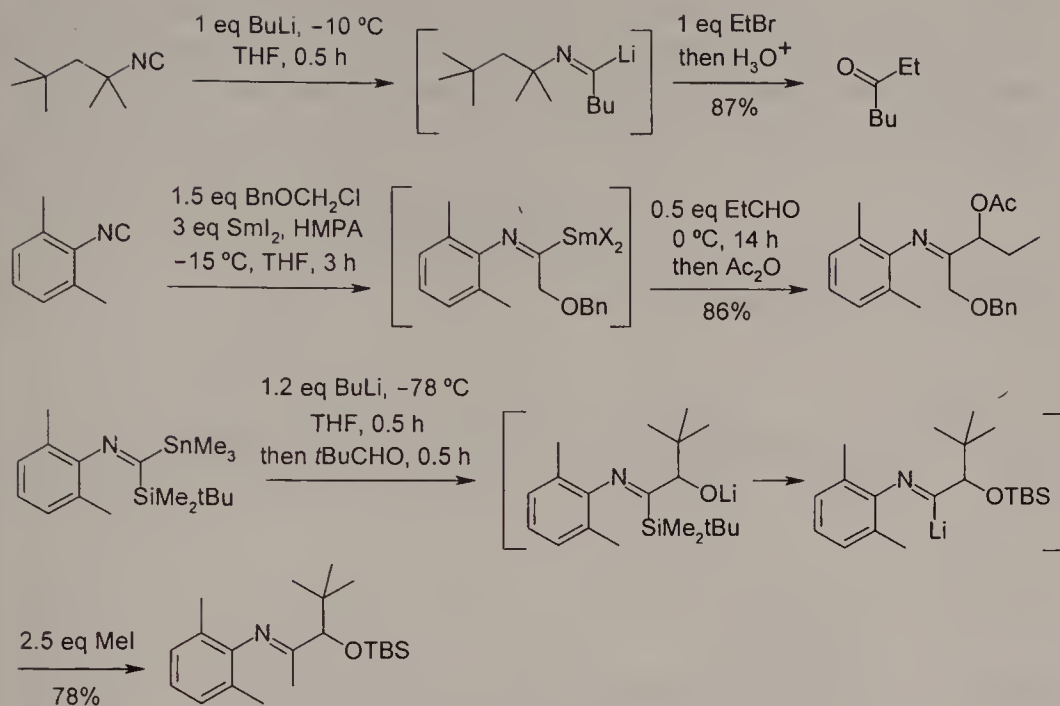
Formamides are usually not deprotonated α to nitrogen but at the formyl group [227–231]. The resulting carbamoyl lithium derivatives (R_2NCOLi), which can also be generated from deprotonated amines [351] or amides [352] and carbon monoxide, react with electrophiles E^+ to yield the expected products (R_2NCOE), despite the carbene character and consequent low stability of these intermediates [179, 351] (Scheme 5.39, see Section 5.4.7). Palladium-catalyzed versions of the reaction have been reported [353, 354].



Scheme 5.39. Formation and reactions of acyllithiums [230, 352].

Metalated imines ($RN=C(R)M$) have usually been prepared not by deprotonation of imines but by addition of Grignard reagents or organolithium compounds to isonitriles devoid of α hydrogen [355] (to avoid α -metalation of the isonitrile; Scheme 5.40). Alternatively, halogen–lithium exchange at imidoyl iodides [356], tin–lithium exchange at imidoyl stannanes [357], Brook rearrangement of imidoyl silanes [357], or reduction of isonitriles with samarium iodide in the presence of an alkylating agent also lead to the formation of metalated imines, which react with alkylating reagents in the expected way [358, 359] (Scheme 5.40). Dimerization of isonitriles under these reaction conditions has, however, also been observed [360].

Related to acyl and imidoyl anions are carbanions such as $(R_3CC(Li)=N^+(R)O^-)$ obtained by deprotonation with $sBuLi$ of nitrones devoid of α hydrogen, at $-78\text{ }^{\circ}C$ [362, 363]. These intermediates can react with a variety of electrophiles to yield the corresponding derivatized nitrones [363], but, as with acyl anions, dimerization can also occur [362, 364].



Scheme 5.40. Generation and alkylation of metalated imines [358, 361].

5.3.10

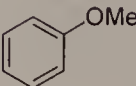
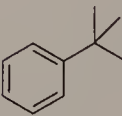
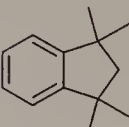
Aromatic Carbanions

Arenes cannot usually be deprotonated with LDA alone, but require mixtures of organosodium [365] or organolithium compounds and tertiary amines [181, 218, 219]. These amines, for instance TMEDA, lead to a partial dissociation of oligomeric BuLi–solvent aggregates and thereby to more powerful metalating reagents [366, 367]. Thus, although benzene cannot be deprotonated with BuLi alone, a mixture of BuLi and TMEDA leads to quantitative lithiation [181].

An important drawback of the use of organolithium compounds as bases is their high nucleophilicity, which limits the scope of suitable substrates. Thus, many carbonyl compounds, benzamides [217], heteroarenes [368], sulfoxides [11, 12], or phosphine oxides [12] will undergo nucleophilic attack instead of deprotonation by organolithium compounds. Organolithium compounds can, furthermore, act as reducing agents by SET. As alternative bases, sterically more demanding lithium [369], zinc [370], or magnesium [371, 372] dialkylamides, or mixtures of LDA and KO t Bu or NaO t Bu [166, 373] can be used.

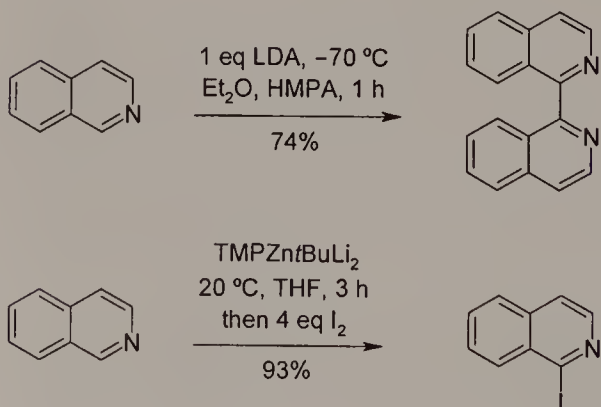
The acidity of arenes does not correlate with their electron density [374], because in a metalated arene there is no significant overlap between the aromatic π system and the Ar–M bond. More important for facile aromatic metalation is the presence of substituents able to form bonds with the metal and thereby direct the base into the proximity of an *ortho* Ar–H bond before metalation, and to form a stabilizing

chelate with the metal when metalation has occurred [181, 366, 375, 376]. Thus, although metalation of aryl ethers or *N*-(alkoxycarbonyl)anilines (i.e. electron-rich arenes) proceeds readily, and even phenolates undergo metalation to form dianions [377], the metalation of simple alkylbenzenes generally proceeds more sluggishly (Scheme 5.41).

	conditions	rate of proton/lithium exchange relative to benzene
	BuLi, TMEDA, 0 °C, pentane	833
	BuLi, KOtBu, 25 °C, hexane	0.047
	BuLi, KOtBu, 25 °C, hexane	0.013

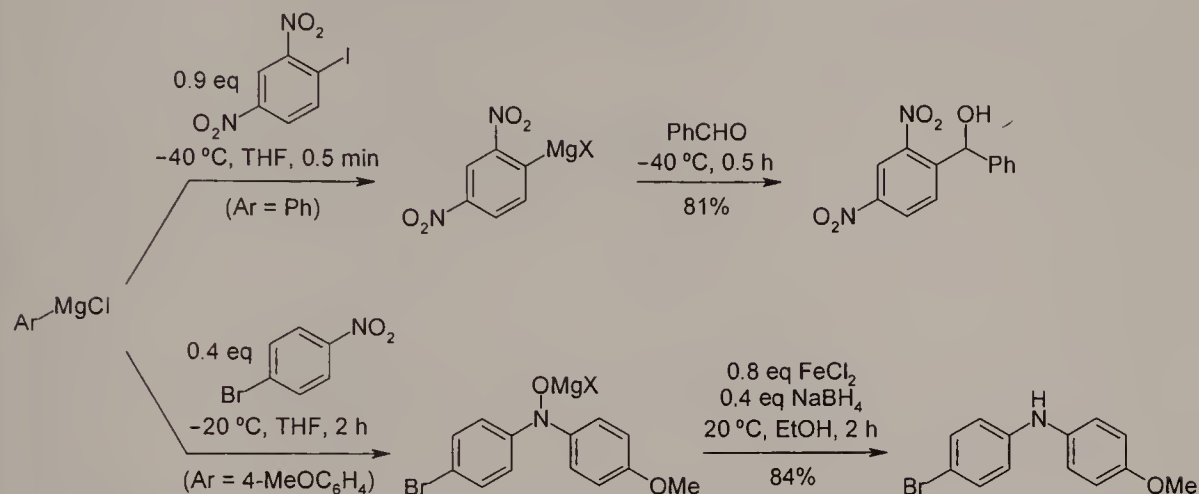
Scheme 5.41. Relative rates of lithiation of arenes [378, 379].

Arenes and heteroarenes which are particularly easy to metalate are tricarbonyl(η^6 -arene)chromium complexes [380, 381], ferrocenes [13, 382, 383], thiophenes [157, 158, 181, 370, 384], furans [370, 385], and most azoles [386–389]. Metalated oxazoles, indoles, or furans can, however, be unstable and undergo ring-opening reactions [179, 181, 388]. Pyridines and other six-membered, nitrogen-containing heterocycles can also be lithiated [59, 370, 390–398] or magnesiated [399], but because nucleophilic organometallic compounds readily add to electron-deficient heteroarenes, dimerization can occur, and alkylations of such metalated heteroarenes often require careful optimization of the reaction conditions [368, 400, 401] (Schemes 5.42 and 5.69).



Scheme 5.42. Metalation and ensuing reactions of isoquinoline [370, 402].

Similarly, nitroarenes can also be lithiated (Scheme 5.43), but reactions of metalated nitroarenes with electrophiles only proceed cleanly if the metalation is performed in the presence of the electrophile [403]. Otherwise, the metalated arene can reduce nitro groups to nitroso groups, which quickly react with additional organo-metallic reagent to yield hydroxylamines [404, 405]. Nitroarylmagnesium halides can be prepared by iodine–magnesium exchange at $-80\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$, and react with electrophiles in the expected way [6] (Scheme 5.43).

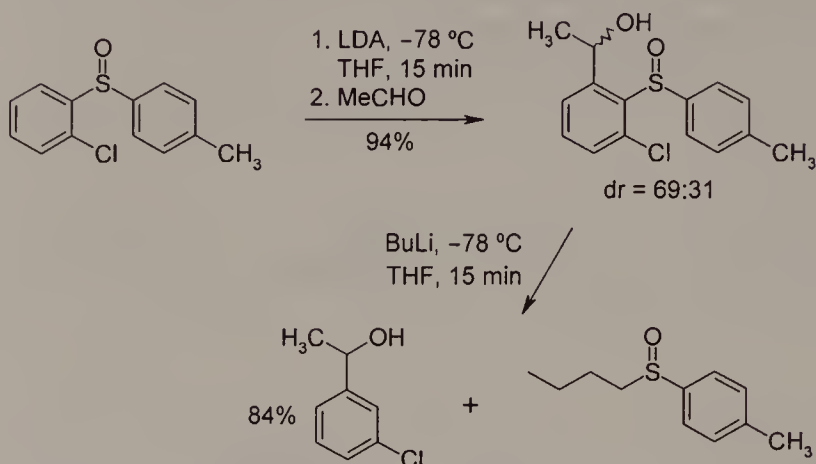


Scheme 5.43. Reactions of arylmagnesium compounds with nitroarenes [404, 406] .

As mentioned above, certain functional groups can increase the kinetic and thermodynamic acidity of the aromatic *ortho* protons and thereby control the regioselectivity of the metalation [181, 218]. Typical *ortho*-directing groups (approximately in decreasing order of *ortho*-directing ability) are OCONR_2 , SO_2tBu , SO_2tBu , CONR_2 , OCH_2OMe , CN , SO_2NR_2 , NHBoc , $(\text{CH}_2)_{1,2}\text{NR}_2$, CO_2H , OPh , OMe , OCSNR_2 , NR_2 , CF_3 , F , and Cl [181, 374, 377, 407]. Surprisingly, fluoroarenes [377, 394, 403, 408], chloroarenes [369, 409–411], bromoarenes [369, 385, 412, 413], trifluoromethyl arenes [377, 392, 414], and trifluoromethoxy arenes [415] can sometimes be metalated and trapped by different electrophiles without undergoing halogen–metal exchange, elimination (to yield arynes), or other decomposition reactions. Because of their inherent instability, however, metalated halo- or trihalomethyl arenes should be handled with great care, especially when performing reactions on a large scale. Grignard reagents derived from trifluoromethyl arenes, for instance, have led to several explosions, some of them even leading to loss of life [3]. *ortho*-Lithiated bromo- or chlorobenzene undergo β -elimination even at temperatures slightly above $-100\text{ }^{\circ}\text{C}$ [412], but some polyhalogenated aryllithium compounds are significantly more stable (Scheme 5.45). Iodoarenes have also been metalated, but migration of iodine (“halogen dance”) is often observed [398].

Strong *ortho*-directing groups, for example SOTol , can facilitate aromatic metalation to such an extent that even LDA at low temperatures can lead to metalation. As shown by the example in Scheme 5.44, astonishing selectivity is sometimes ob-

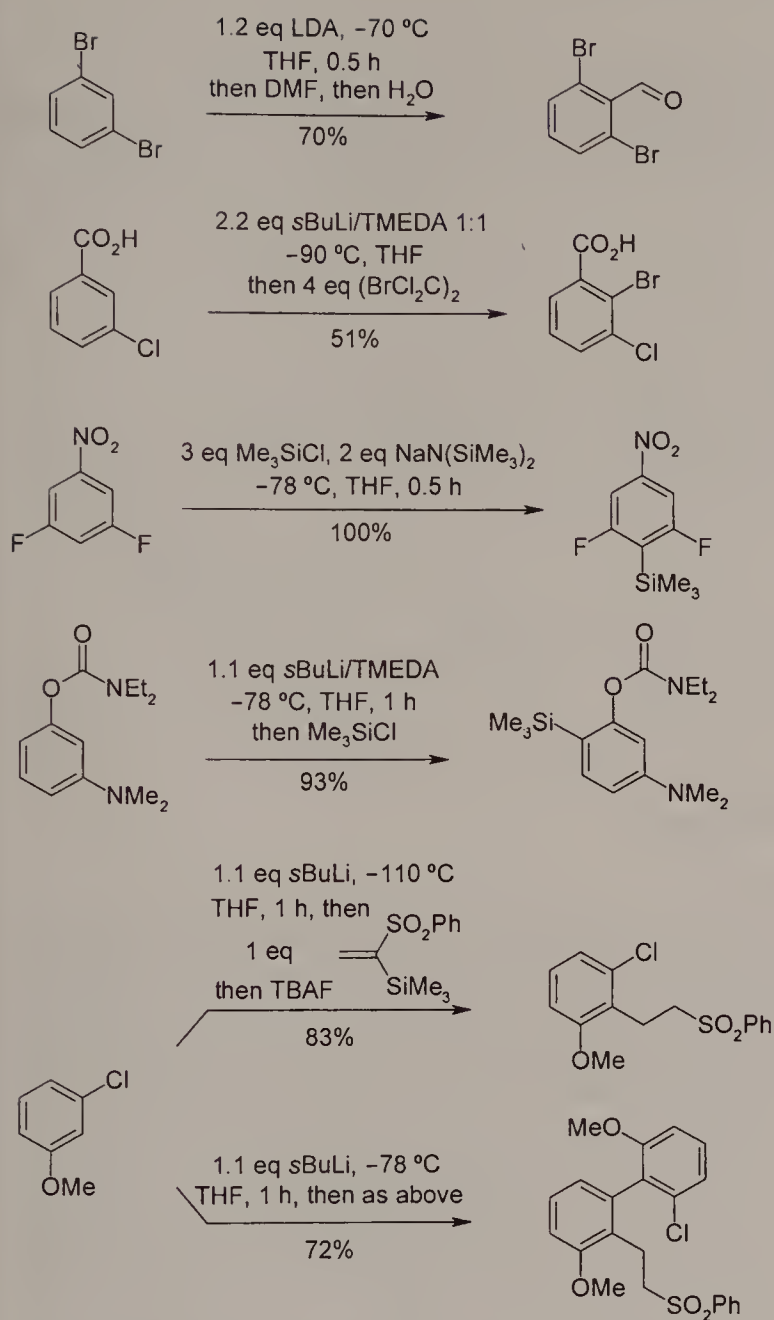
served. That the chlorophenyl group is deprotonated faster than the tolyl group (Scheme 5.44) is in agreement with other studies [243, 410] which show that chlorine strongly enhances the rate of aromatic metalation, in particular at the *meta* position. Chlorobenzene, however, undergoes *ortho*-metalation when treated with *s*BuLi [411].



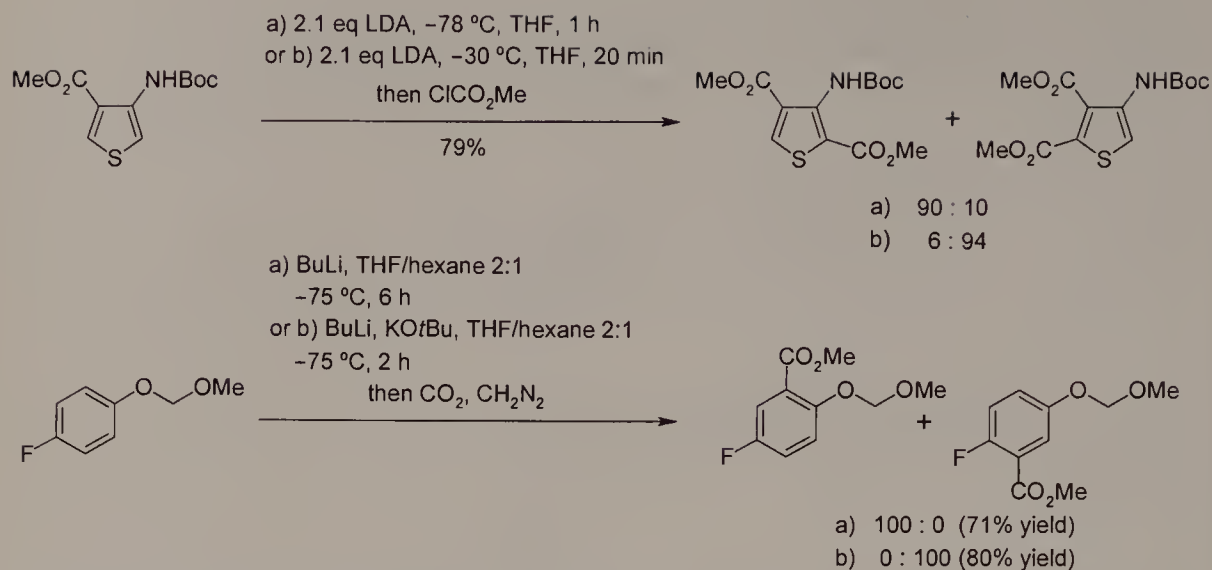
Scheme 5.44. *ortho*-Metalation of diaryl sulfoxides. All reactions proceed without racemization at sulfur[11].

The preferred site of deprotonation of di- or polysubstituted arenes is not easy to predict. In 1,3-disubstituted benzenes in which both substituents facilitate *ortho*-metalation, deprotonation will usually occur between these two groups [181, 365, 408, 416–419] (Scheme 5.45). Dialkylamino groups, however, can sometimes deactivate *ortho* positions (fourth reaction, Scheme 5.45), but this does not always happen [181, 420]. 3-Chloroanisole [411] and 3-fluoroanisole [421] are deprotonated by organolithium compounds between the two functional groups, but the lithiated arenes dimerize readily at -78°C , presumably via intermediate aryne formation (last example, Scheme 5.45).

For other polysubstituted arenes or heteroarenes, deprotonation at different sites can compete and yield product mixtures. The first reaction in Scheme 5.46 is an example of kinetically controlled carbanion formation, which shows that for some substrates regioselective metalations might be achieved by careful control of the reaction conditions.



Scheme 5.45. Regioselective metalation of 1,3-disubstituted arenes [403, 411–413, 422].



Scheme 5.46. Regioselective metalation of a substituted thiophene [384] and MOM-protected 4-fluorophenol [377].

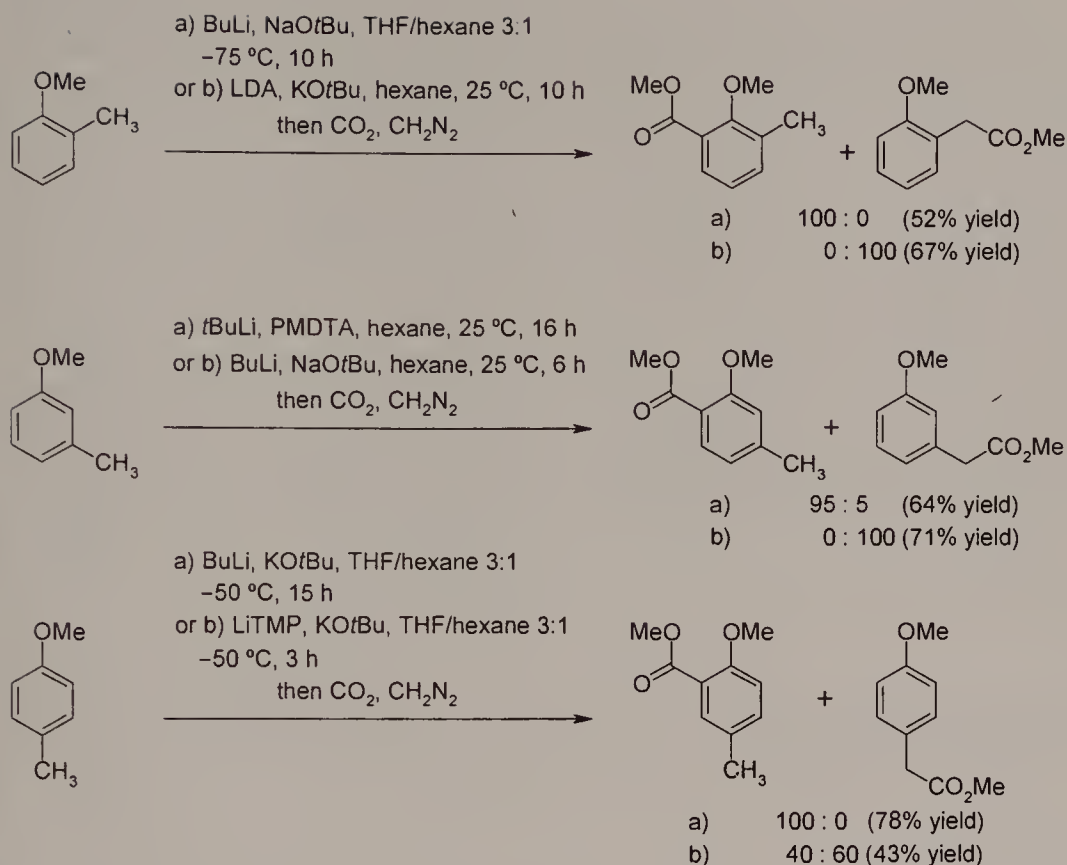
5.3.11

Aromatic vs Benzylic Deprotonation

According to the “principle of least nuclear motion” [45] aromatic deprotonation should be faster than benzylic metalation, because the benzylic carbanion is expected to rehybridize slightly toward sp^2 to achieve stabilization by conjugation with the aromatic π system. This is, in fact, often observed [217, 401, 423–425], but with some substrates benzylic metalation can effectively compete with aromatic metalation [181, 425, 426] (Scheme 5.47). Thus, treatment of toluene with BuLi/TMEDA or BuLi/DABCO at 80 °C for 0.5 h or with BuLi/KOtBu in Et₂O at -20 °C for 4 h leads to clean formation of benzyllithium [85, 427, 428]. The kinetic preference for aromatic deprotonation, because of the principle of least nuclear motion, thus seems to be too weak to control the regioselectivity of deprotonations in all instances.

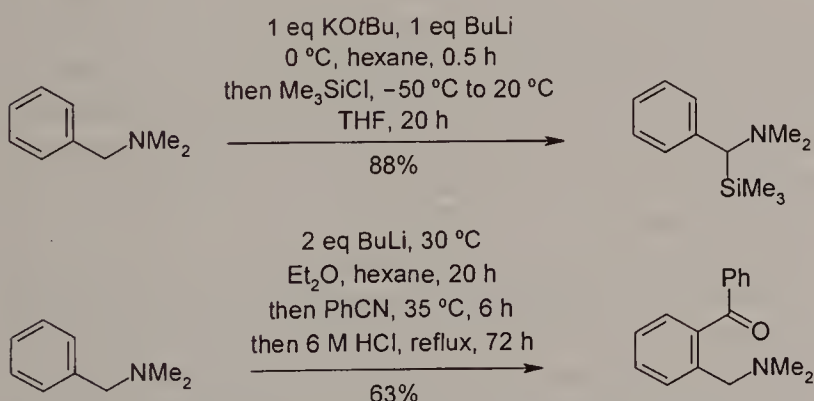
The regioselectivity of aromatic metalation can depend on the structure of the base and on the solvent [429], because these will define the structure of the initially formed complex of substrate and base, and thus the site of deprotonation. Similarly, the precise ability of a functional group to be *ortho*-directing will also depend on the solvent and base chosen [430]. This dependence is impressively illustrated by the results obtained by metalation of all the isomers of methoxytoluene (Scheme 5.47).

The metalation of benzylamines is similarly interesting, because slight variations of the reaction conditions can significantly alter the regioselectivity of proton removal. Treatment of *N,N*-dimethylbenzylamine with organolithium compounds leads to clean *ortho*-metalation of the phenyl group [418, 431]. If, however, phenylsodium [432] or mixtures of organolithium compounds and KOtBu [193, 209, 433]



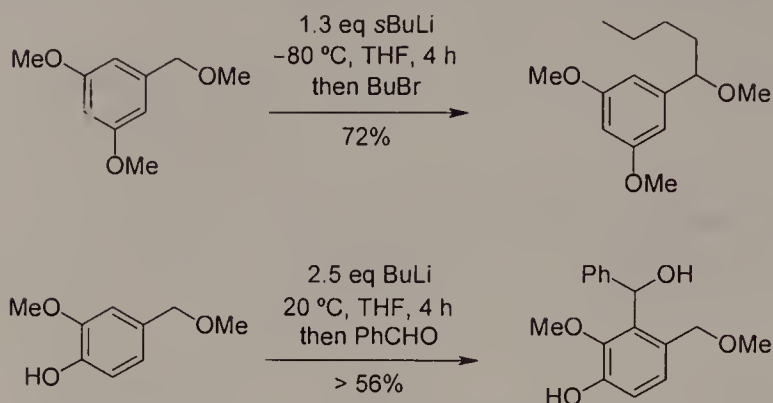
Scheme 5.47. Regioselective metalation of methoxytoluenes [373].

are used as base, exclusive metalation of the benzylic methylene group occurs (Scheme 5.48). The acidity of the benzylic position of benzylamines can also be enhanced by conversion to an amine–borane complex [209].



Scheme 5.48. Regioselective metalations of *N,N*-dimethylbenzylamine [193, 431].

Similarly, benzyl ethers can be metalated either at the benzylic position or at the arene (Scheme 5.49). As with benzylic amines it seems that benzylic deprotonation is kinetically favored, whereas the metalated arene is the thermodynamically more stable product. The metalation of benzyl alcohols is discussed in Section 5.3.7.2.



Scheme 5.49. Regioselective metalations of benzyl ethers [252, 255].

5.4

The Stability of Carbanions

5.4.1

Introduction

Carbanions can be highly reactive and can therefore undergo not only the expected reaction with an electrophile but also several other, unwanted, transformations. The most common reactions of carbanions in the absence of electrophiles include oxidation, elimination, and rearrangement. The tendency to undergo these reactions usually increases with the basicity and nucleophilicity of a carbanion, which in turn depend on the structure of the organic fragment and on the type of metal chosen. If organolithium compounds are prepared by halogen–lithium exchange with *t*BuLi at temperatures ≥ 0 °C, substantial amounts of *tert*-butylalkanes, alkenes, and homodimers of the alkyl halide can result [8]. These side reactions can effectively be avoided by reducing the reaction temperature or by using mixtures of hydrocarbons and small amounts of ethers as solvent [8].

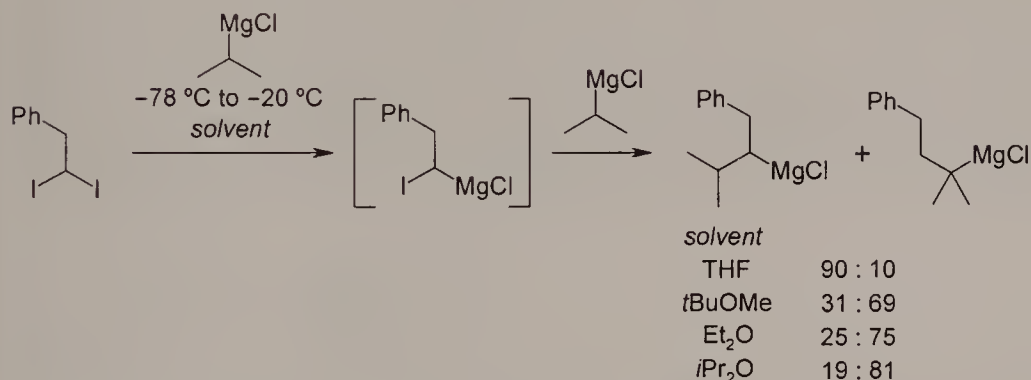
Simultaneous treatment of a carbonyl compound with a Lewis acid and a tertiary amine or another weak base (“soft enolization”) can sometimes be used to generate enolates of sensitive substrates which would have decomposed under strongly basic reaction conditions [434]. Boron enolates, which readily react with aldehydes at low temperatures, can also be prepared in situ from sensitive, base-labile ketones or carboxylic acid derivatives [293, 295, 299]. Unwanted decomposition of a carbanion may also be prevented by generating it in the presence of an electrophile which will not react with the base (e.g. silyl halides or silyl cyanides [435]).

5.4.2

 α -Elimination

In Section 5.3.7.3 the formation of α -halogen carbanions and their alkylation was discussed. If these or related intermediates are left to warm, α -elimination will usually occur to yield carbenes, which either react with the solvent, dimerize, or undergo inter- or intramolecular C–H or C–C bond insertion [291, 292, 309, 436]. Because of the electron deficit at the carbene carbon atom (six valence electrons only), these intermediates are highly energetic, and their formation by α -elimination is therefore much slower than the formation of alkenes by β -elimination.

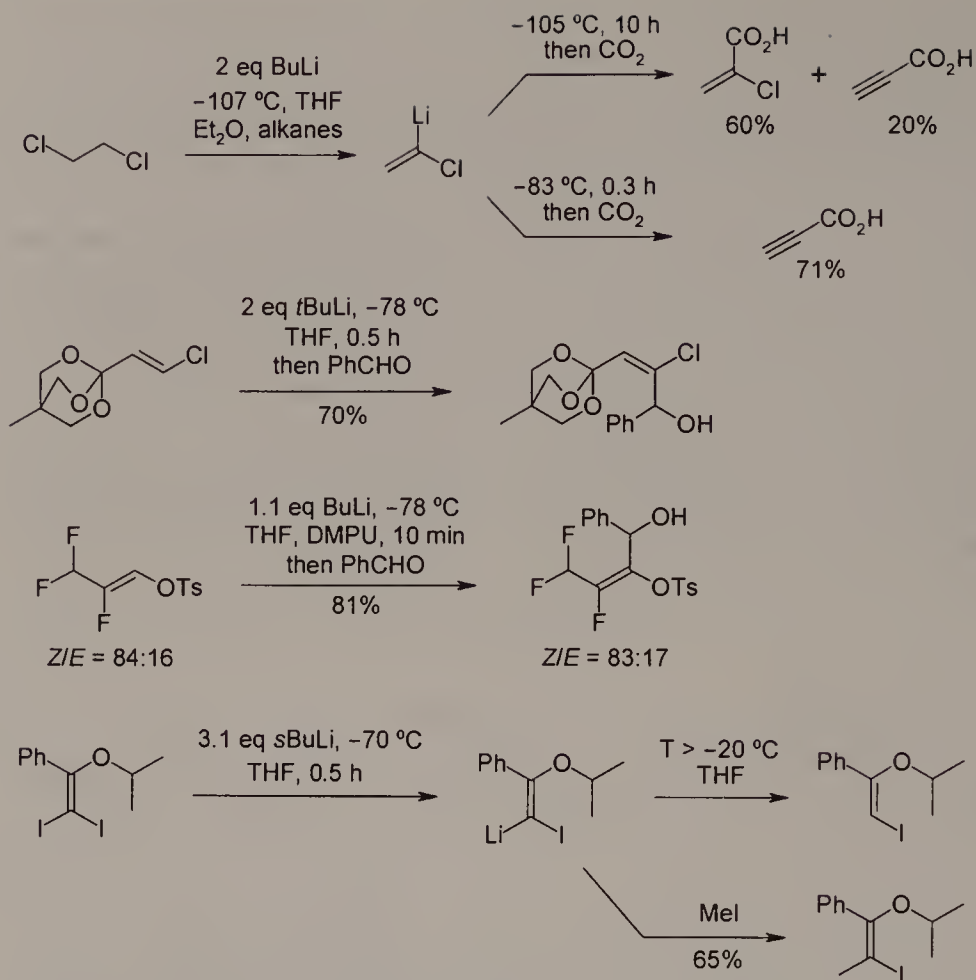
An interesting example of unexpected product formation because of the carbenoid character of α -haloorganometallic reagents is depicted in Scheme 5.50. Depending on the complexing properties of the solvent, treatment of an α -iodo Grignard reagent with *i*PrMgCl either yields the product of nucleophilic substitution of iodide or the product of carbene C–H insertion into the isopropyl group of *i*PrMgCl.



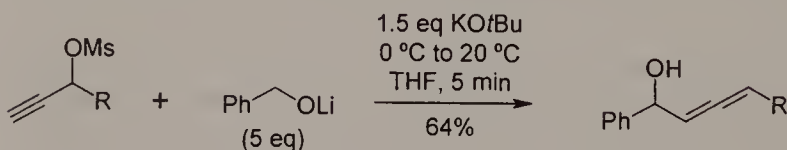
Scheme 5.50. Reactions of an α -iodo Grignard reagent as electrophile or as carbene [437].

Vinyl carbanions with a geminal leaving group can undergo α -elimination to yield vinylidenes and rearrange to yield alkynes (Fritsch–Buttenberg–Wiechell rearrangement). These processes can, however, often be suppressed by keeping the reaction temperature low, and numerous examples of the α -lithiation and alkylation of vinyl halides have been reported [327, 438] (Scheme 5.51). Again, the solvent can have a strong influence on the stability of these intermediates [439]. The examples in Scheme 5.51 illustrate the reaction conditions required for such conversions. Some vinyl lithium compounds are sufficiently basic to abstract a proton from THF if allowed to warm (last reaction, Scheme 5.51). The solvent mixture of the first example is required because pure THF (mp -108°C) becomes too viscous at these low temperatures [440].

Deprotonation of the alkyne group of propargyl halides or sulfonates can also lead to elimination and formation of a vinylidene. Interestingly, these derivatives react with alcoholates, not yielding enol ethers via O-alkylation but undergoing C–H bond insertion instead (Scheme 5.52).



Scheme 5.51. Generation and alkylation of α -halo or α -(tosyloxy)vinyl lithium compounds [332, 440–442].



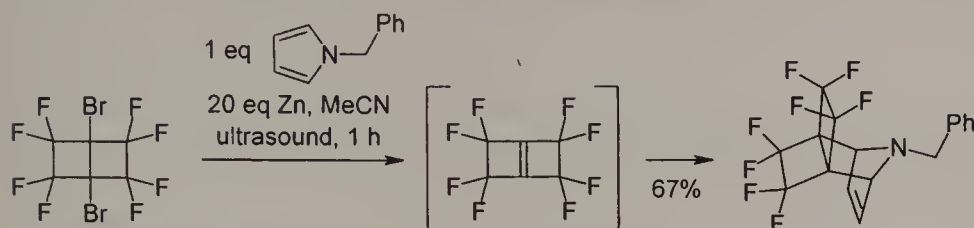
Scheme 5.52. Generation of vinylidenes from propargyl mesylates and their reaction with alcoholates [443].

5.4.3

β -Elimination

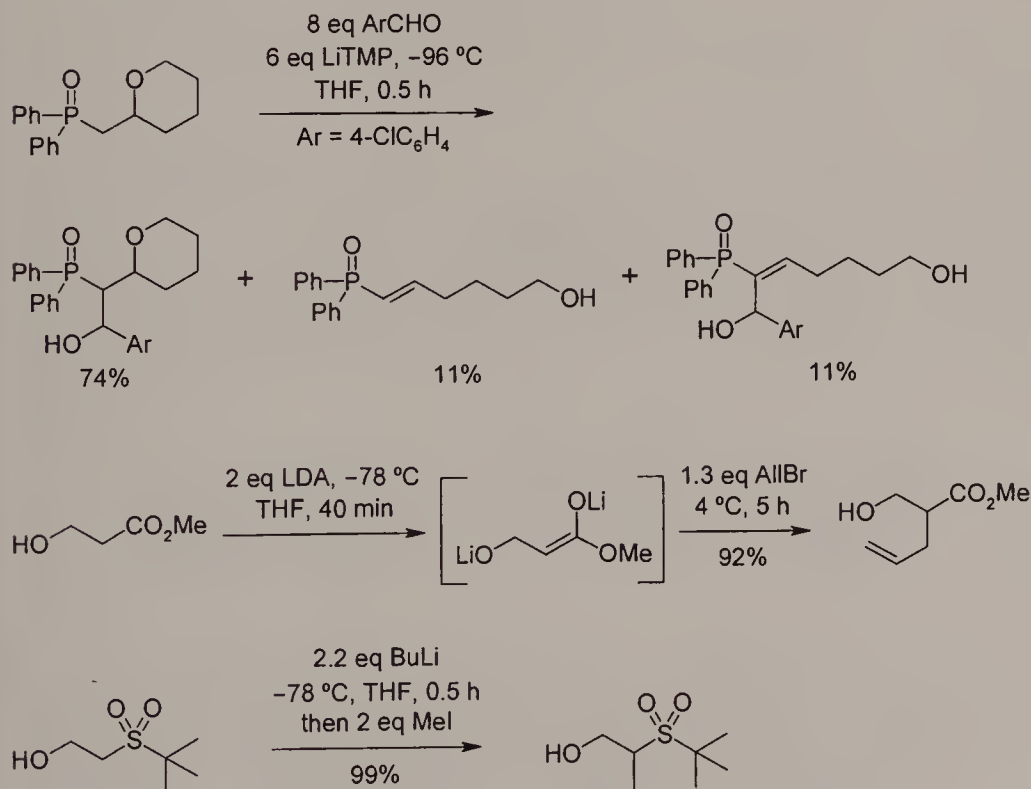
In carbanions with a leaving group in the β position β -elimination may compete efficiently with attack by an electrophile. The rate of elimination will increase with increasing reactivity of the carbanion and with increasing ability of the leaving group to act as such [444]. Higher reaction temperatures, moreover, can also promote elimination reactions, which are usually accompanied by a gain of entropy.

Thus, almost no examples have been reported of α -alkylation of β -halo or β -alkoxy ketones, nitriles, sulfones, or propanoic acid derivatives under basic reaction conditions. 1,2-Dihalides are usually converted into alkenes when halogen-metal exchange is attempted, even if highly strained alkenes are thereby formed (Scheme 5.53).



Scheme 5.53. Generation of a strained alkene by elimination of ZnBr_2 from an intermediate 2-bromoethylzinc compound [445].

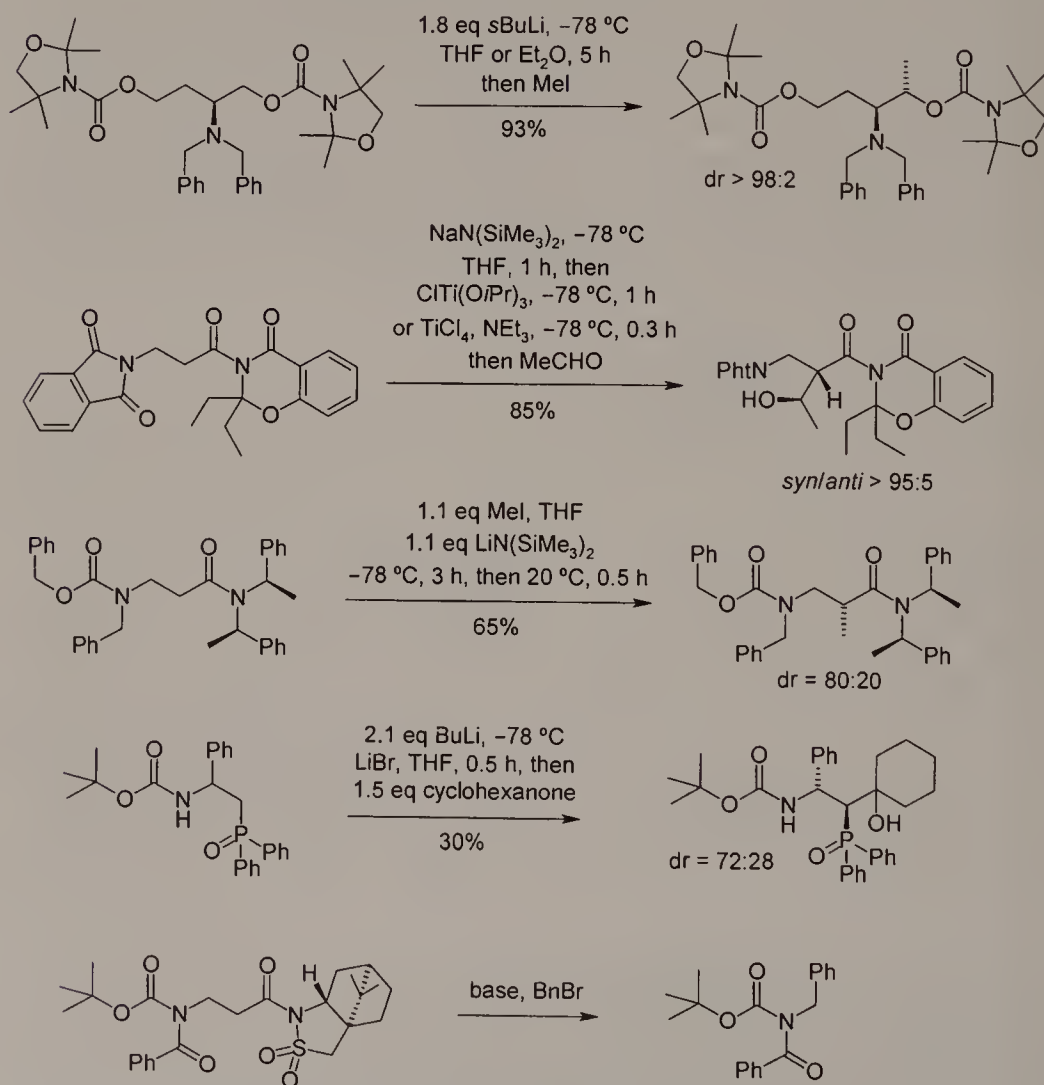
β -Elimination can be prevented by choosing a substrate with a worse leaving group in the β position or by reducing the basicity of the carbanion, for instance by selecting a different metal [446]. An alkoxy group, which is a rather good leaving group, might, for instance, be replaced by a hydroxyl group (which can be alkylated at a later stage of the synthesis) and the α -alkylation conducted with the corresponding dianion [162–165] (Scheme 5.54). Because oxide (O^{2-}) is more difficult to generate and a worse leaving group than alkoxide (RO^-), no elimination of oxide usually occurs at low temperatures. *O*-Alkylation will not compete with *C*-alkylation if a soft electrophile and a low reaction temperature are chosen.



Scheme 5.54. Alkylation of β -alkoxy and β -hydroxy carbanions [163, 165, 447].

Cyclic substrates, for example 4-pyranones or 4-chromanones, are usually less prone to β -elimination, and can usually be converted into the corresponding enolates and then C-alkylated in high yield.

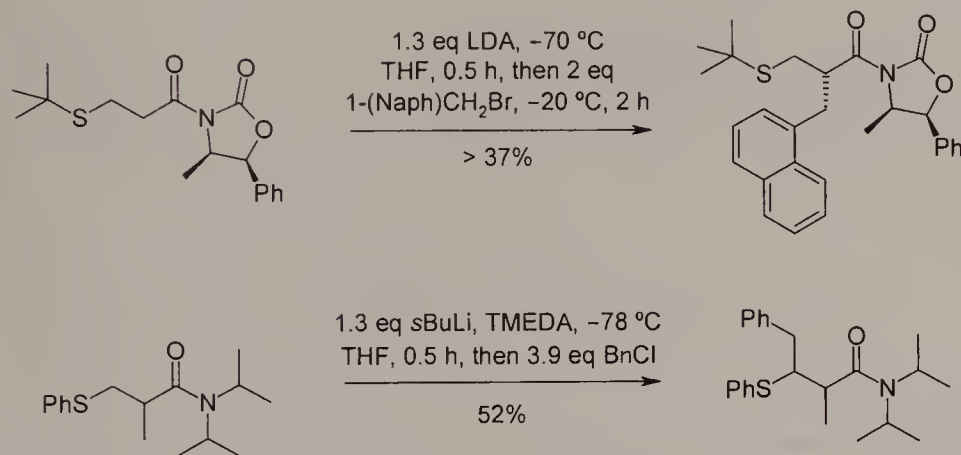
The amino group is a rather poor leaving group [444], and numerous examples of the alkylation of β -amino carbanions are known. Thus, 2-(dialkylamino)ethyl phosphine oxides [448], sulfoxides [449], and sulfones [450, 451], 3-(dialkylamino)propionic acid esters [452], or 3-aminopropionamides [453] can all be alkylated at the α position of the electron-withdrawing group without loss of the amino group. Even 2-(dialkylamino)ethyl carbamates, which upon lithiation yield highly reactive α -oxy organolithium derivatives, do not eliminate the dialkylamino group [454–456] (first reaction, Scheme 5.55). Similar substrates, in which the amino group is acylated or alkoxy-carbonylated can, however, become unstable upon metalation and eliminate RCONR^- . In such instances a monoacylated primary amino group, which will also be deprotonated when the carbanion is formed, would be expected to be less likely



Scheme 5.55. α -Alkylation of β -amino carbanions [452, 454, 457–459].

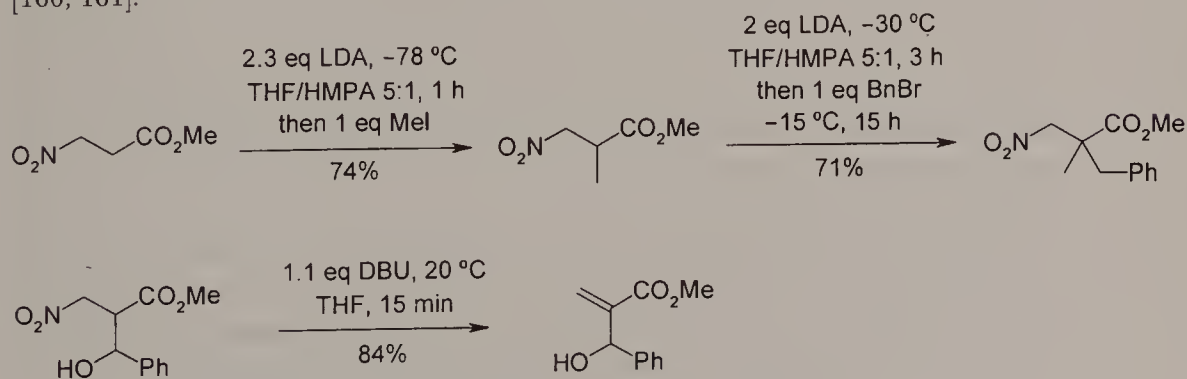
to be eliminated. Substrates of this type (i.e. $\text{ZNHCH}_2\text{CH}_2\text{Z}$), however, often yield only small amounts of C-alkylated product [457, 458] (fourth reaction, Scheme 5.55). Transmetalation (second reaction, Scheme 5.55) or a more effective carbanion-stabilizing group can also prevent elimination in critical cases. In the last reaction in Scheme 5.55, which is closely related to the second example in this scheme, the amino group is obviously too strongly activated, and elimination becomes the dominant reaction [457].

Carboxylic acid derivatives or ketones with an alkylthio group at C-3 can be metalated and alkylated at the α position without elimination of thiolate [446] (Scheme 5.56). Amides of 3-(alkylthio)-2-alkylpropanoic acids can, however, also be alkylated at the β position if strong metalating agents are used as base [53, 460].



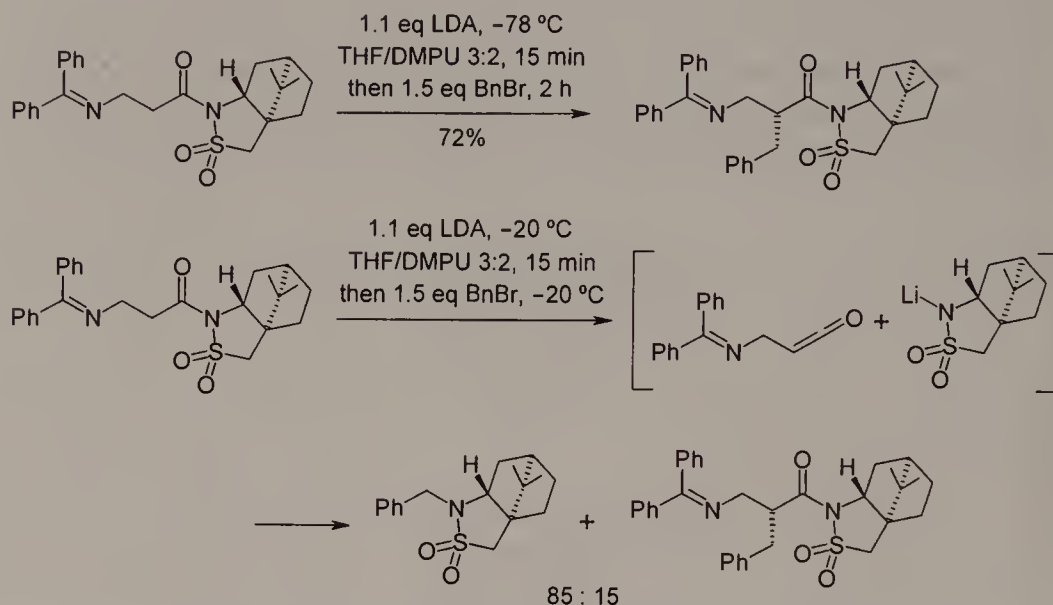
Scheme 5.56. Alkylation of 3-(alkylthio)propanoic acid derivatives [53, 461].

3-Nitropropanoic acid esters can be converted into acrylic acid derivatives by treatment with a slight excess of DBU in THF or DMSO at room temperature. If 3-nitropropanoates are treated with two equivalents of LDA at -78°C in THF/DMPU or THF/HMPA, however, the resulting dianion can be cleanly C-alkylated, and the product isolated without elimination of the nitro group [160, 161] (Scheme 5.57). Without the addition of a cosolvent (DMPU, HMPA, or quinuclidine *N*-oxide [161]) alkylation of the 3-nitropropanoate dianion does not proceed sufficiently quickly [160, 161].



Scheme 5.57. Alkylation of 3-nitropropanoates [160].

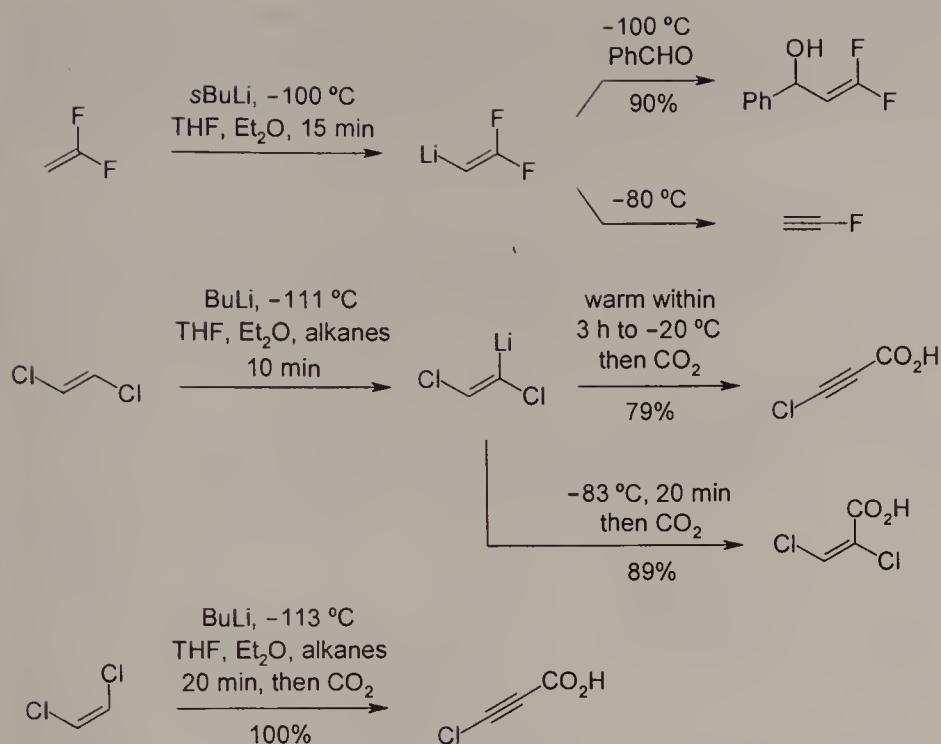
Enolates prepared by deprotonation of carboxylic acid derivatives can also undergo elimination to yield ketenes. This is rarely seen with amides, but esters, thioesters, imides, or *N*-acylsulfonamides can readily decompose to ketenes if left to warm to room temperature (Scheme 5.58). At -78°C , however, even aryl esters can be converted into enolates stoichiometrically without ketene formation [462, 463].



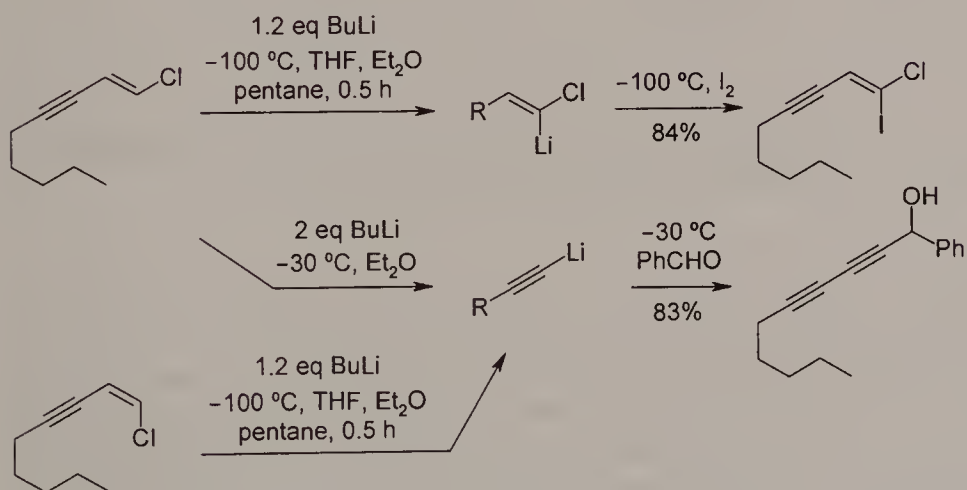
Scheme 5.58. Temperature-dependent alkylation of *N*-(β -aminopropanoyl)sulfonamides and decomposition via ketene formation [457].

Vinylic carbanions with a vicinal leaving group can undergo β -elimination to yield alkynes. This can sometimes be avoided by keeping reaction temperatures low and by adding the electrophile as soon as possible (Scheme 5.59). The outcome of these reactions often depends not only on the metal and on the substituents at the alkene but also on its configuration. Substrates in which the metal and the leaving group are arranged *anti* undergo elimination more readily than the corresponding *cis* isomers (compare last two reactions in Scheme 5.59 and the reactions in Scheme 5.60). As illustrated by the examples in Scheme 5.59, β -fluorovinylolithiums are sufficiently stable at -100°C to enable their alkylation before loss of lithium fluoride [464–466]. Similarly, *cis*-2-chlorovinylolithium derivatives require temperatures above -80°C to undergo elimination. *trans*-2-Chlorovinylolithiums, on the other hand, are extremely unstable, and are transformed into alkynes as soon as they are formed, even at temperatures below -110°C [440].

Examples have been reported, in which one isomer of a chloroalkene can be α -lithiated whereas the other isomer undergoes β -elimination (Scheme 5.60). Such subtle differences in reactivity will depend on the precise reaction conditions and the substitution pattern of the alkene, and will only rarely be foreseeable.



Scheme 5.59. Generation and reactions of lithiated vinyl halides [440, 465, 466].

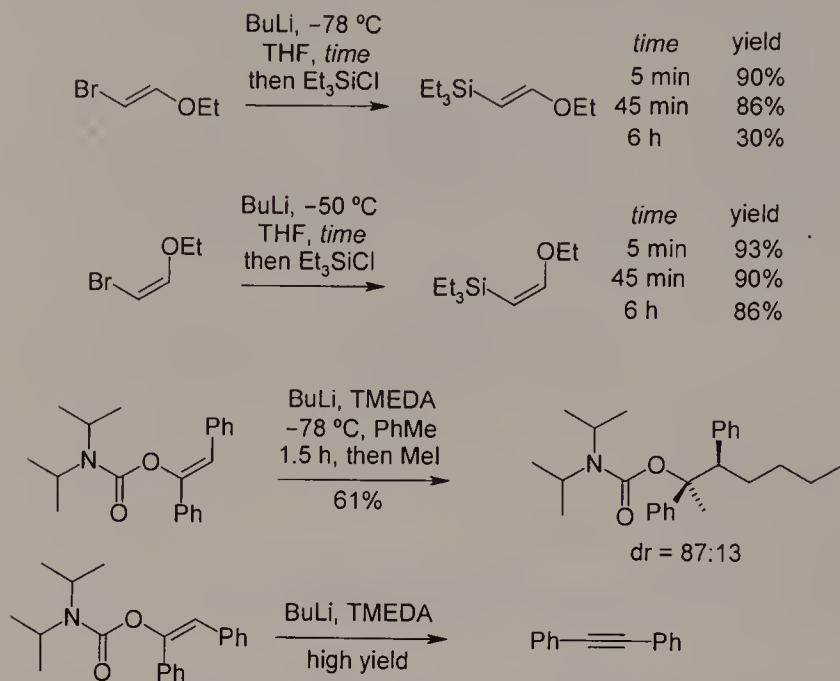


Scheme 5.60. Formation and reactivity of lithiated 1-chloro enynes [331].

Not only halides but also alcoholates or carbamates can act as leaving groups (Scheme 5.61). 2-Lithiovinyl ethers, which cannot be prepared by deprotonation [330] but are accessible by halogen-metal exchange [317], are rather stable when lithium and the alkoxy group are configured *cis*. The corresponding *trans* isomers are, though, less stable, and undergo β -elimination if too much time elapses before the addition of an electrophile.

O-Vinyl carbamates can act as Michael-acceptors toward alkylolithiums (third reaction, Scheme 5.61), because the resulting α -lithiated carbamates are stabilized by

chelate formation. A competing process is vinylic metalation, which can lead to elimination of the carbamate and formation of an alkyne. Again, as already mentioned above, the configuration of the alkene can decisively affect the outcome of the reaction (compare third and fourth examples, Scheme 5.61).



Scheme 5.61. Formation and reactions of β -lithiated vinyl ethers [57, 317].

1-Lithio-2-haloarenes are significantly more stable than 1-lithio-2-haloalkenes. The stability of metalated haloarenes is discussed in Section 5.3.10.

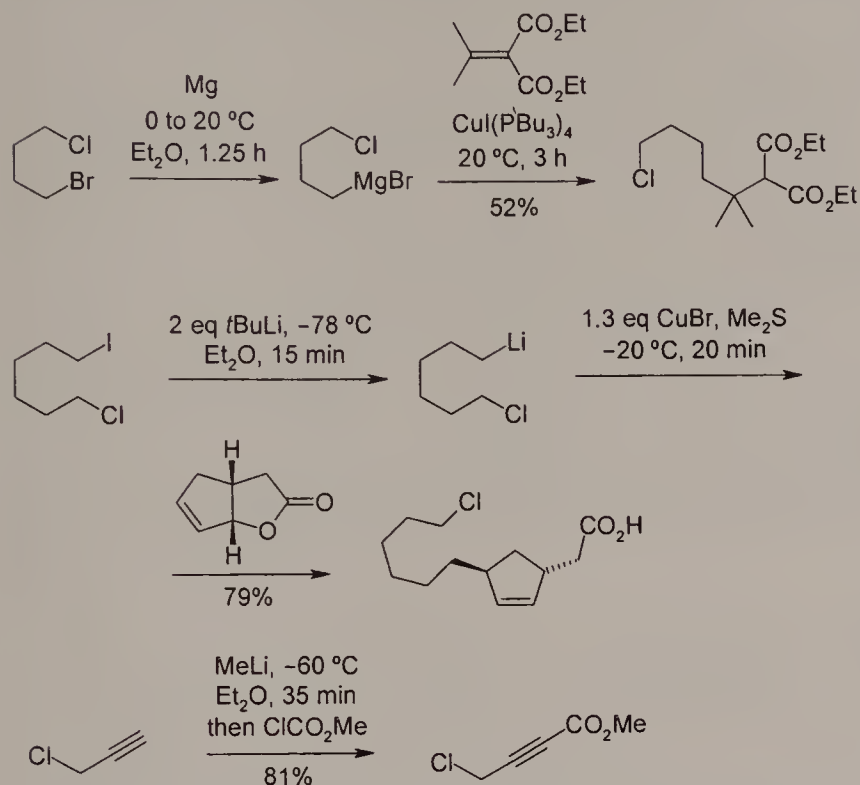
5.4.4

Cyclization

Carbanions with a leaving group or another electrophilic functional group in a suitable position can cyclize or oligomerize instead of reacting intermolecularly with an electrophile, and numerous examples of such cyclizations have been reported [467–470]. Highly reactive carbanions can lead to the formation of strained rings, for example cyclopropanes [272, 292, 471], benzocyclopropanes [472], or benzocyclobutenes [469, 473, 474]. Alternatively, the intermediate carbanion can oligomerize. For the organic chemist it is particularly important to know how readily such cyclizations/oligomerizations will occur, and under which conditions it will be possible to trap the intermediate carbanion intermolecularly with an added electrophile.

Several ω -haloalkyllithiums and Grignard reagents have been described which are sufficiently stable to react intermolecularly with electrophiles before cyclizing (Scheme 5.62). Particularly stable are ω -chloroalkyl derivatives [475–477] whereas, not surprisingly, the ω -bromo- or ω -iodoalkyl carbanions are usually more difficult to prepare and handle (see below). Propargyl chloride has been lithiated at the alky-

nyl group by treatment with MeLi at low temperatures, and the resulting intermediate could be C-acylated with methyl chloroformate in high yield without loss of chloride (Scheme 5.62).

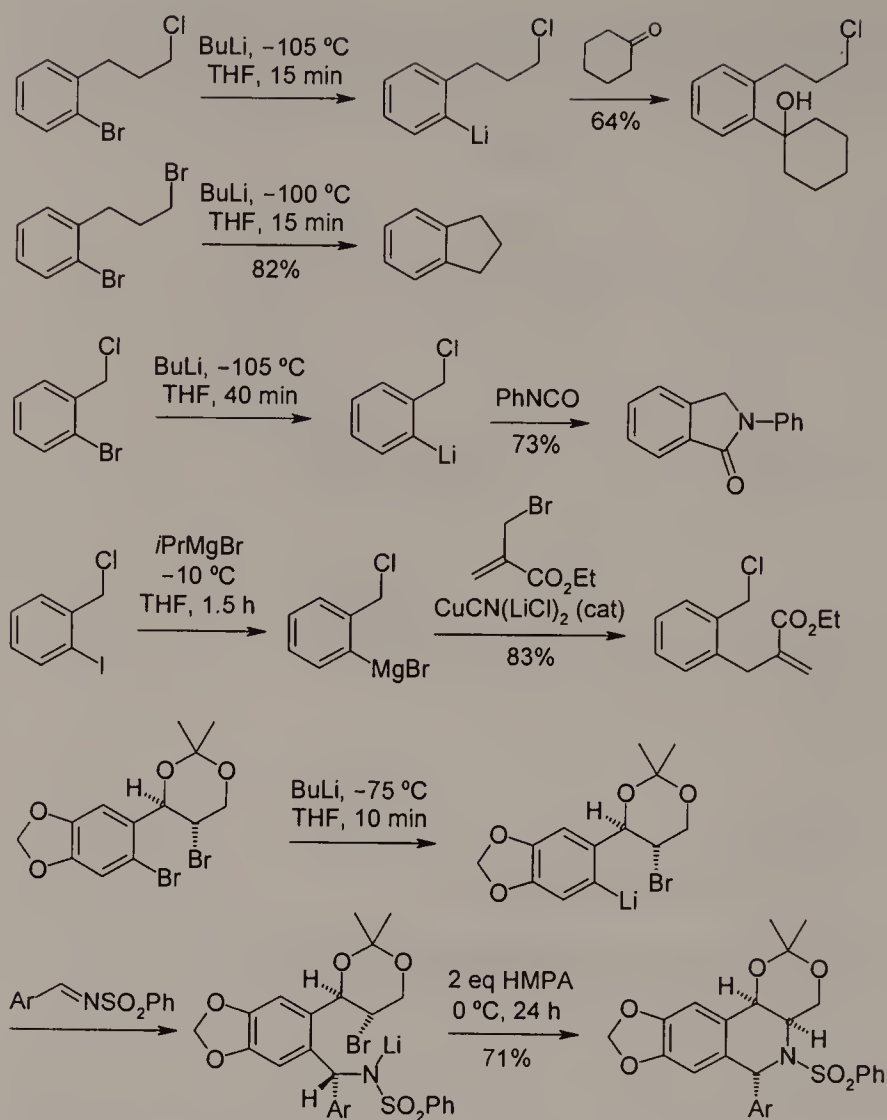


Scheme 5.62. Preparation and reactions of haloalkyl Grignard reagents [478], haloalkyllithium compounds [479], and lithiated propargyl chloride [480].

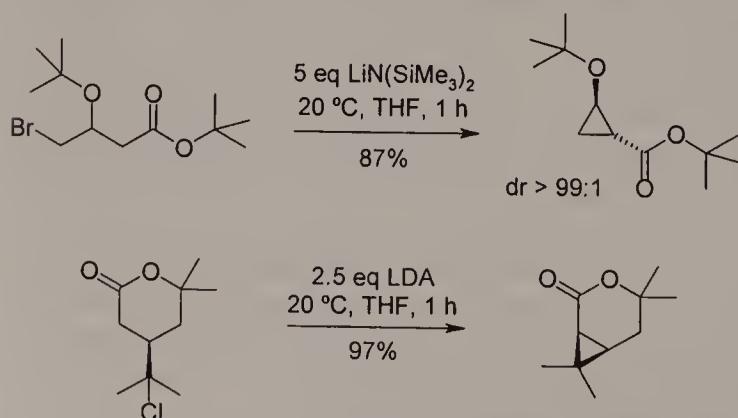
Dihalides containing an aliphatic and an aromatic halide often undergo selective halogen–metal exchange at the arene [468]. If the aliphatic halogen is chlorine the resulting intermediates are quite stable and can be trapped with external electrophiles (Scheme 5.63). The corresponding bromides are, however, more reactive and cyclize more readily than the chlorides. The stability of these intermediates can also be enhanced by choosing magnesium instead of lithium as the metal.

Enolates with a leaving group in the γ position can cyclize to yield cyclopropanes instead of reacting intermolecularly with an electrophile. 3-Halopropyl ketones or 4-halobutyric acid esters, for instance, are readily converted to cyclopropane derivatives when treated with a base (Scheme 5.64; see also Section 9.4.1).

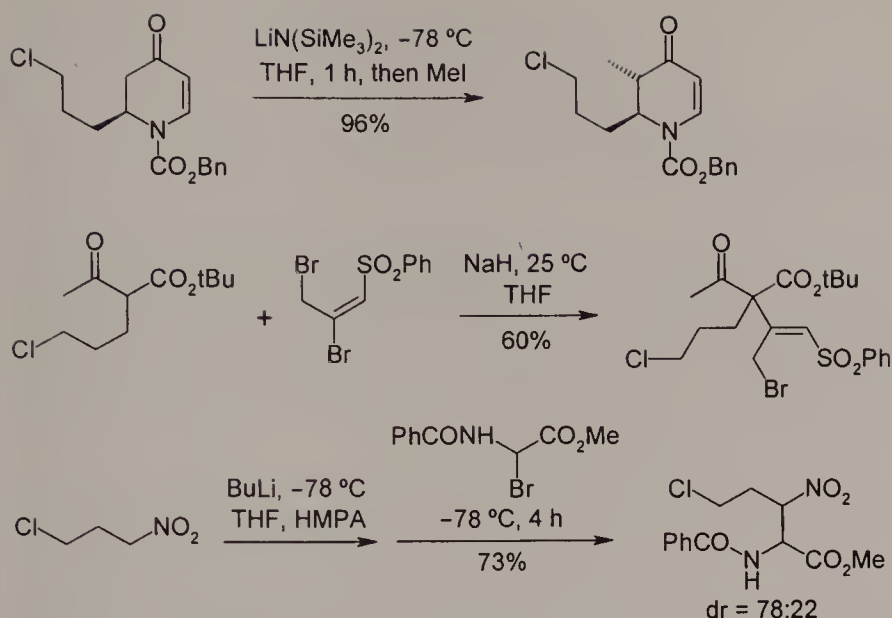
3-Alkoxypropyl ketones and even 3-acyloxypropyl ketones, however, do generally not cyclize, and can be cleanly metalated and alkylated intermolecularly with an electrophile [485]. Similarly, chloroalkyl enolates with more than two atoms between the nucleophilic and electrophilic carbon atoms do not cyclize readily. Examples of chloroalkyl ketones and nitro compounds, which can be deprotonated and alkylated without undergoing cyclization are shown in Scheme 5.65.



Scheme 5.63. Preparation and reactions of partially metalated arylalkyl dihalides [474, 481, 482]. Ar = 3,4,5-trimethoxyphenyl.

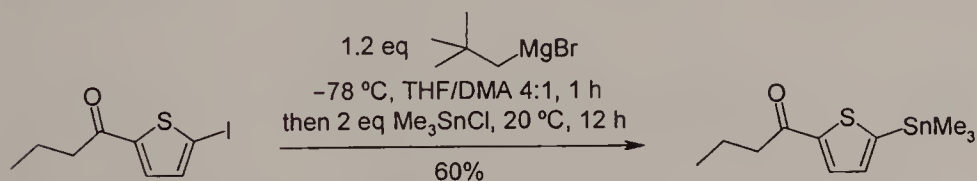


Scheme 5.64. Formation of cyclopropanes from 4-halobutyrate [483, 484].



Scheme 5.65. Deprotonation and alkylation/vinylation of chloroalkyl ketones and nitro compounds [486–488].

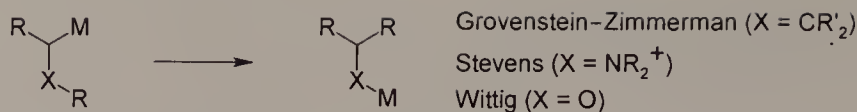
Ketones usually react quickly with Grignard reagents, even at low temperatures. 2- or 3-Iodoaryl ketones can, however, be converted into Grignard reagents by iodine–magnesium exchange with neopentylmagnesium bromide, which does neither add to nor reduce ketones at significant rates when compared with the rate of halogen–magnesium exchange. These metalations require dipolar aprotic solvents such as NMP or DMA to proceed at acceptable rates. The resulting Grignard reagents are sufficiently stable to enable intermolecular coupling with a variety of electrophiles [489, 490] (Scheme 5.66).



Scheme 5.66. Formation and derivatization of ketone-containing Grignard reagents [489].

5.4.5 Rearrangement

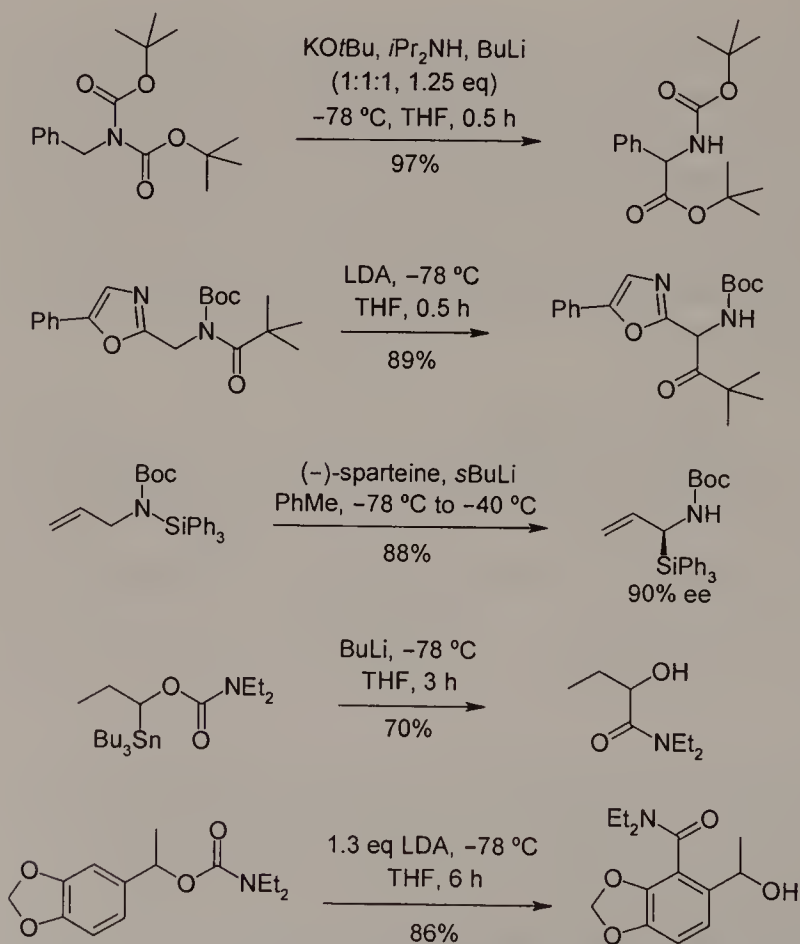
Carbanions which cannot achieve stabilization by charge delocalization to a more electronegative atom than carbon might undergo substantial rearrangement to achieve such stabilization. The Wittig, Stevens, or Grovenstein–Zimmerman rearrangements are examples of such transformations (Scheme 5.67). Such rearrangements are non-concerted when a simple alkyl group migrates, but can become concerted if the migrating groups are allylic or benzylic (2,3-sigmatropic rearrangements).



Scheme 5.67. Rearrangements of carbanions (M = alkali metal, R' = carbanion stabilizing group).

The ease with which these reactions will occur depends to a large extent on the precise structure of the substrate and can be difficult to predict. Low reaction temperatures will generally prolong the half-life of the initially formed carbanions, which might then be trapped intermolecularly with reactive electrophiles before rearrangement can occur [193, 252]. Intramolecular trapping of such carbanions can also be used to prevent their rearrangement [253, 491].

Not only alkyl groups, but also aryl [492, 493], vinyl [494], acyl [276, 495–497], alkoxycarbonyl [498], aminocarbonyl [499–501], silyl [502–504], or phosphoryl groups [279, 280] can migrate to a vicinal carbanion (Scheme 5.68). Because some of these groups can be used to stabilize α -heteroatom-substituted carbanions by chelate formation, migration of these groups to the carbanion is a potential side reaction in the generation and alkylation of chelate-stabilized carbanions.

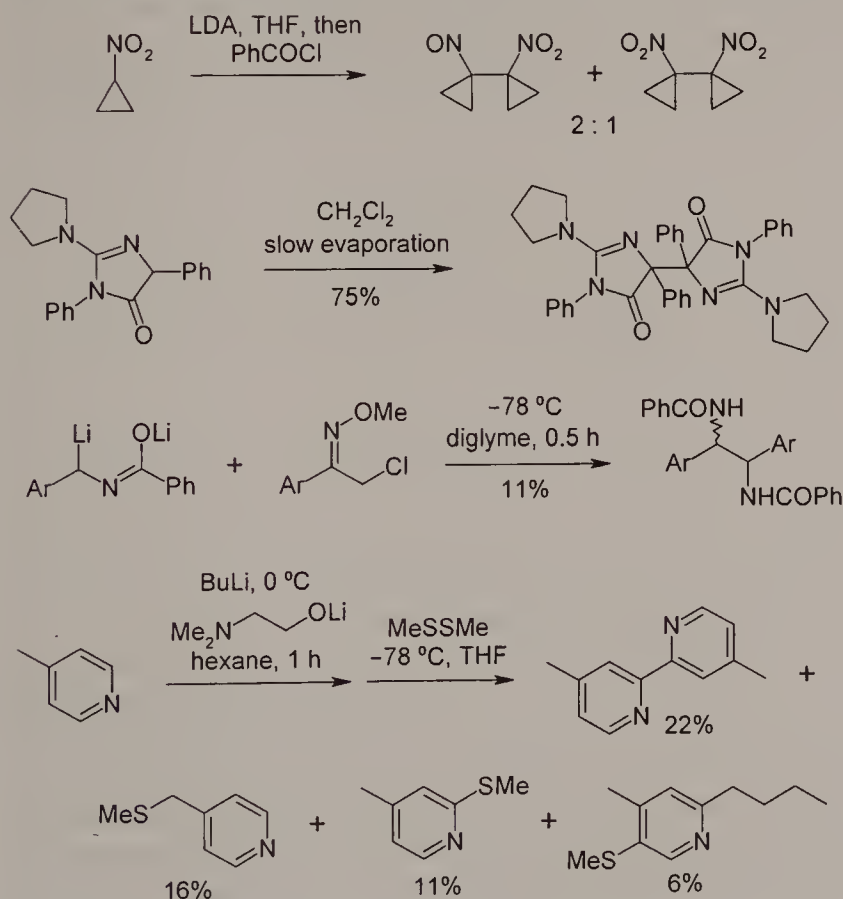


Scheme 5.68. Rearrangements of chelate-stabilized carbanions [496, 498, 500, 502].

5.4.6

Oxidation

Electron-rich organic compounds, for example carbanions, can readily be transformed into radicals by transfer of a single electron to a suitable oxidant. The resulting radicals can dimerize if their half-life is sufficiently long, or undergo fragmentation or other reactions characteristic of radicals. Particularly facile is the formation of radicals substituted with both electron-donating and electron-withdrawing substituents [505, 506]. Potential oxidants can be air, the solvent, the carbanion itself (disproportionation), or an added oxidant or electrophile. Electrophiles with a high tendency to act as single-electron oxidants are alkyl, allyl, and benzyl iodides and bromides, benzophenone, nitro compounds, and electron-poor aldehydes [233, 507]. Carbanions with a high tendency to become oxidized by SET are deprotonated nitroalkanes [508, 509] and carbanions substituted with both electron-donating and electron-withdrawing groups [510–513] (Scheme 5.69). Non-resonance-stabilized carbanions, such as metalated formamidines [233] (Scheme 5.25) or metalated benzyl alcohols [256], can also act as reducing agents. If oxidation of a carbanion by an added electrophile becomes the main reaction pathway, addition of a cosolvent such as DMPU (to accelerate bond formation with the electrophile) or transmetalation



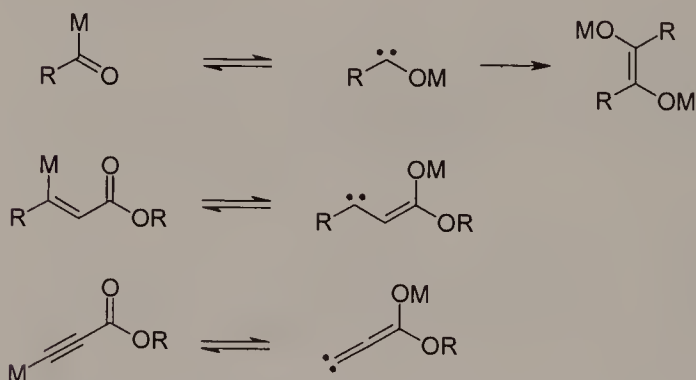
Scheme 5.69. Dimerization of organolithium compounds and imidazolones [401, 508, 511, 515]. Ar = 4-(MeO)C₆H₄.

can be useful strategies for retarding or suppressing SET processes. Carbanions can also dimerize if treatment with an alkyl halide leads to C-halogenation rather than C-alkylation [514]. Reaction of the newly formed alkyl halide with the carbanion will then yield symmetric dimers.

5.4.7

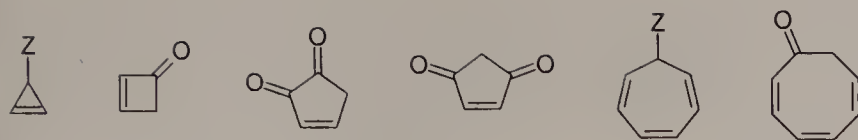
Other Factors which Influence the Stability of Carbanions

Carbanions which could, in principle, achieve stabilization by charge delocalization to a more electronegative atom might be rather unstable, anyway, if this tautomer or canonical form is a carbene (Scheme 5.70). This is, for instance, observed for acyl anions, which are difficult to trap with electrophiles and undergo rapid dimerization even at low temperatures [179]. Vinylogous acyl anions, such as metalated propiolic acid esters [75, 516–518], metalated 2-ethynylpyridine [519], or β -metalated acrylic acid derivatives (Section 5.3.8) are more stable than acyl anions, but must still be kept at low temperatures [520] and should be treated with an electrophile immediately after their generation. The stability of these anions can sometimes be enhanced by reducing the electron-withdrawing strength of the group in the β position of the carbanion. The dianions of propiolic acid [175], *N*-alkyl propiolic acid amides [151], or acrylic acid [334], for instance, are more stable than the corresponding metalated esters. The stability can also be enhanced by choosing a metal, for example magnesium, which forms a more covalent bond with carbon than do the alkali metals [340].



Scheme 5.70. Carbanion–carbene tautomerism of vinylic or alkyne-derived carbanions substituted with electron-withdrawing groups.

Another group of unstable carbanions are those with antiaromatic character (Scheme 5.71). Thus, cyclopropenyl anions or oxycyclobutadienes, generated by deprotonation of cyclopropenes or cyclobutenones, respectively, will be highly reactive and will tend to undergo unexpected side reactions. Similarly, cyclopentenones are difficult to deprotonate and alkylate, because the intermediate enolates are electronically related to cyclopentadienone and thus to the antiaromatic cyclopentadienyl cation.



Scheme 5.71. Compounds which upon deprotonation yield antiaromatic carbanions.

5.4.8

Configurational Stability of Carbanions

5.4.8.1 Introduction

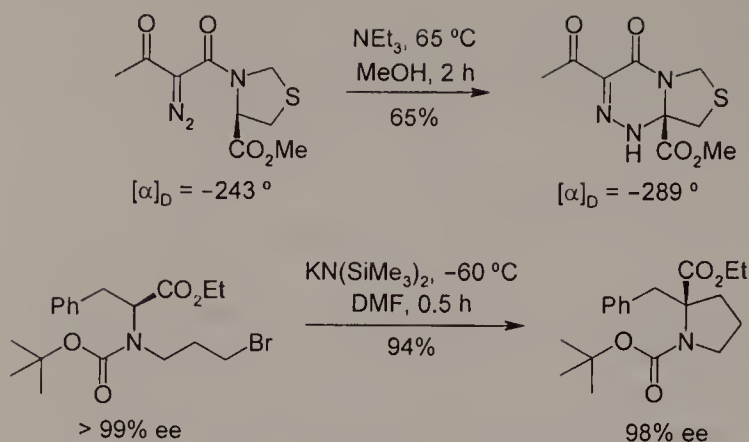
A deprotonation is a nucleophilic attack by a base at hydrogen. The formation of aliphatic organolithium compounds ($C(sp^3)-Li$) by deprotonation of C,H groups with other organolithium compounds or lithium amide bases usually occurs with retention of configuration at carbon [238, 274, 521], as do tin–lithium transmetalations [236, 240, 261, 521, 522] or sulfoxide–magnesium exchanges [9, 311]. Halogen–metal exchange, which can involve radicals [523, 524], can either proceed with retention of configuration [6, 525, 526] or with racemization [527–529].

In carbanions, for instance enolates, in which delocalization of the negative charge to a more electronegative atom (N, O, S) is possible, the cation is usually bound to this atom if the cation is hard (e.g. alkali metal cations, Mg^{2+} [530], Zn^{2+}); in this case the nucleophilic carbon atom becomes a planar sp^2 hybrid. If the cation is soft (e.g. the cations of late transition metals) it will often be bound to the deprotonated carbon atom; these organometallic compounds are, however, usually only weak nucleophiles and will not be treated here.

Electrophilic substitutions at carbon, for example the reaction of an organometallic reagent with an electrophile, can occur either with retention [236, 238, 274, 275, 525, 529] or inversion [234, 471] at the nucleophilic carbon atom [57, 189, 522, 531, 532].

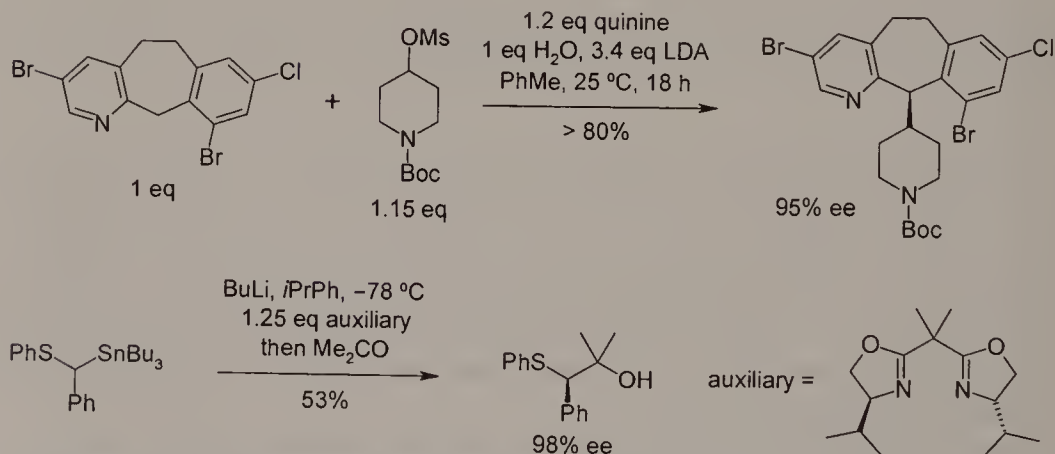
The structures of organometallic compounds prepared by deprotonation of a $C(sp^3)$,H-group range from completely dissociated ion pairs to covalent compounds with strong, kinetically stable C–M bonds. Not only the latter, but also ionic carbanions, can be configurationally stable, for instance if the carbanion is strongly pyramidalized, as some metalated sulfones [533–535], or if inversion is precluded by the structure of the carbanion, as for bridgehead carbanions. Vinylic or cyclopropane-derived carbanions also tend to have high configurational stability, even if the C–M bond is strongly polarized.

The formation of enolates or related compounds with a planar nucleophilic carbon atom by deprotonation of a center of asymmetry does not necessarily mean that the stereochemical information is lost. Examples have been reported in which the enolate remains chiral by assuming a different form of chirality (e.g. axial chirality) and the ensuing reaction with an electrophile proceeds with high enantioselectivity, despite the transient planarization of the stereogenic center (Scheme 5.72).



Scheme 5.72. Intramolecular amination and alkylation of enolates with retention of configuration [536, 537].

Configurationally stable carbanions are not a prerequisite for stereoselective reactions with electrophiles. If the organometallic reagent is configurationally labile, as is the case for many organolithium or Grignard reagents at room temperature, highly stereoselective reactions with electrophiles can occur via electrophile- or additive-controlled dynamic kinetic resolution. Examples of such reactions are shown in Scheme 5.73. The intermediate organolithium compound of the second reaction has been shown to be configurationally labile [283], but in the presence of an enantiomerically pure bisoxazoline one of the two enantiomers reacts significantly faster with the electrophile than the other. The first reaction in Scheme 5.73 requires toluene as solvent; in THF no alkylation but mainly elimination of MsOLi occurs [538].



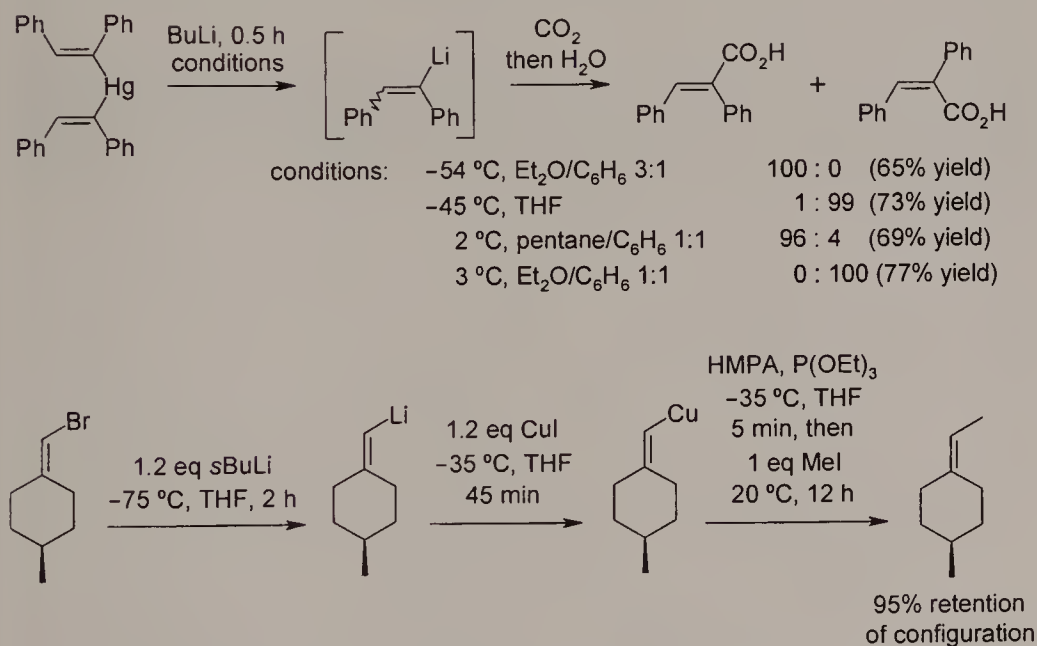
Scheme 5.73. Dynamic kinetic resolution via configurationally labile carbanions [283, 538, 539].

Organometallic compounds with covalent, sparsely polarized C–M bonds do not usually epimerize readily. Thus, organoaluminum or organomercury compounds are configurationally stable up to 150 °C [540, 541] if oxidants or other radical chain

initiators are carefully excluded (footnote 10 in Ref. [542]). Similarly, boranes, stannanes, or silanes are configurationally stable at the temperatures usually chosen for most synthetic organic reactions with these intermediates.

5.4.8.2 Organolithium Compounds

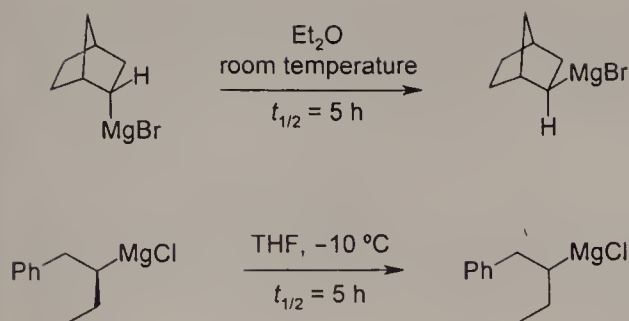
Organolithium compounds devoid of heteroatoms have little configurational stability [531, 543, 544]. Thus, lithiation of (–)-2-iodooctane with *s*BuLi at –70 °C in Et₂O followed by treatment with CO₂ after 2 min led to 80% racemized 2-methyloctanoic acid [545]. Similarly, lithioalkenes often undergo rapid *cis/trans* isomerization, even at low temperatures, in particular if the alkene is substituted with aryl or electron-withdrawing groups [546–548]. For example, *cis*-lithiostilbene isomerized completely to *trans*-lithiostilbene within 0.5 h in THF at –45 °C (Scheme 5.74). Such isomerizations proceed more quickly in ethers as solvent than in pure hydrocarbons [544, 549, 550]. A remarkably stable vinylic organolithium compound is (4-methylcyclohexylidene)methylolithium (second example, Scheme 5.74).



Scheme 5.74. Configurational stability of lithiostilbene [549] and cyclohexylidenemethylolithium and -copper derivatives [551].

Some heteroatom-substituted or chelate-stabilized organolithium compounds, on the other hand, can be sufficiently stable toward racemization to enable their use in stereoselective reactions with electrophiles [223, 225, 271, 531, 543, 552–554] (Scheme 5.75). This increased configurational stability of α -heteroatom-substituted carbanions might be due to the stronger pyramidalization of such carbanions [261, 555] and fixation of the metal by chelate formation.

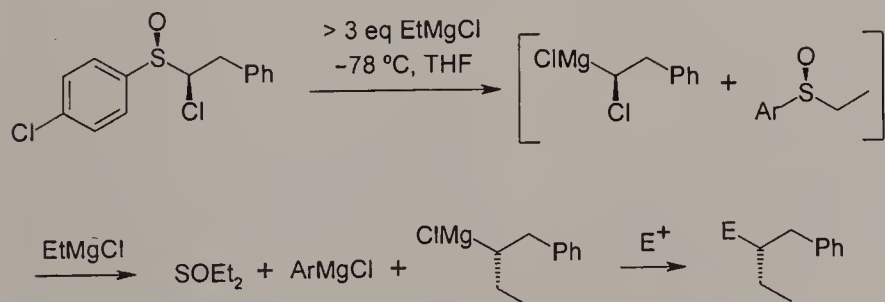
Enantiomerically pure organolithium compounds have been prepared by tin–lithium exchange [261], mercury–lithium exchange [549], or by lithiation in the presence of a chiral, enantiomerically pure or enriched amine, for example sparteine [271]



Scheme 5.77. Isomerization of Grignard reagents [261, 311].

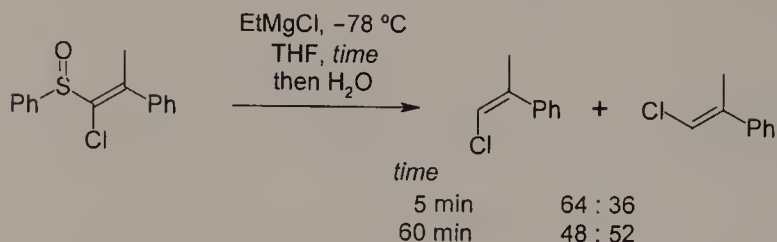
Unfunctionalized, enantiomerically enriched secondary Grignard reagents cannot be prepared by halogen–magnesium exchange with metallic magnesium, because these reactions proceed via radicals [523] and lead to racemates. Halogen–magnesium or sulfoxide–magnesium exchange with other Grignard reagents is not possible either, because Grignard reagents with secondary alkyl groups are too energy-rich and will not be formed in substantial amounts by thermodynamic equilibration with other Grignard reagents [311]. One possible means of access to these compounds is the reaction of enantiomerically pure α -chloro sulfoxides (prepared by chlorination of enantiomerically pure sulfoxides [312, 565]) with excess primary Grignard reagent (Scheme 5.78). First, a sulfoxide–magnesium exchange occurs with retention of configuration, to yield an α -chloro Grignard reagent. The latter undergoes an S_N2 -like reaction with inversion of configuration with a further equivalent of primary Grignard reagent to yield an enantiomerically enriched secondary organomagnesium compound [9, 564]. These reagents react with a variety of electrophiles (peroxides, PhNCS , PhNCO , CO_2 , PhCHO , allyl chloride, aminals [565], vinyl bromide (on catalysis with a transition metal [566]), ZnCl_2 [567], boronic esters [568], azides [568]) with retention of configuration; with electrophiles prone to undergo reduction by SET (Ph_2CO , $\text{C}_6\text{F}_5\text{CHO}$, allyl iodide), however, partial or complete racemization is observed [507, 565].

Vinylmagnesium compounds, which can be prepared by halogen–magnesium or sulfoxide–magnesium exchange, usually have high configurational stability [6]. This is, however, not observed for 1-halo-1-magnesioalkenes. Because of their vinylidene



Scheme 5.78. Generation of enantiomerically enriched secondary Grignard reagents [311, 568]. $\text{Ar} = 4\text{-ClPh}$, E^+ = see text.

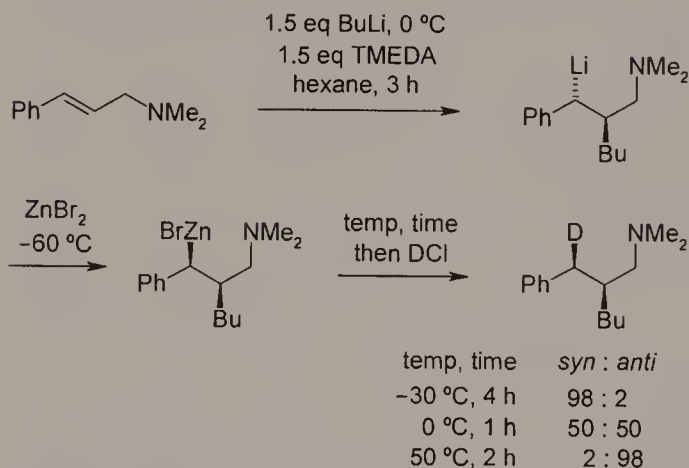
character, both the C–Mg and C–Hal bonds are weakened [327]; this leads to facile halogen–halogen exchange reactions [569] and rapid loss of stereochemical information (Scheme 5.79).



Scheme 5.79. Conformational lability of 1-chloro-1-magnesioalkenes [569].

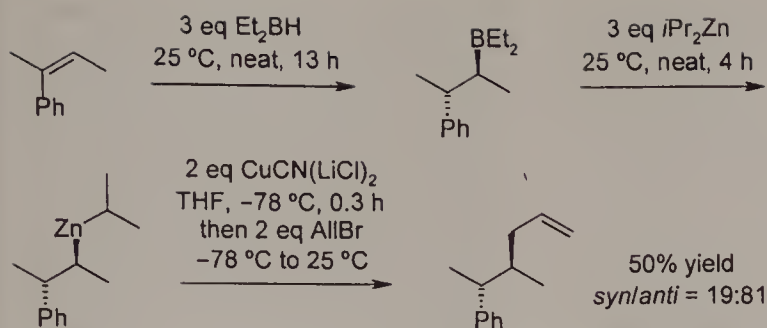
5.4.8.4 Organozinc and Organocopper Compounds

The configurational stability of organozinc reagents is greater than that of structurally similar Grignard reagents [540], and configurationally defined organozinc derivatives react with electrophiles at room temperature, usually without epimerization and with retention of configuration [15, 526, 570–572]. An example of the temperature-dependent epimerization of a benzylic organozinc derivative is shown in Scheme 5.80.



Scheme 5.80. Preparation and epimerization of a benzylic organozinc compound [471].

Configurationally defined and stable organozinc reagents have been prepared by reaction of (*sec*-alkyl)dialkylboranes with diisopropylzinc [14, 15, 570, 571] or from secondary Grignard reagents and ZnCl_2 [567], giving (*sec*-alkyl)zinc reagents with retention of configuration. These reagents are configurationally stable at room temperature, and undergo transmetalation (Cu(I), Pd(0)) or reaction with electrophiles with retention of configuration (Scheme 5.81). Zinc–copper transmetalation is required when organozinc reagents are too unreactive toward a given carbon electrophile [573]. Other routes to stereochemically defined organocopper reagents are mercury–copper and lithium–copper exchange [542, 551].



Scheme 5.81. Stereoselective formation and allylation of organozinc compounds [570, 571].

Direct magnesium–copper transmetalation, however, leads to racemization with most types of copper(I) salts, probably because the large difference between the oxidation potentials of Grignard reagents and copper(I) leads to SET [567]. Similarly, transmetalation of enantiomerically enriched Grignard reagents with iron(III) or cobalt(II) leads to partial racemization [566]. Thus, if enantiomerically enriched Grignard reagents are to be transformed into non-racemic organocopper reagents, a detour via an organozinc intermediate might be required [567].

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6

The Alkylation of Heteroatoms

Although carbon–heteroatom bonds are often easier to make than C–C bonds, and are therefore often chosen as retrosynthetic points of disconnection, some non-carbon nucleophiles can be difficult to alkylate. Problems can arise when the nucleophile is highly basic and hard, for these will preferentially attack (hard) protons and cause elimination instead of being alkylated [1]. Similarly, sterically demanding nucleophiles will also tend to attack protons faster than undergo alkylation. Ambident nucleophiles, such as amides, phenols, thiocyanate, or nitrite, can be a further cause of problems, because a variety of different products can be formed, depending on the type of electrophile chosen and on the precise reaction conditions [2]. Substrates with two or more similar nucleophilic groups, for example aminophenols or hydroxybenzoic acids, can often be alkylated with high chemoselectivity, but the outcome of these reactions can be difficult to predict. In the following sections the alkylation of the most common, trouble-causing non-carbon nucleophiles will be discussed.

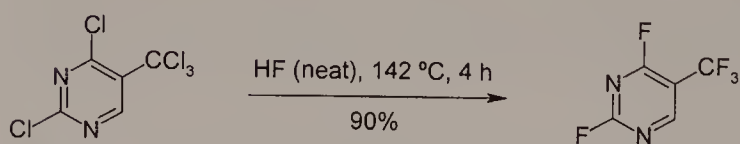
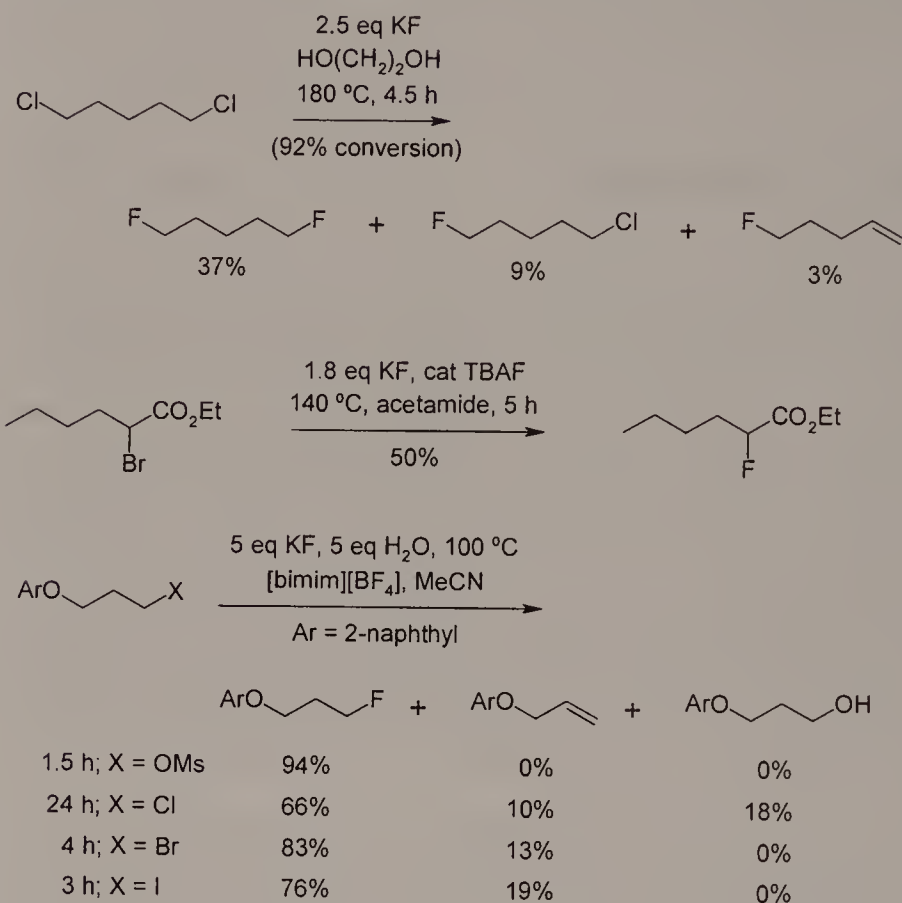
As for carbanions, the reactivity of anionic non-carbon nucleophiles depends on the cation. The nucleophilicity and basicity of a given anionic nucleophile will usually be enhanced if it does not form strong bonds either with the cation or with the solvent. Hard cations, for example Li^+ or Ti^{4+} , will significantly reduce the reactivity of hard anions (RO^- , R_2N^- , F^-), whereas soft cations (Cs^+ , Cu^+ , Pd^{2+}) will form strong bonds with soft anions (RS^- , I^- , CN^- , H^- , R^-) and thereby reduce their reactivity.

6.1

Alkylation of Fluoride

Hydrogen fluoride ($\text{p}K_{\text{a}}$ 3.2 in water) is the hydrogen halide with the lowest acidity, and fluoride is, therefore, a rather strong base. Nucleophilic substitutions with fluoride do not usually proceed smoothly, despite the strength of the C–F bond, and alkenes are often obtained instead of alkyl fluorides if simple alkyl monohalides are treated with fluoride under basic reaction conditions. Eliminations occur particularly readily from alkyl fluorides with an electron-withdrawing group in the β position. Common reagents for displacing halides or related leaving groups by fluoride include AgF , KF , CsF , Bu_4NF [3], HF , and SbF_5 , and suitable solvents are ethylene

glycol or ionic liquids such as *N*-butyl-*N'*-methylimidazolium tetrafluoroborate ([bimim][BF₄], Scheme 6.1). The best results are obtained with hard electrophiles, for example sulfonates or chlorides. The selective displacement of iodide by fluoride in the presence of other halogens by treatment with TlIF₂ has been reported [4].

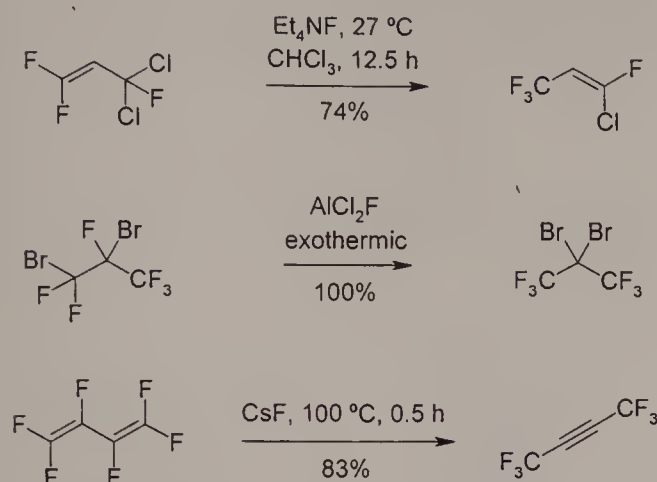


Scheme 6.1. Displacement of different leaving groups by fluoride [5–8].

Replacement of the hydroxyl group of alcohols by fluoride using the phosphine-derived reagent Ph₃PF₂ is successful, but requires much higher reaction temperatures (150–170 °C, 5–7 h) than the analogous conversions to the other halides [9], probably because of the low nucleophilicity of fluoride and the strength of the P–F bond. The conversion of alcohols into fluorides or of carbonyl compounds into geminal difluorides under mild conditions can be achieved with diethylaminosulfur trifluoride (DAST).

A further peculiarity of fluoride is its high tendency to add to fluorinated alkenes and to form stable CF₂ and CF₃ groups (Scheme 6.2). The high stability of these

groups is because of negative hyperconjugation between the (antibonding) $\sigma^*_{\text{C-F}}$ orbitals and the lone pairs on fluorine (see Section 3.4).



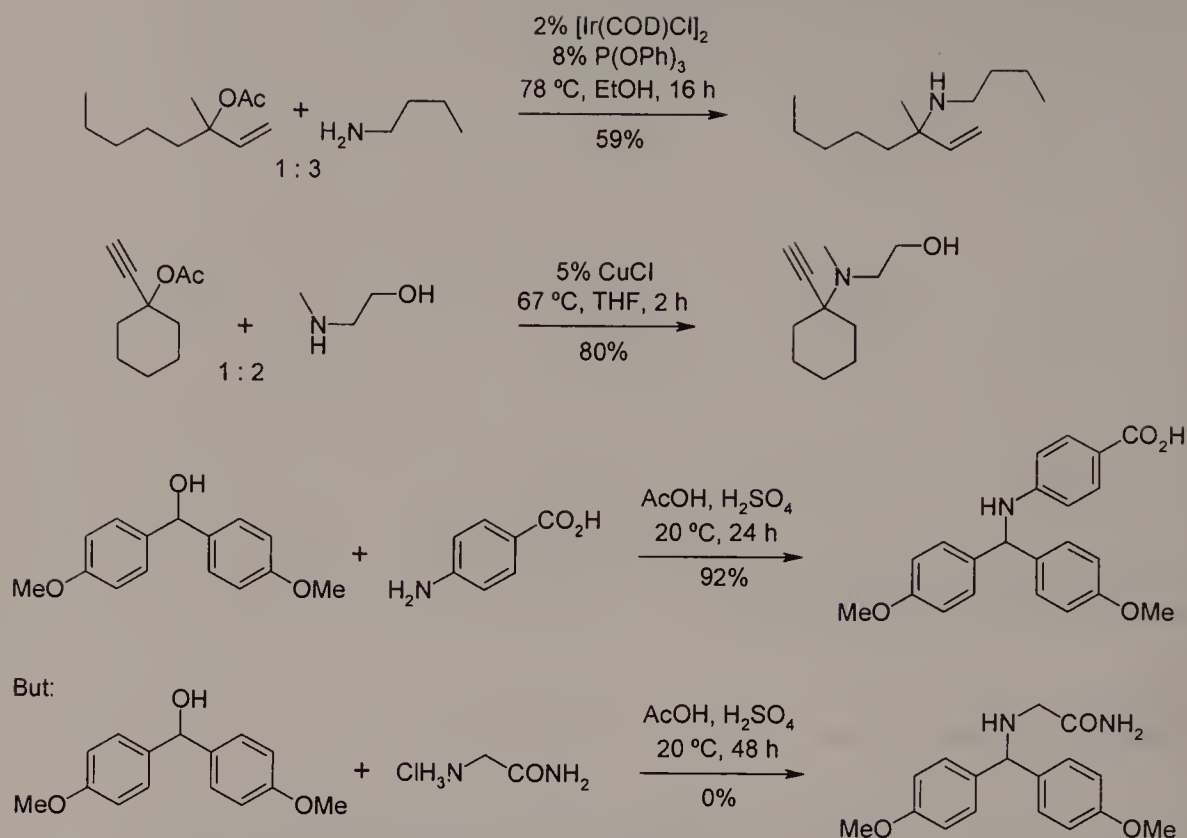
Scheme 6.2. Formation of CF_3 groups by addition of fluoride to fluorinated alkenes [10] and by isomerization [11, 12].

6.2

Alkylation of Aliphatic Amines

The most conspicuous property of aliphatic amines, apart from their fishy smell, is their high basicity, which usually precludes *N*-alkylations under acidic reaction conditions (last reaction, Scheme 6.3). Hence, alkylation of amines with tertiary alkyl groups is not usually possible without the use of highly stabilized carbocations which can be formed under basic reaction conditions. Rare exceptions are *N*-alkylations of amines via radicals (Scheme 4.2), copper-catalyzed propargylations (Scheme 6.3), and the addition of amines to some Michael acceptors and allyl palladium or iridium complexes. Better strategies for the preparation of *tert*-alkylamines include the addition of Grignard reagents to ketone-derived imines [13] or the reduction of *tert*-alkyl nitro compounds.

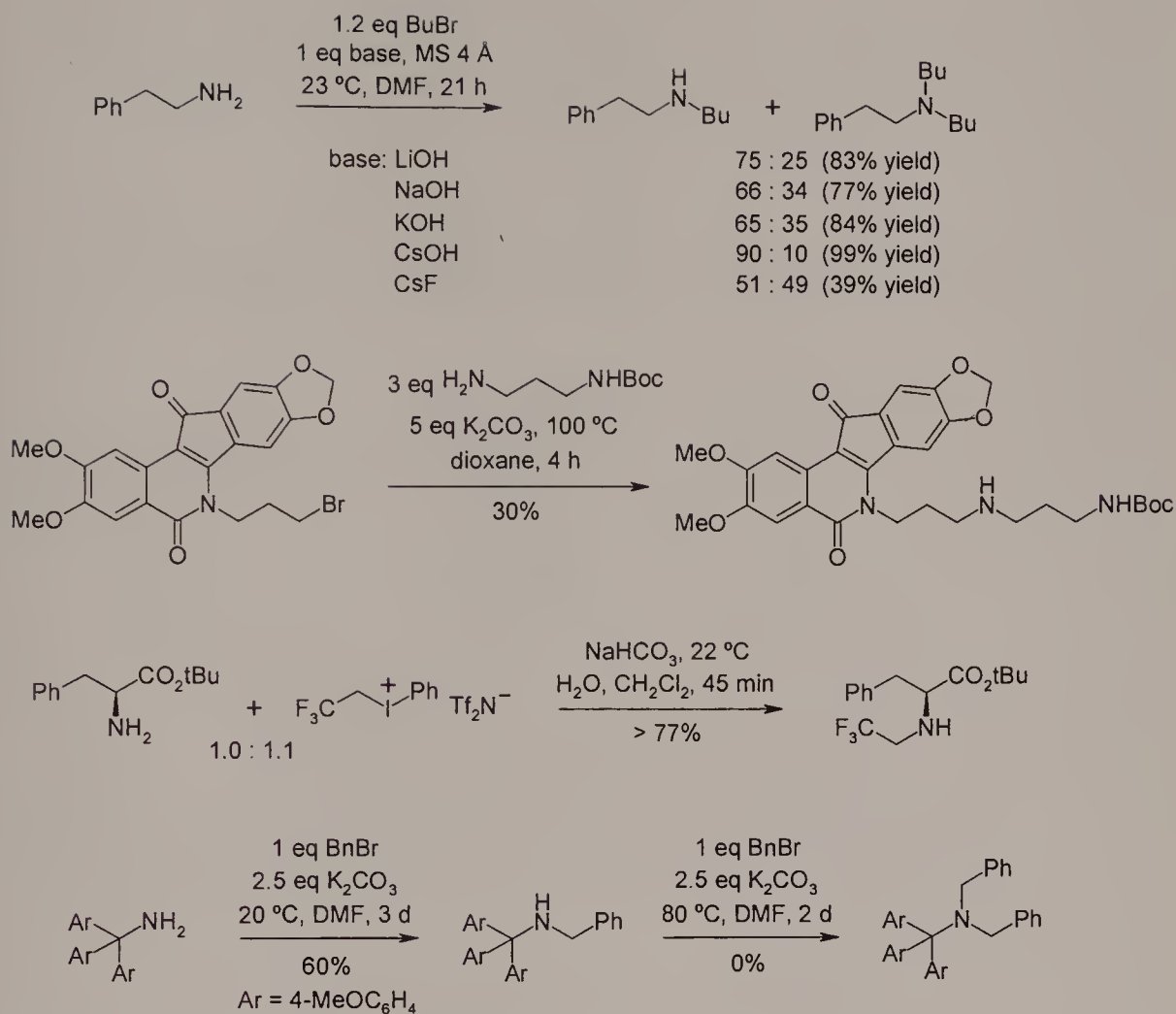
The direct alkylation of primary or secondary amines with alkyl halides can lead to the formation of secondary or tertiary amines or of quaternary ammonium salts [17]. The conversion of primary aliphatic amines into secondary amines with alkylating agents is difficult, because secondary amines are often more nucleophilic than primary amines. Hence, the product will be alkylated faster than the starting amine, and product mixtures will often result (Scheme 6.4), unless a large excess of primary amine can be used. Only if sterically demanding alkylating agents, for example diarylmethyl halides or alkyl halides with an electron-withdrawing group are used ($\text{Hal}-\text{CR}_2-\text{Z}$; third reaction in Scheme 6.4; these lead to the formation of electronically deactivated secondary amines), or if the primary amine is bulky, can clean monoalkylations be achieved. Small, reactive alkylating agents, on the other hand, for example methyl iodide or triflate, will usually lead to peralkylation or quaternization of aliphatic amines. It has been found empirically that addition of CsOH



Scheme 6.3. Alkylation of amines with allyl iridium complexes and with carbocations [14–16].

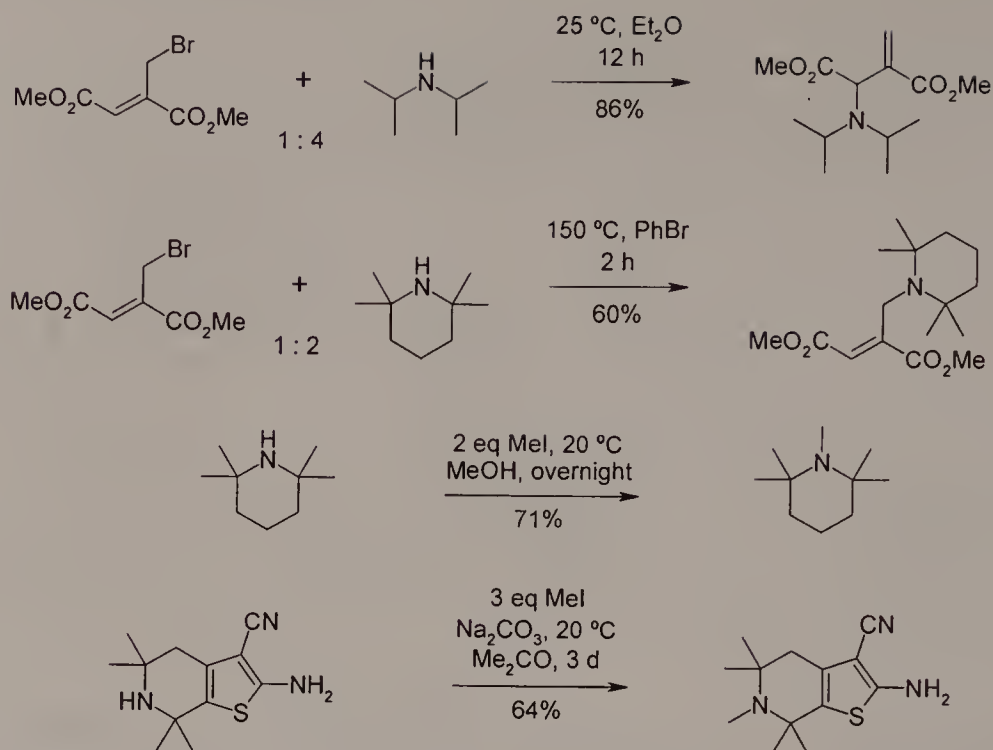
can occasionally promote the formation of secondary amines from primary amines and alkylating agents and inhibit the formation of tertiary amines (Scheme 6.4) [18, 19]. Polyamines may be partially protected from alkylation by complexation with Lewis acids, for example ZnCl_2 [20].

A better strategy for monoalkylation of primary aliphatic amines is their condensation with aldehydes or ketones followed by reduction of the resulting imine. Alternatively, primary amines can be converted into sulfonamides, which can be readily *N*-alkylated and then hydrolyzed (less readily) with strong acids [21–23] or cleaved with thiols (Scheme 6.32).



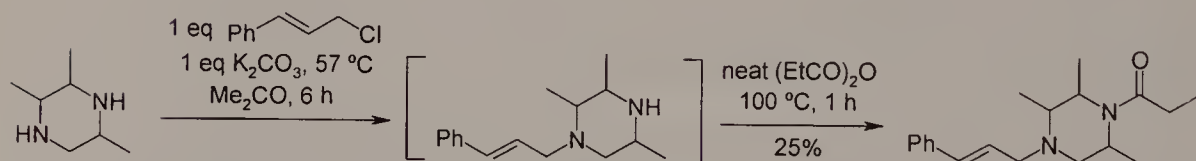
Scheme 6.4. Alkylation of primary aliphatic amines [19, 24–26].

Sterically demanding amines have a high tendency to induce β -elimination when treated with alkyl halides. Their alkylation is, however, feasible with reactive alkylating agents, and even 2,2,6,6-tetramethylpiperidines have been *N*-alkylated (Scheme 6.5). Secondary tritylamines, however, cannot usually be alkylated or acylated intermolecularly (last reaction, Scheme 6.4), but examples of intramolecular alkylations have been reported [27].



Scheme 6.5. Alkylation of sterically hindered amines [17, 28, 29].

Unsymmetric diamines can be monoalkylated regioselectively if the reactivity of both amino groups is substantially different. If the two groups are similar, however, such reactions are usually difficult to perform, and low yields are usually obtained (Scheme 6.6).

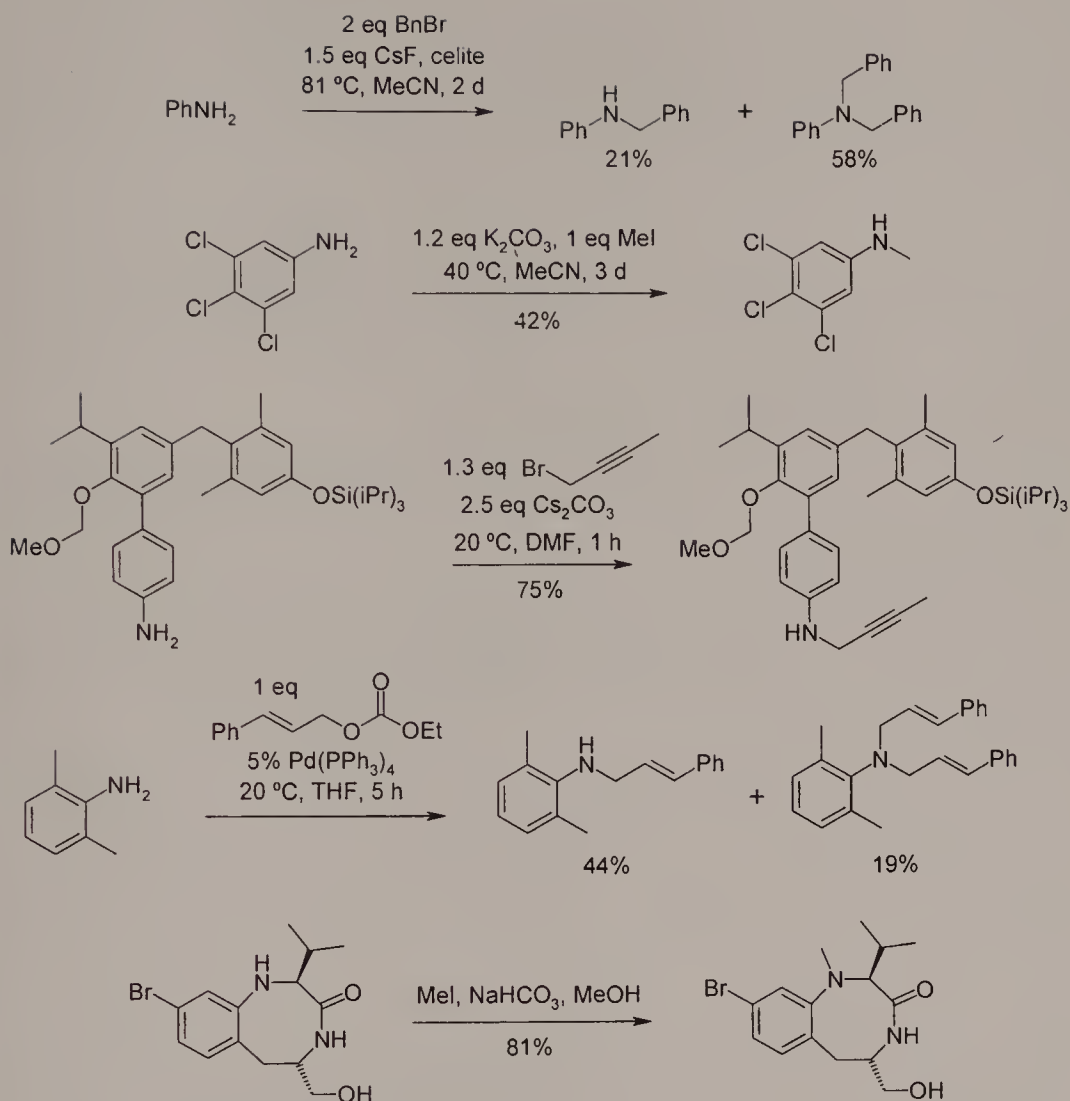


Scheme 6.6. Monoalkylation of an unsymmetric diamine [30].

6.3

Alkylation of Anilines

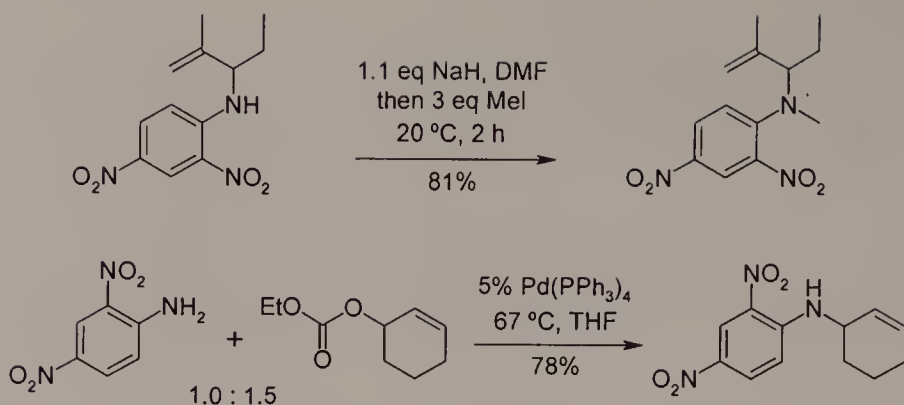
Anilines are generally less basic and nucleophilic than aliphatic amines, but can still be alkylated with alkyl halides under relatively mild reaction conditions under which, for instance, aliphatic alcohols will not undergo alkylation (Scheme 6.7). Monoalkylations of primary anilines with highly reactive alkylating agents can be difficult, and usually require use of excess of aniline and/or careful optimization of the reaction conditions [31–33].



Scheme 6.7. Alkylation of anilines [32, 34–37].

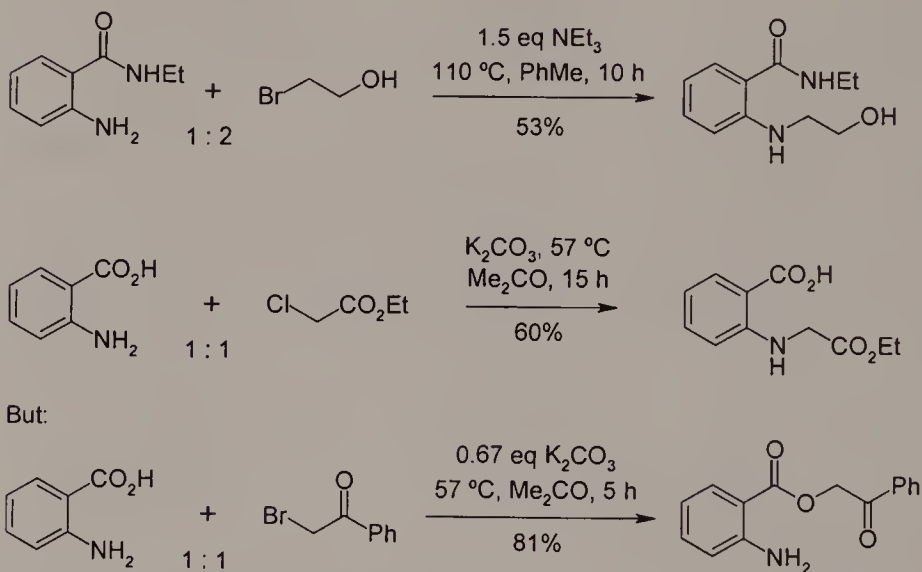
Anilines with strongly electron-withdrawing groups or diarylamines [38] are only weak nucleophiles, and might require deprotonation to react with electrophiles at acceptable rates (Scheme 6.8). These anilines can also be allylated by allyl palladium complexes [34]. Electron-deficient anilines are electrophiles themselves, and can transfer the aryl group to other nucleophiles by aromatic nucleophilic substitution [39].

Anthranilic acid derivatives are also rather poor nucleophiles. Unsubstituted anthranilic acid can be *N*-alkylated selectively with some electrophiles under basic reaction conditions without the formation of esters by *O*-alkylation (Scheme 6.9) [40]. Even use of excess alkylating agent still gives reasonable yields of monoalkylated derivatives; this indicates that the second *N*-alkylation is significantly slower than



Scheme 6.8. N-Alkylation of electron-deficient anilines [34, 39].

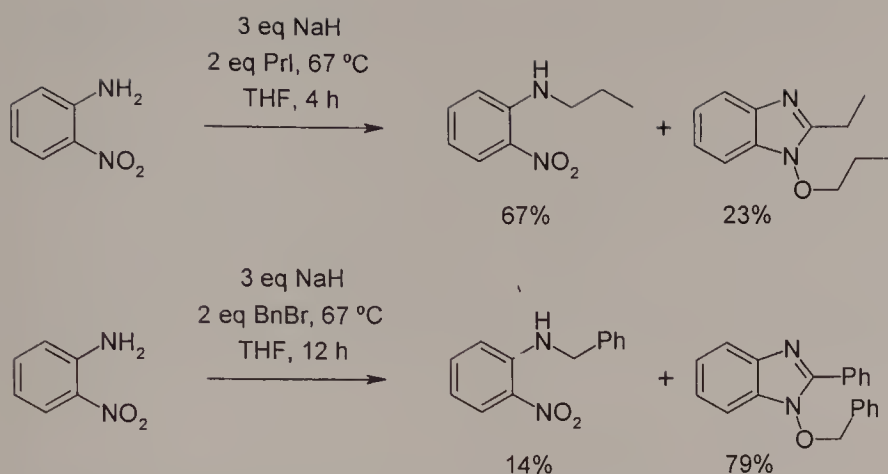
the first. Phenacyl halides, however, lead to the clean O-alkylation of anthranilic acid [41, 42] (Scheme 6.9).



Scheme 6.9. Alkylation of N-ethyl anthranilamide and of anthranilic acid [40, 41, 43].

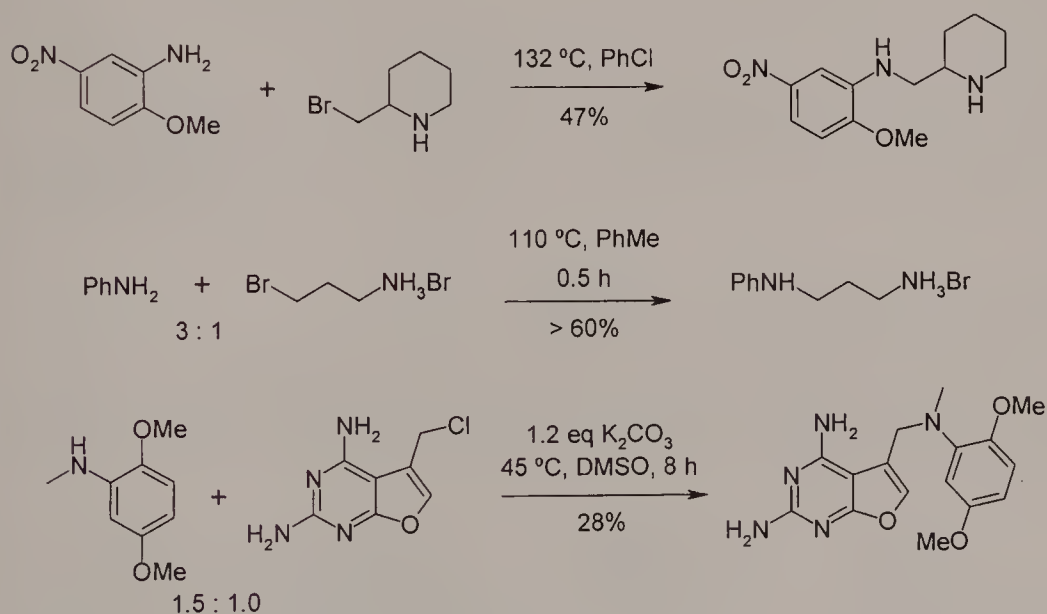
The close proximity of functional groups in 1,2-disubstituted benzenes can sometimes bring about an unexpected reactivity. Attempts to N-alkylate *ortho*-nitroanilines under strongly basic reaction conditions, for instance, lead to the formation of N-alkoxybenzimidazoles (Scheme 6.10). The main force driving this reaction is the formation of an imidazole ring, a heteroarene with high resonance energy and thermal stability.

Haloalkylamines are problematic reagents which will readily polymerize or cyclize under basic conditions and must always be stored as ammonium salts. Because anilines are not very basic, their direct alkylation with salts of haloalkylamines under neutral or acidic reaction conditions can sometimes be achieved



Scheme 6.10. Formation of benzimidazoles during the alkylation of 2-nitroanilines [44].

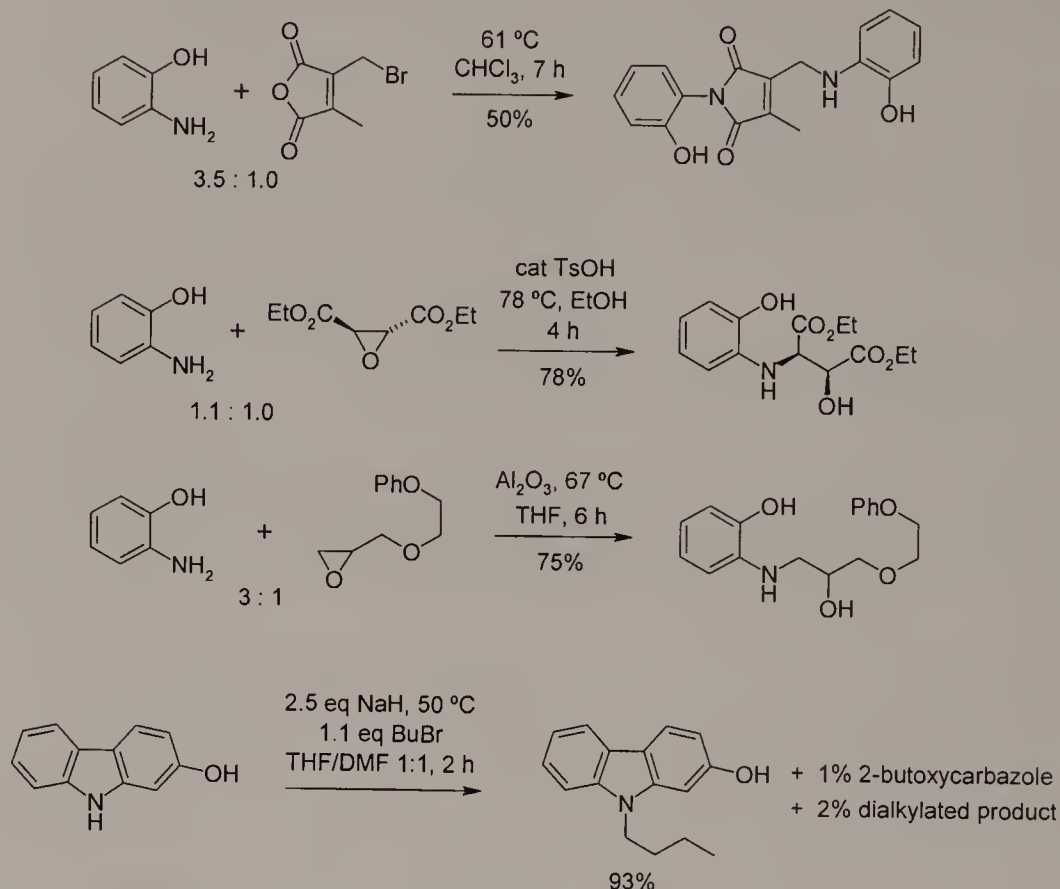
(Scheme 6.11). Reactions of this type will only proceed well with electron-rich, nucleophilic anilines, but fail with electron-deficient anilines. Yields will usually be low if the reaction is conducted under basic conditions [35].



Scheme 6.11. Alkylation of anilines with haloalkylamines [35, 45, 46].

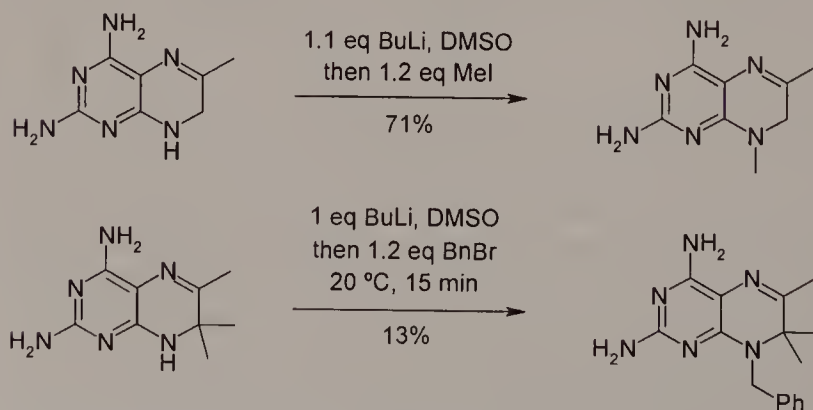
Treatment of aminophenols with alkylating agents can yield either *O*- or *N*-alkylated products, depending on the type of electrophile used and on the reaction conditions. If weak bases and hard electrophiles are used, either clean *O*-alkylation or mixtures of products can result (Scheme 6.20). Acid-catalyzed alkylation of aminophenols with epoxides usually yields *N*-alkylated products [47] (Scheme 6.12). Selective *N*-alkylation of aminophenols can also be achieved by using softer electrophiles or by conversion of the aminophenol into a dianion, followed by treatment with one

equivalent of alkylating agent (Scheme 6.12). Comparison of the examples in Schemes 6.12 and 6.20 show that the chemoselectivity of these reactions is difficult to predict.



Scheme 6.12. N-Alkylation of aminophenols [48–51].

Polyaminoheteroarenes have also been selectively monoalkylated by metalation and treatment with an electrophile. As illustrated by the examples shown in Scheme 6.13, astonishing selectivity can sometimes be achieved.

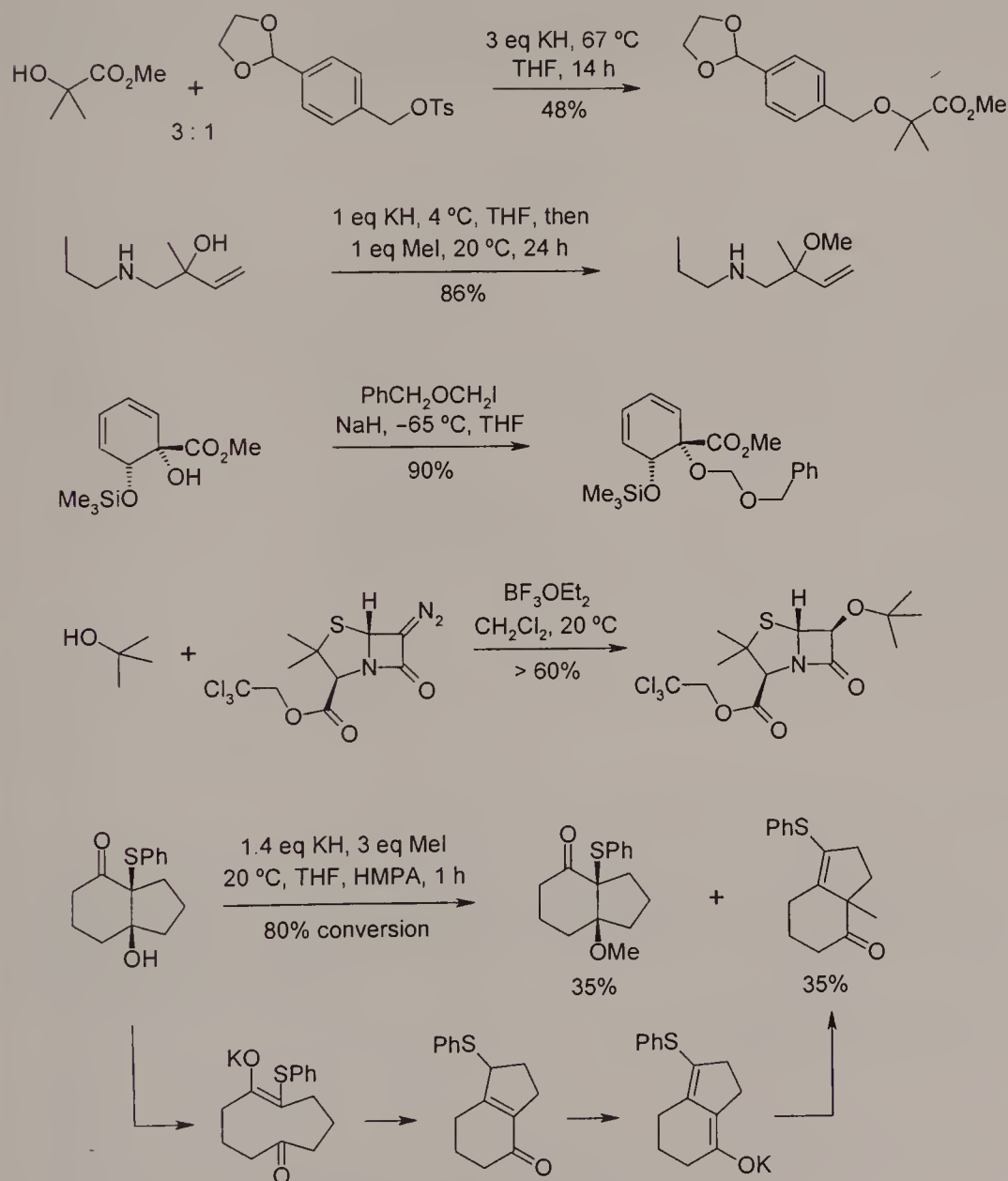


Scheme 6.13. Monoalkylation of diaminopteridines [52, 53].

6.4

Alkylation of Alcohols

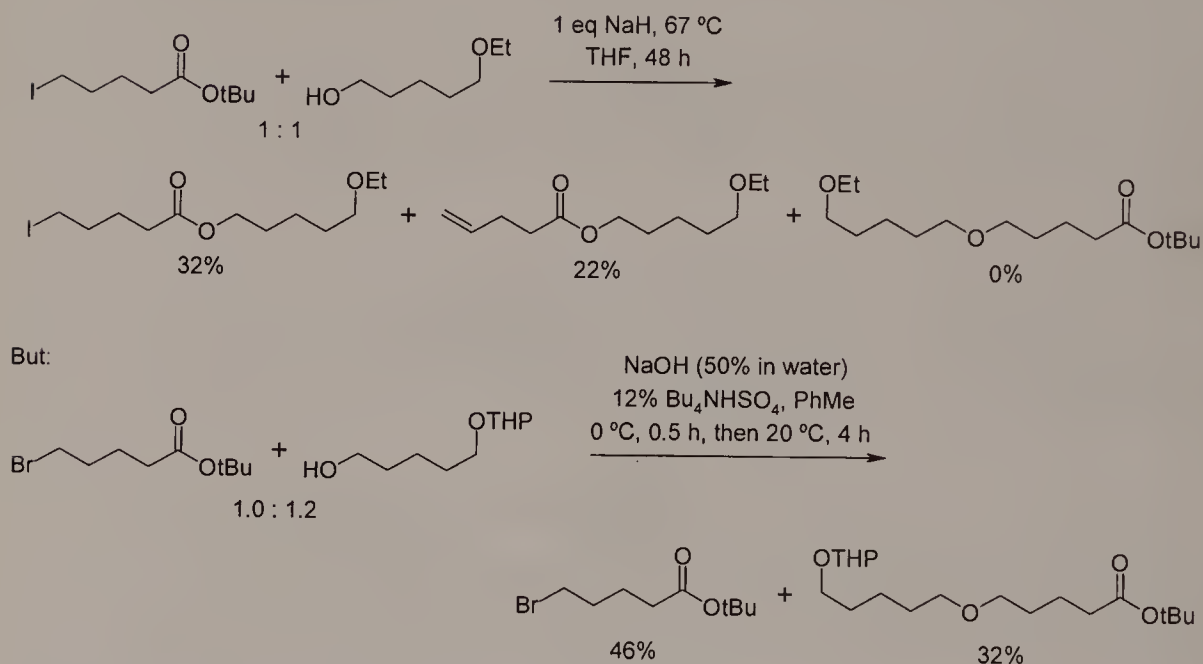
In the absence of strong bases alcohols will only be alkylated by strong alkylating agents, for example trialkyloxonium salts and some triflates, or by carbocations via the S_N1 mechanism. The scope of the Williamson ether synthesis, in which the alcohol is first converted stoichiometrically into an alcoholate which is then alkylated with an alkyl halide, is significantly broader. Most primary, secondary, and tertiary alcoholates can be readily alkylated, although for tertiary alcoholates this reaction proceeds only slowly (Scheme 6.14), and alkylating reagents with β hydrogen will



Scheme 6.14. Alkylations of sterically demanding alcohols [54–58].

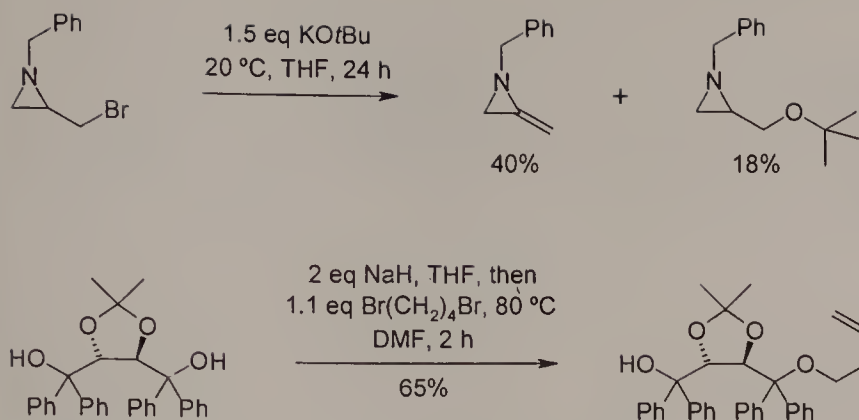
usually undergo β -elimination when treated with tertiary alcoholates (Scheme 6.16). Alkali metal alcoholates are strong (but basic) nucleophiles which can be alkylated even with weak electrophiles. The best results are obtained with sodium or potassium alcoholates; lithium alcoholates, on the other hand, are less reactive, and are not always readily alkylated or acylated. The alkylation of alcoholates usually proceeds more rapidly than alkylation of non-metalated amines, and amino alcohols can be selectively *O*-alkylated without extensive *N*-alkylation (Scheme 6.14).

If the alcoholate or the alkylating reagent contains a carboxylic acid ester, acylation of the alcoholate can compete with alkylation. This potential side reaction does not cause trouble in the examples sketched in Scheme 6.14 (first and third reactions), because these esters are sterically hindered and devoid of α hydrogen (no ketene formation can occur) but, as illustrated in Scheme 6.15, less hindered esters can readily undergo transesterification with alcoholates.



Scheme 6.15. Reactions of *tert*-butyl 5-halovalerates with alcoholates [59].

Secondary alkyl halides will mainly undergo elimination when treated with alcoholates, particularly if the alcoholate is sterically demanding and if the reaction is conducted at high temperatures [60]. Because of the high basicity of alcoholates, even primary alkyl halides can undergo dehydrohalogenation on treatment with alcoholates (Scheme 6.16).



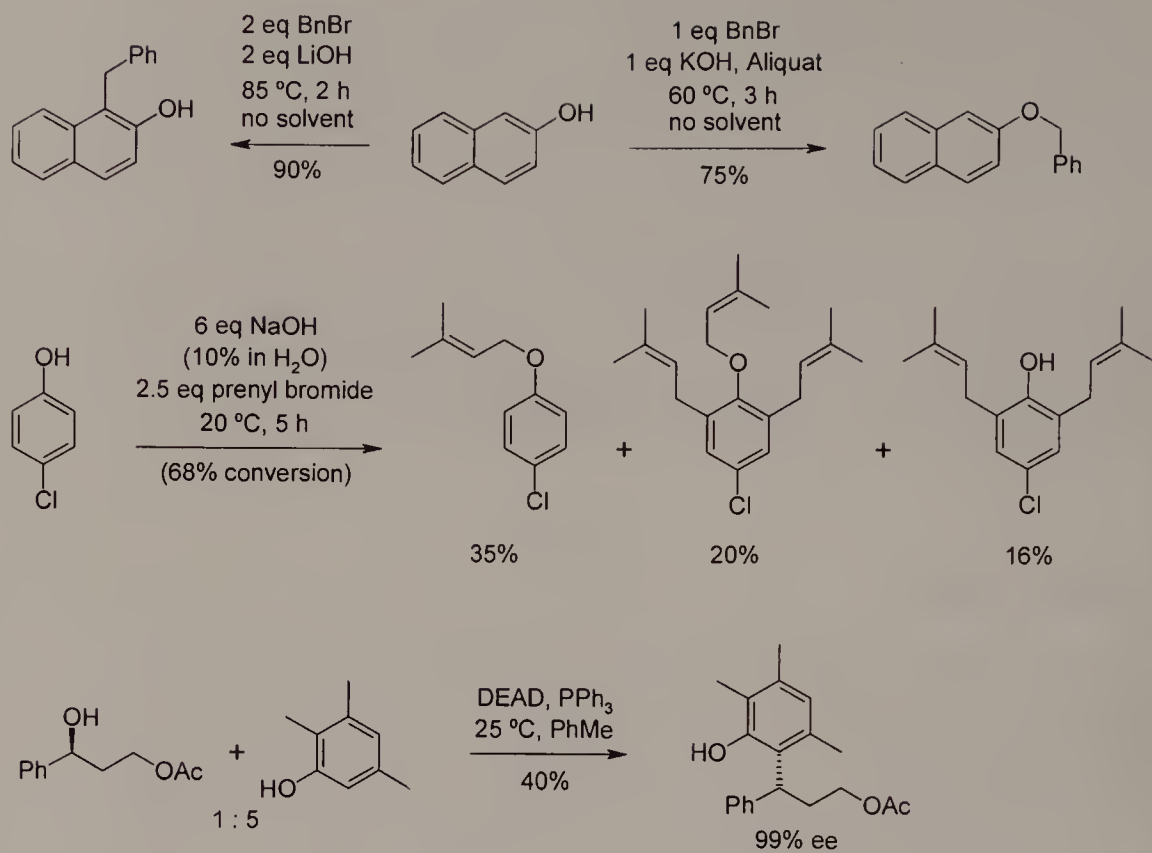
Scheme 6.16. The formation of alkenes during the Williamson ether synthesis [61, 62].

6.5 Alkylation of Phenols

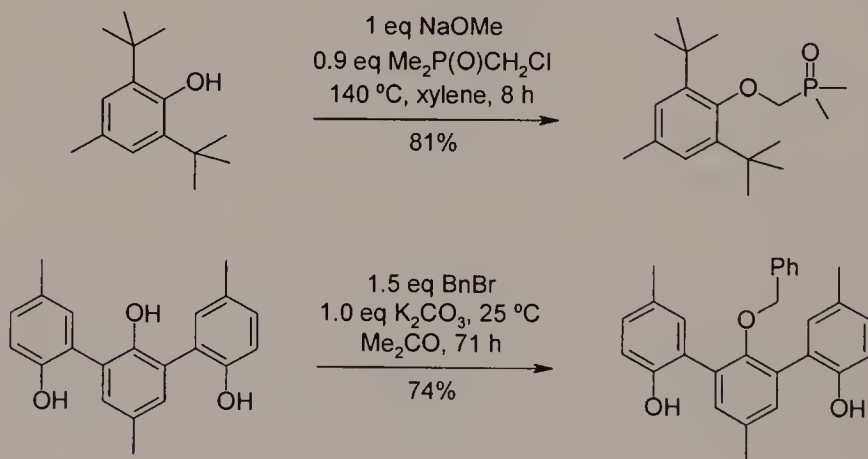
The most common strategies for the alkylation of phenols are the Williamson ether synthesis and the Mitsunobu reaction. Phenolates are ambident nucleophiles which can yield products from either of O- or C-alkylation on treatment with an alkylating agent (Scheme 6.17). C-Alkylations will usually occur if the electrophile forms a bond with the oxygen atom reversibly (e.g. on treatment of phenols with aldehydes or benzylic electrophiles under acidic conditions [63], or with α,β -unsaturated ketones), or if the nucleophilicity of oxygen is reduced by a hard cation (e.g. Li^+ [64]) or an acidic, protic solvent (e.g. $\text{CF}_3\text{CH}_2\text{OH}$). Poorly cation-solvating solvents, for example THF, will also enhance the yield of C-alkylated product, because the phenolate salt will not dissociate and the cation will remain strongly bound to oxygen. Dipolar aprotic solvents, on the other hand, will enhance the accessibility to oxygen by solvating the cation, and will therefore promote the formation of aryl ethers [2, 65–67]. Treatment of phenols with alkenes at high temperatures under pressure mainly yields C-alkylated products [68, 69].

If the right reaction conditions are chosen, most phenols can be cleanly O-alkylated with a broad range of alkylating agents. Even sterically demanding phenols (Scheme 6.18) or highly acidic phenols, for example picric acid [73], react with alkyl halides to yield the expected ethers. It has been suggested that the regioselectivity of the last reaction in Scheme 6.18 is because the 2,6-diarylphenol is more acidic than the monoarylphenols [74].

Interestingly, it is possible to etherify hydroxybenzoic acids without the need to protect the carboxyl group (Scheme 6.19). The high charge delocalization of the carboxylate obviously leads to a sufficient decrease of nucleophilicity to enable clean ether formation under certain conditions. During the planning of such reactions it should, however, be kept in mind that carboxylates can be O-alkylated under conditions similar to those required for the O-alkylation of phenols (see Section 6.9).

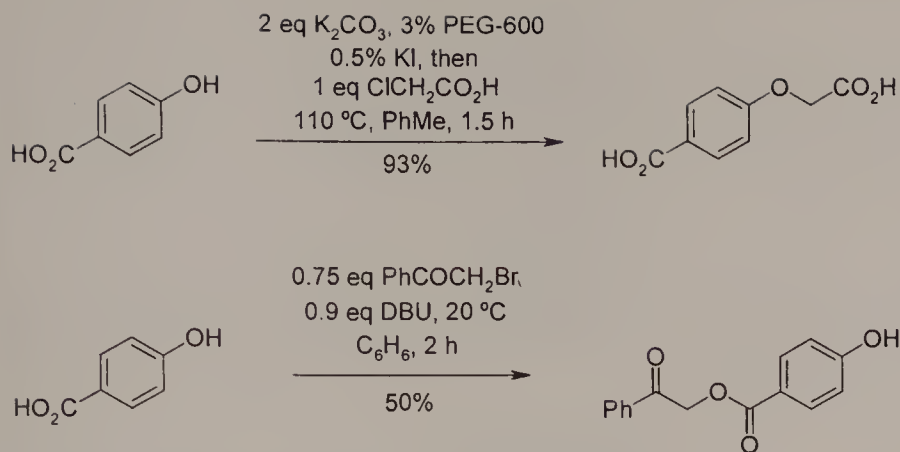


Scheme 6.17. O- and C-alkylations of phenols [70–72].



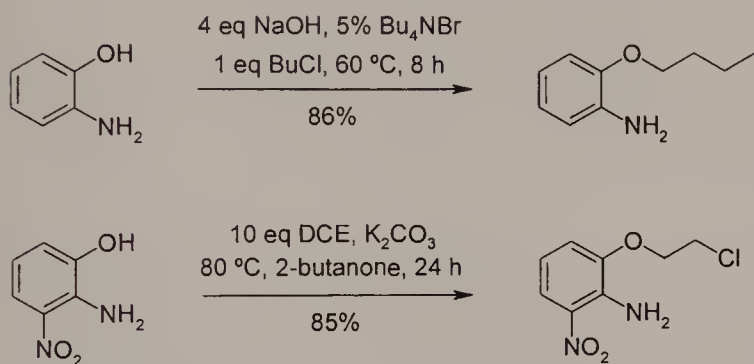
Scheme 6.18. Alkylation of sterically demanding phenols [74, 75].

Phenacyl halides tend, for instance, to alkylate carboxylates faster than anilines or phenols, as illustrated by the example shown in Scheme 6.19 [76].



Scheme 6.19. Alkylation of 4-hydroxybenzoic acid [76, 77].

Aminophenols can be selectively *O*-alkylated under basic reaction conditions [78–81] (Scheme 6.20). If a large excess of alkylating agent or too little base is used, however, mixtures of *O*- and *N*-alkylated products can result [78].



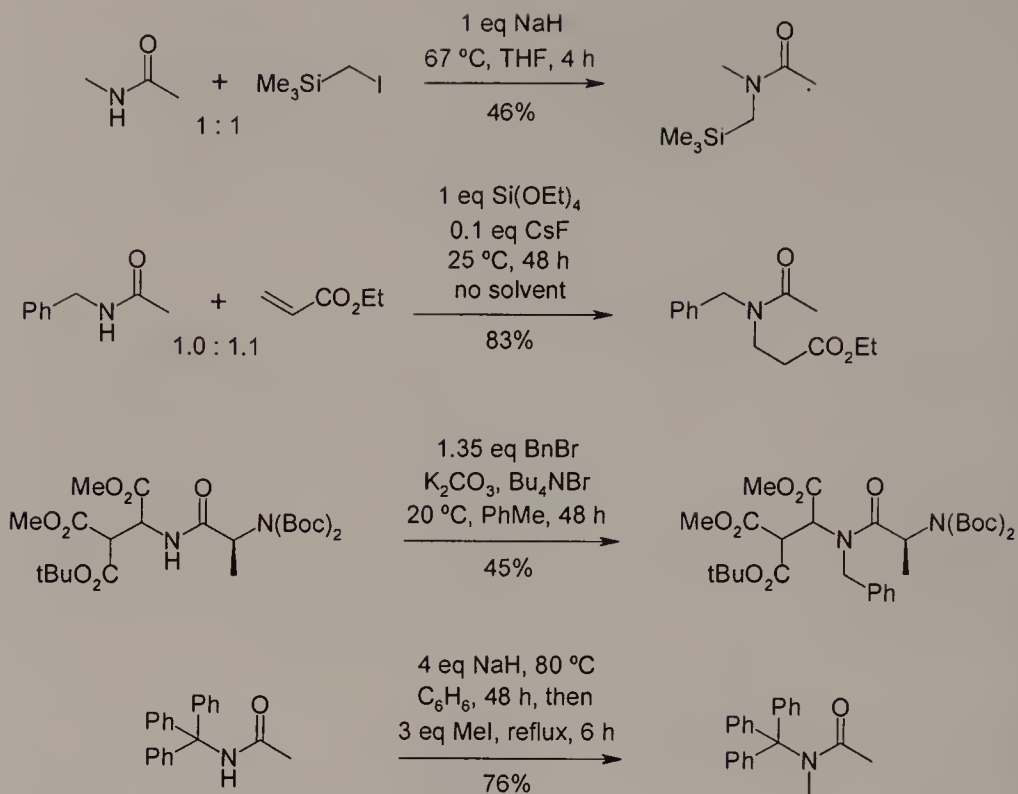
Scheme 6.20. *O*-Alkylation of aminophenols [79, 82].

6.6

Alkylation of Amides

Non-deprotonated amides are weak nucleophiles and are only alkylated by trialkyloxonium salts or dimethyl sulfate at oxygen or by some carbocations at nitrogen [16, 83]. Alkylation with primary or secondary alkyl halides under basic reaction conditions is usually rather difficult, because of the low nucleophilicity and high basicity of deprotonated amides. Non-cyclic amides are extremely difficult to *N*-alkylate, and few examples of such reactions (mainly methylations, benzylations, or allylations) have been reported (Scheme 6.21). 4-Halobutyramides, on the other hand, can often be cyclized to pyrrolidinones in high yield by treatment with bases (see Scheme 1.8) [84–86].

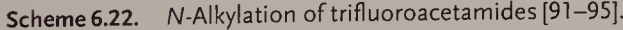
Secondary amines can be prepared by conversion of primary amines into sulfonamides, followed by *N*-alkylation and hydrolysis. Because sulfonamides are often difficult to hydrolyze, the *N*-alkylation of trifluoroacetamides has been investigated. Tri-



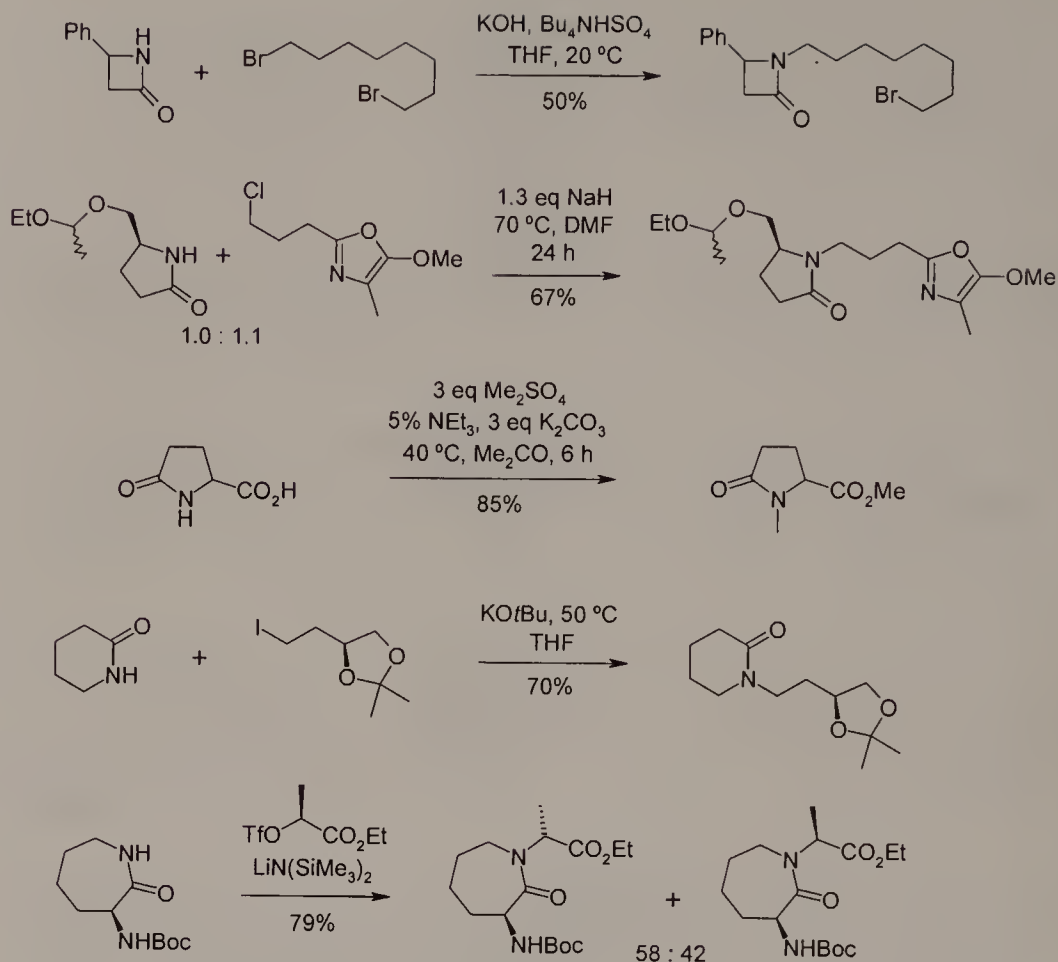
Scheme 6.21. Alkylation of acyclic amides [87–90].

fluoroacetamides are more acidic than, e.g., acetamides, and can sometimes be *N*-alkylated under mild reaction conditions and with high yields (Scheme 6.22). This reaction is a valuable tool for the preparation of secondary amines, because trifluoroacetamides are readily hydrolyzed and are therefore more suitable than most sulfonamides as transient protective and activating groups. As illustrated by the two last reactions in Scheme 6.22, some trifluoroacetamides are sufficiently acidic to undergo Pd(0) catalyzed *N*-allylation in the absence of stoichiometric amounts of base.

Lactams or related cyclic, conformationally fixed amides are more readily *N*-alkylated than acyclic amides [96]. As illustrated by the examples in Scheme 6.23, structurally elaborate alkylating agents can be used to alkylate lactams. During the work-up of such reactions it should be kept in mind that four- and six-membered lactams are readily hydrolyzed by aqueous base (Scheme 3.8), and most lactams are also readily hydrolyzed by aqueous acids. Prolonged treatment of lactams with alkali metal hydroxides or acids during the work-up should therefore be avoided.



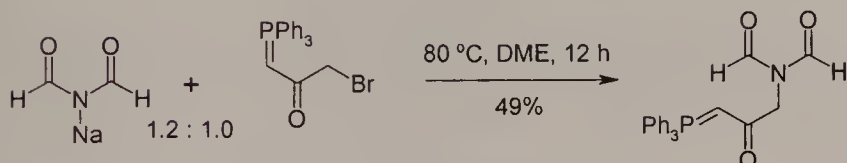
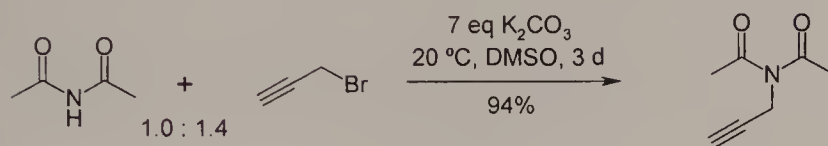
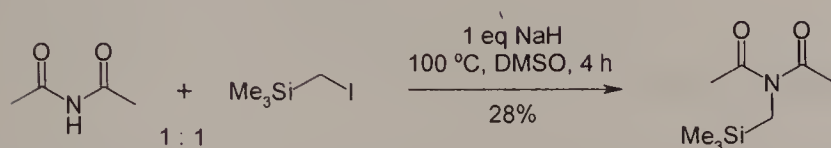
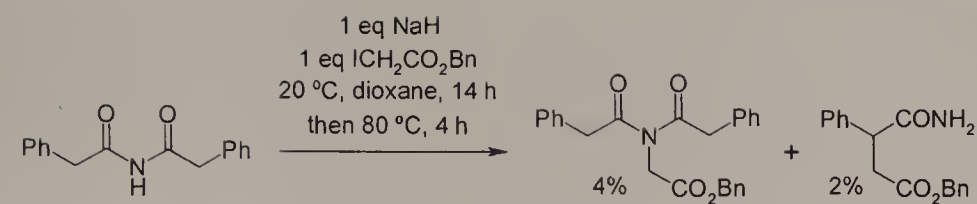
Scheme 6.22. *N*-Alkylation of trifluoroacetamides [91–95].



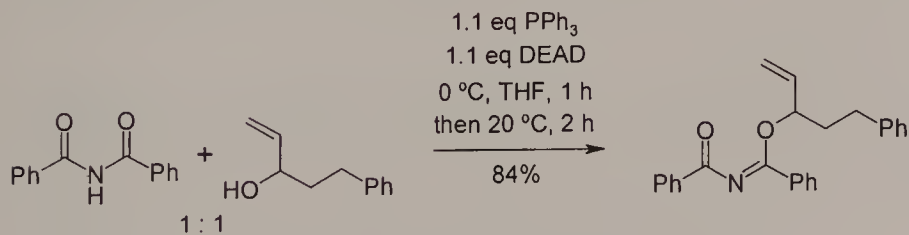
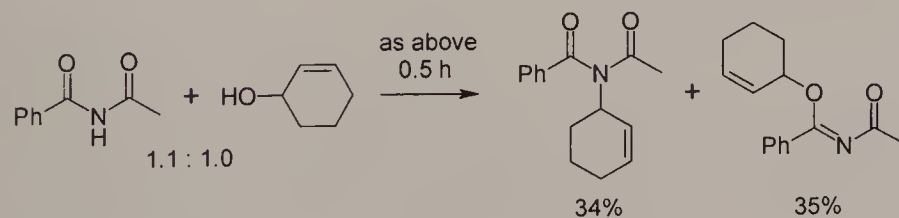
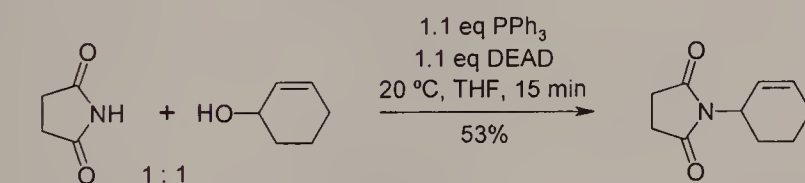
Scheme 6.23. N-Alkylation of lactams [97–101].

Cyclic or acyclic imides can be N-alkylated with soft alkylating agents (Scheme 6.24). Cyclic imides generally give better results than acyclic imides.

Imides are sufficiently acidic to enable N-alkylation via the Mitsunobu reaction. As with amides, only cyclic imides are readily N-alkylated whereas acyclic imides tend to yield mixtures of N- and O-alkylated products or O-alkylated products exclusively when treated with an alkylating agent (Scheme 6.25).



Scheme 6.24. Alkylation of imides [87, 102–104].



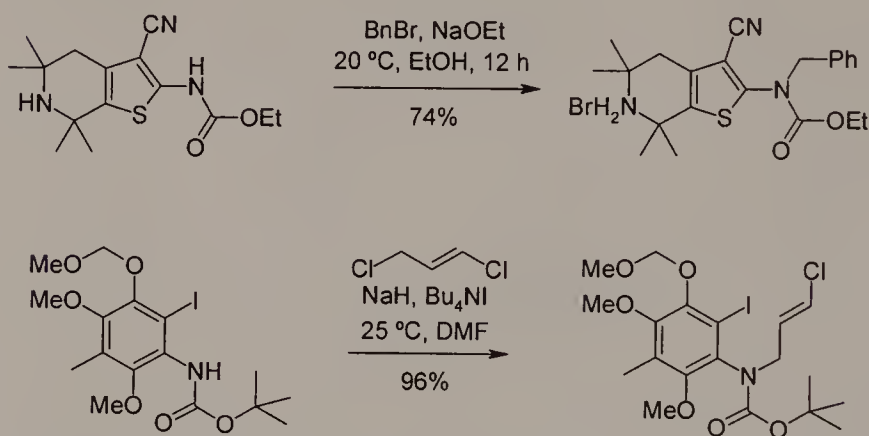
Scheme 6.25. Alkylation of imides by the Mitsunobu reaction [105, 106].

The alkylation of pyridones [107–109], quinolones [110, 111], and acridinones [112] can yield either *O*- or *N*-alkylated products (Scheme 1.7). Hard alkylating agents will generally have a higher tendency to alkylate oxygen whereas softer electrophiles will tend to alkylate nitrogen. The chemoselectivity (*O*- or *C*-alkylation) is, however, less easy to predict than for phenols, because the difference between the chemical hardness of oxygen and nitrogen is smaller than that for oxygen and carbon.

6.7

Alkylation of Carbamates and Ureas

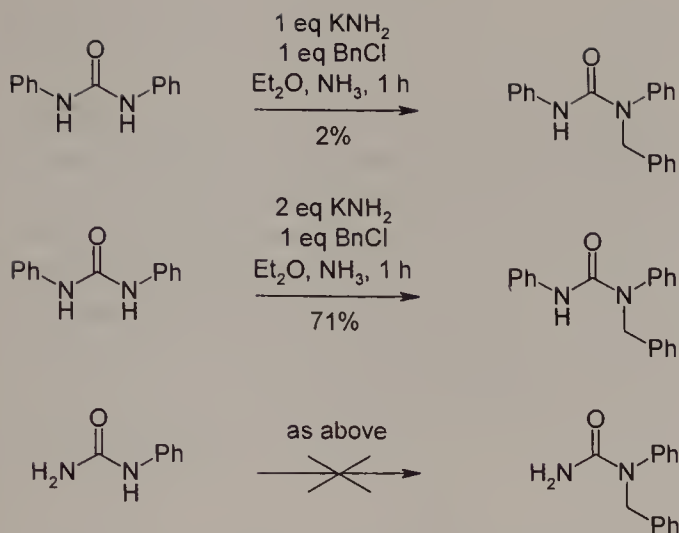
The alkylation of carbamates and ureas is similarly difficult as the alkylation of amides. Non-deprotonated carbamates or ureas are weak nucleophiles which will react only with carbocations or other, similarly reactive alkylating agents. Metalated carbamates and ureas, on the other hand, are strong bases but poor nucleophiles, and most of the reported examples of their alkylation are limited to methylations, allylations, or benzylations, or to cyclic carbamates and ureas. Two examples of the alkylation of *N*-aryl carbamates are given in Scheme 6.26.



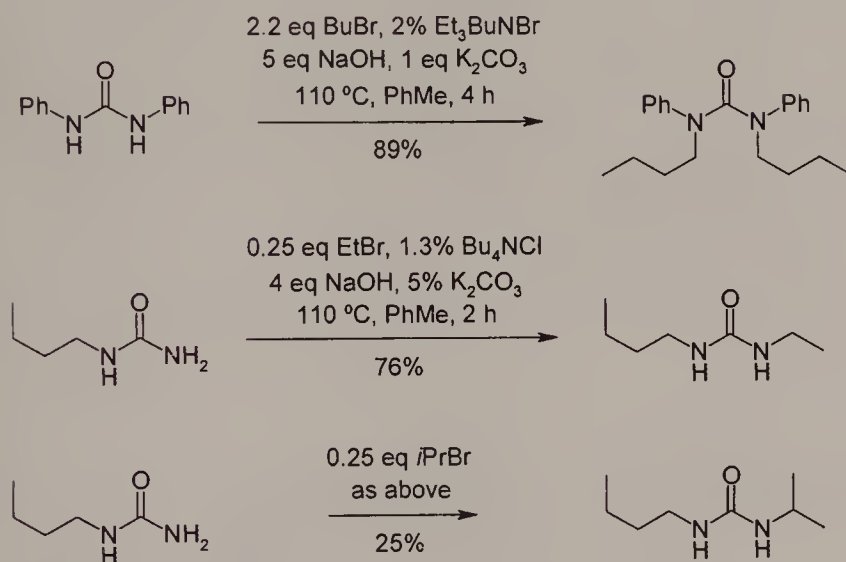
Scheme 6.26. *N*-Alkylation of carbamates [29, 113].

The *N*-benzylation of *N*-phenylureas in liquid ammonia does not proceed smoothly and requires the formation of a dianion (Scheme 6.27). Only *N,N'*-diphenylurea can be benzylated under these conditions; *N*-phenylurea or *N*-acylureas, on the other hand, remain unchanged [114]. Attempts to alkylate ureas with alkyl halides in DMSO at room temperature using solid KOH as base yielded only small amounts of *N*-alkylated ureas [115].

Better results are obtained when the alkylation of ureas is performed in toluene in the presence of a phase-transfer catalyst (Scheme 6.28). This method enables the use of primary alkyl bromides as alkylating agents and both *N*-aryl or *N*-alkylureas as substrates.

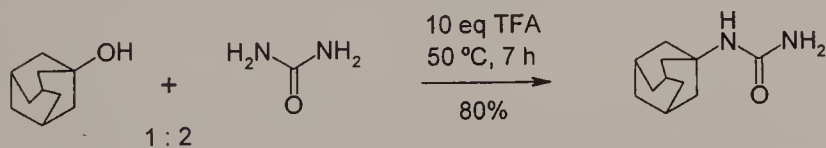


Scheme 6.27. Benzylation of phenylureas in liquid ammonia [114].



Scheme 6.28. N-Alkylation of ureas in the presence of phase-transfer catalysts [115, 116].

As alternative to alkylations under basic conditions, some ureas can also be N-alkylated by carbocations under acidic reaction conditions (Scheme 6.29). The scope of such reactions is, however, rather limited.

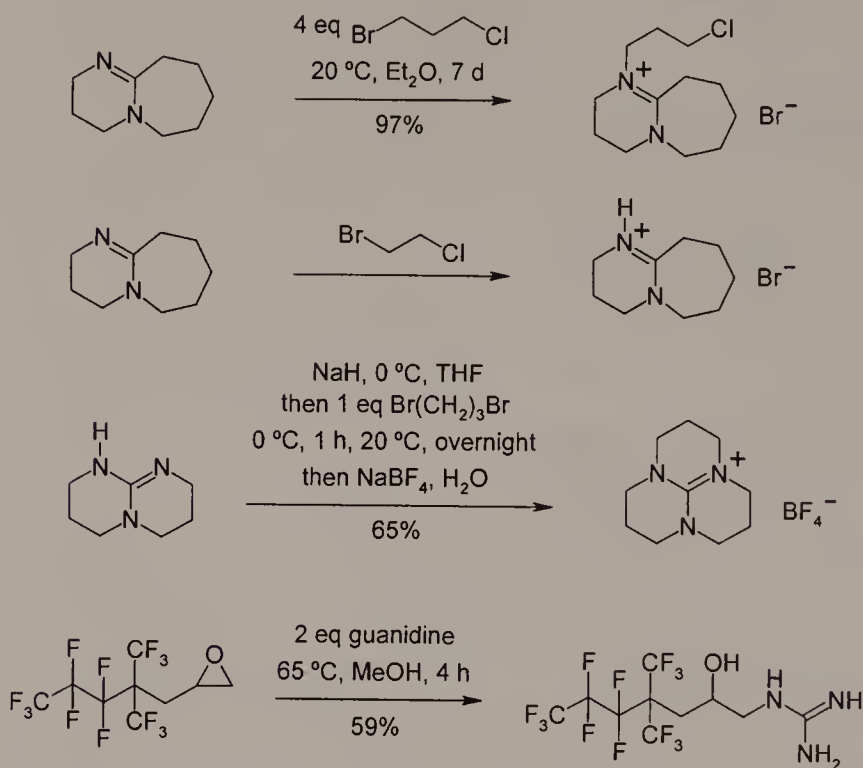


Scheme 6.29. Alkylation of urea under acidic reaction conditions [83].

6.8

Alkylation of Amidines and Guanidines

Amidines and guanidines are slightly more basic than aliphatic amines, and sterically crowded amidines (e.g. DBU) or guanidines are often used to mediate dehydrohalogenations. Conditions can, however, sometimes be found which lead to the *N*-alkylation of these organic bases (Scheme 6.30). Identification of appropriate conditions for such reactions is mostly empirical, because small changes can have important but unforeseeable effects on the selectivity of a reaction (compare, e.g., the first and second reactions in Scheme 6.30). If the reactivity of a given substrate is too low, its nucleophilicity can be enhanced by deprotonation.



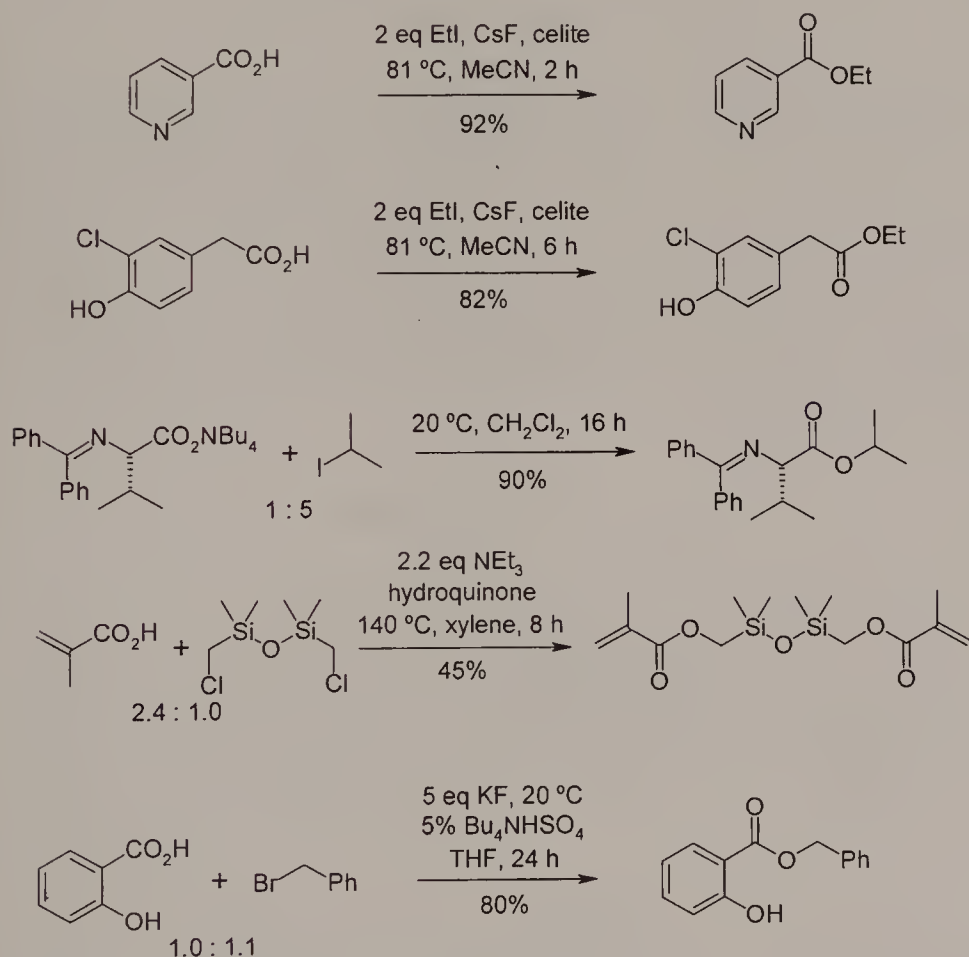
Scheme 6.30. Alkylation of amidines and guanidines [117–119].

N-Acyl or *N*-alkoxycarbonyl amidines or guanidines can be deprotonated and then alkylated [120]. The scope and limitations of these reactions are similar to those of the *N*-alkylation of amides or carbamates. *N,N'*-Bis(*tert*-butoxycarbonyl)guanidine is sufficiently acidic to undergo clean *N*-alkylation under the conditions of the Mitsunobu reaction [121].

6.9

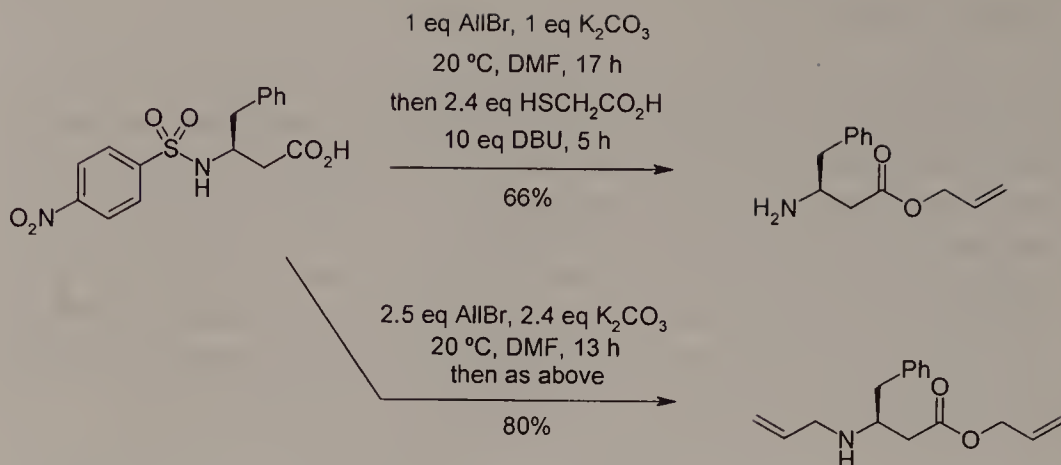
Alkylation of Carboxylates

The *O*-alkylation of carboxylates is a useful alternative to the acid-catalyzed esterification of carboxylic acids with alcohols. Carboxylates are weak, hard nucleophiles which are alkylated quickly by carbocations and by highly reactive, carbocation-like electrophiles (e.g. trityl or some benzhydryl halides). Suitable procedures include treatment of carboxylic acids with alcohols under the conditions of the Mitsunobu reaction [122], or with diazoalkanes. With soft electrophiles, such as alkyl iodides, alkylation of carboxylic acid salts proceeds more slowly, but in polar aprotic solvents, such as DMF, or with non-coordinating cations acceptable rates can still be achieved. Alkylating agents with a high tendency to *O*-alkylate carboxylates include α -halo ketones [42], dimethyl sulfate [100, 123], and benzyl halides (Scheme 6.31).



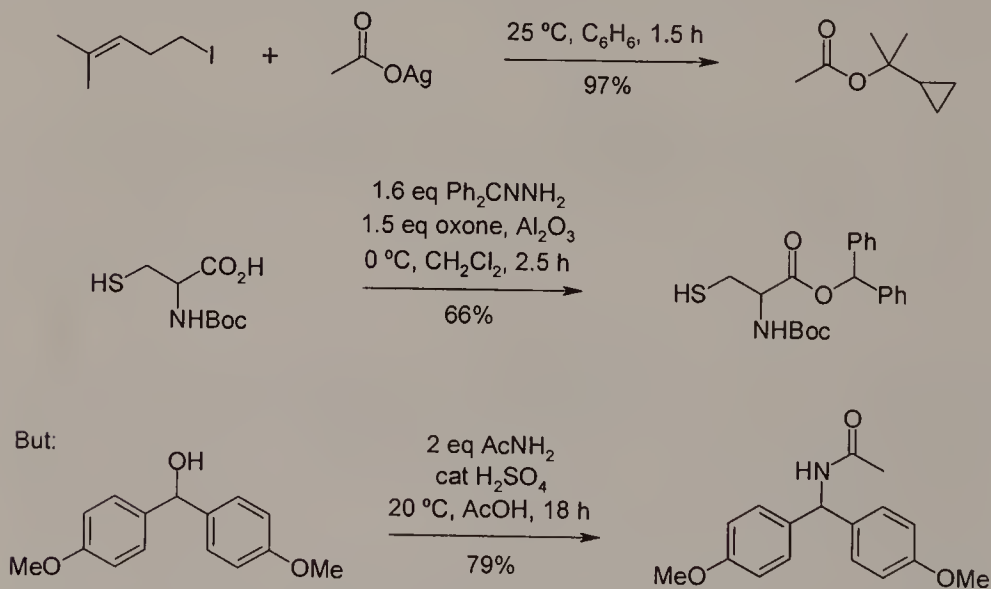
Scheme 6.31. *O*-Alkylation of carboxylates [124–127].

Although sulfonamides (pK_a 9–11) are rather acidic and undergo deprotonation as quickly as carboxylic acids, selective *O*-alkylations of sulfonamide-containing carboxylic acids are possible under carefully controlled conditions (Scheme 6.32).



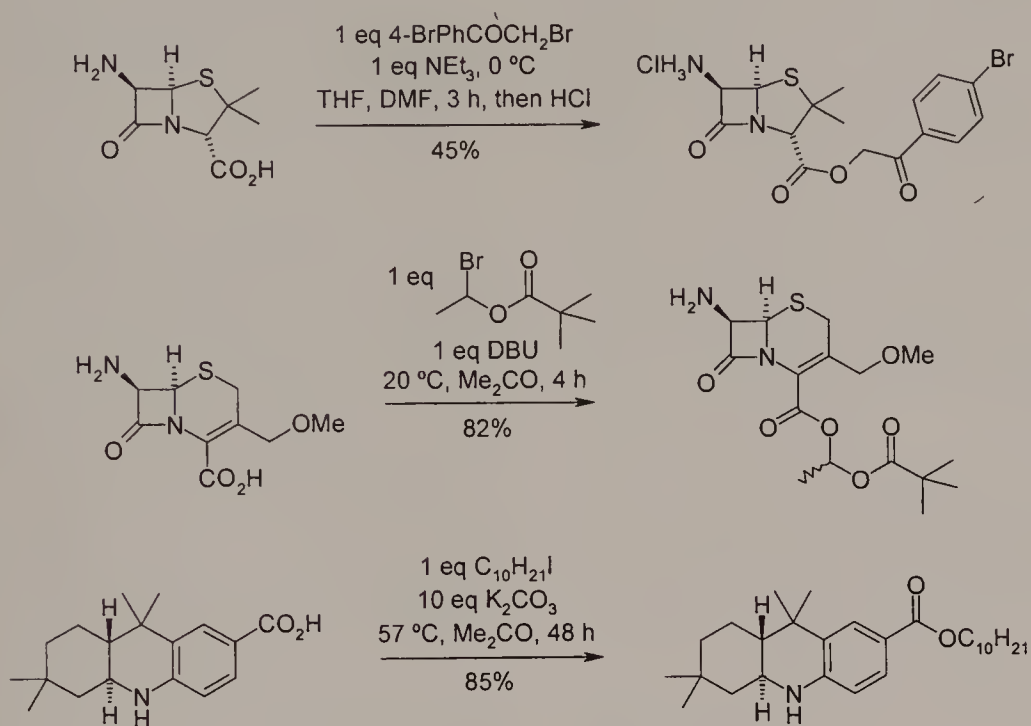
Scheme 6.32. Alkylation of carboxylates in the presence of sulfonamides [128].

Carbocations such as those generated by halogen abstraction with Ag⁺ or by protolysis of diazoalkanes preferentially alkylate negatively charged functional groups and can, therefore, be used to alkylate carboxylates with high chemoselectivity (Scheme 6.33). Under strongly acidic reaction conditions, however, no carboxylate but only the protonated carboxylic acid will be present in the reaction mixture, and other functional groups may be alkylated more rapidly by carbocations than the carboxyl group. Thus, treatment of acetamide with 4,4'-dimethoxybenzhydrol in acetic acid only yields the *N*-alkylated acetamide but no benzhydryl acetate (last reaction, Scheme 6.33; see also Scheme 6.3).



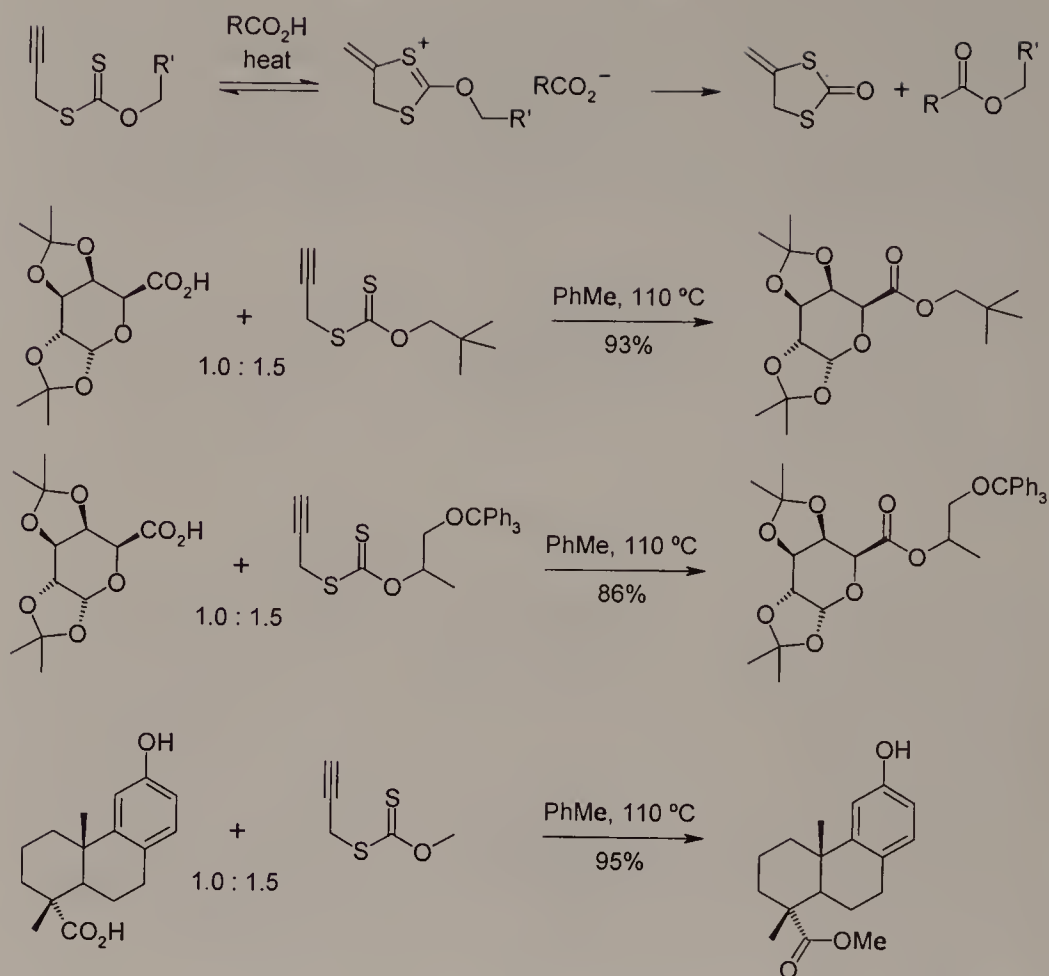
Scheme 6.33. O-Alkylation of carboxylates with carbocations [16, 129, 130].

Alkyl halides with a high tendency to form carbocations, for example trityl halides or α -halo ethers, can alkylate carboxylates under basic reaction conditions with high selectivity. Neutral functional groups, for example the amino group, are not alkylated as quickly as carboxylates by these reagents and do not always need to be protected. During carboxylate alkylation with simple alkyl halides amines of low nucleophilicity can, similarly, not compete efficiently with carboxylates, and might remain unchanged (last reaction, Scheme 6.34; see also Scheme 6.9).



Scheme 6.34. O-Alkylation of unprotected amino acids [131–133].

One little-known alternative to diazoalkanes or to the Mitsunobu reaction is the alkylation of carboxylates or other negatively charged functional groups with S-propargyl xanthates (Scheme 6.35). On heating in the presence of an acid these propargyl xanthates cyclize, yielding cationic, O-alkylated dithiolanones which efficiently alkylate negatively charged, hard nucleophiles (including fluoride). Interestingly, even neopentyl esters can be prepared by means of this method (Scheme 6.35).



Scheme 6.35. O-Alkylation of carboxylic acids with S-propargyl xanthates [134].

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7

The Acylation of Heteroatoms

One of the most common strategies for preparation of carboxylic acid derivatives is the acylation of nucleophiles of general formula RXH ($X = NR, O, S$). If the right reaction conditions are chosen and if the product is stable these reactions usually proceed swiftly and in high yield. Some carboxylic acids and nucleophiles, however, do not react smoothly or lead to unexpected results. The following sections cover a selection of representative examples of problematic starting materials.

7.1

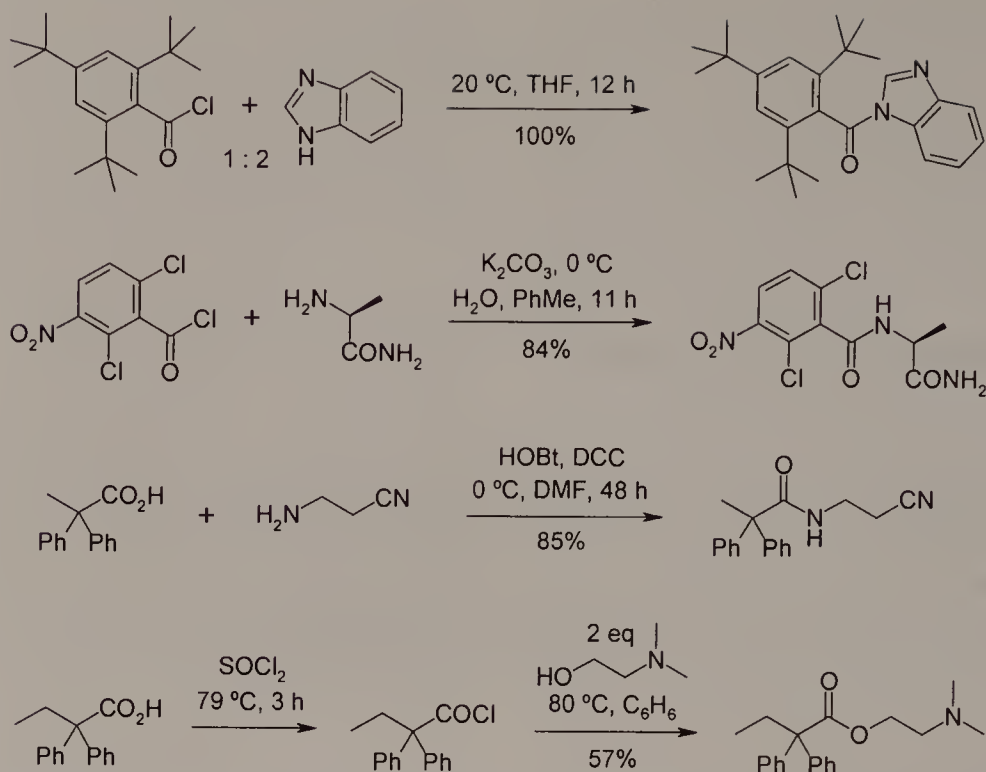
Problematic Carboxylic Acids

7.1.1

Sterically Demanding Carboxylic Acids

Despite the huge structural diversity of known carboxylic acids, most of these are readily converted into esters or amides. Even sterically hindered acids, for example pivalic, triphenylacetic [1], or 2,6-disubstituted benzoic acids [1, 2], can be converted into suitable acylating reagents for alcohols or amines (Scheme 7.1). Esters of sterically demanding carboxylic acids can, alternatively, also be prepared by *O*-alkylation of the corresponding carboxylates [3, 4].

The high yields obtained in the examples shown in Scheme 7.1 are surprising, because of the strong steric shielding of the carbonyl group of the acylating agents. The difficult approach of nucleophiles to the carbonyl group renders esters or amides of such sterically shielded carboxylic acids highly resistant to hydrolysis, reduction, or nucleophilic attack by organometallic reagents [1]. The corresponding acyl chlorides or HOBt-esters, though, are obviously sufficiently reactive to undergo such an attack under mild reaction conditions.



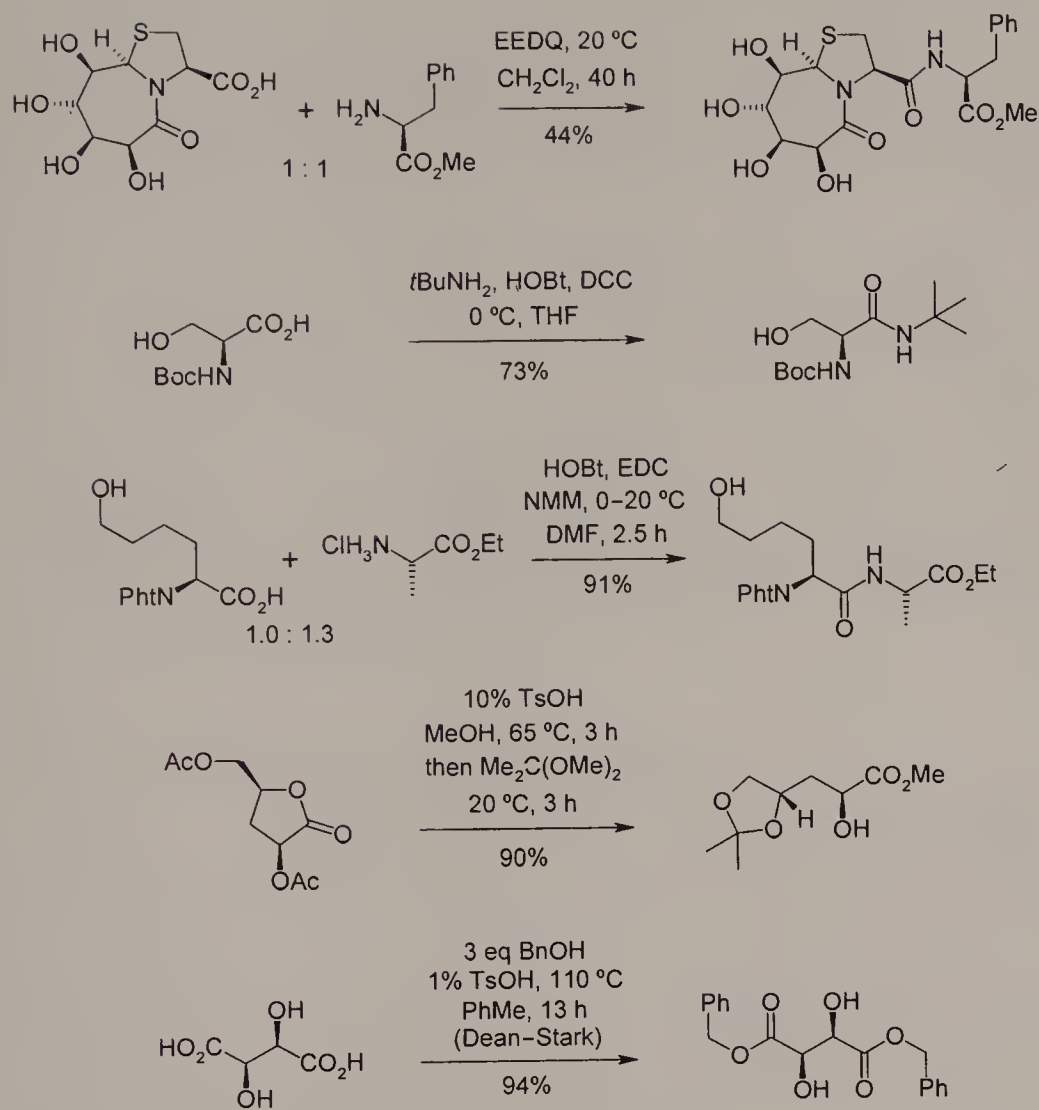
Scheme 7.1. Acylations with sterically hindered carboxylic acids [5–8].

7.1.2

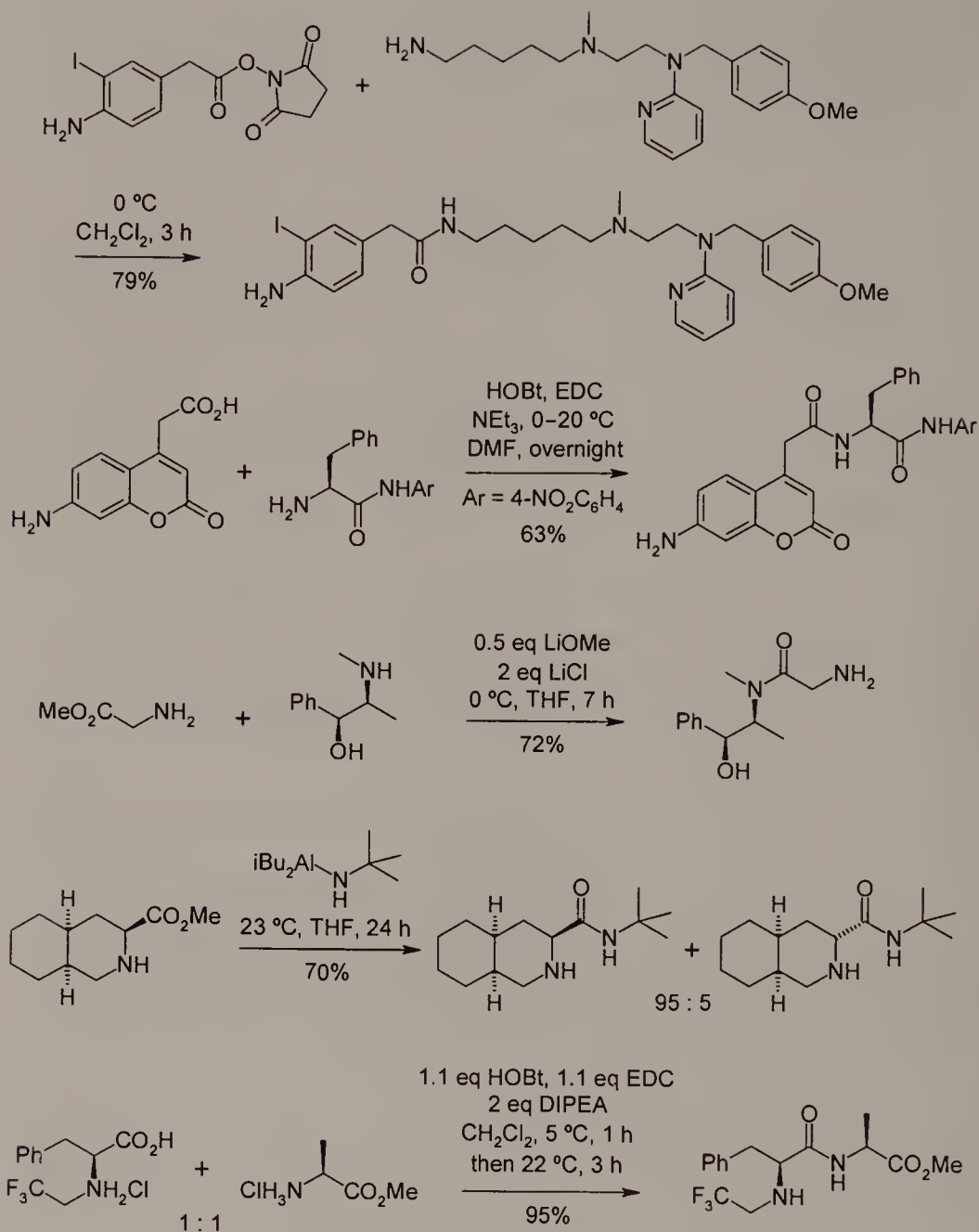
Unprotected Amino and Hydroxy Carboxylic Acids

Carboxylic acids which contain a hydroxyl or amino group may oligomerize if an activation of the acyl group is attempted, and protection of the hydroxyl or amino group will usually be required. It is, however, sometimes possible to acylate a strong nucleophile with unprotected hydroxy or amino acids if these are converted into weak acylating agents only (Scheme 7.2). Unprotected hydroxy acids can usually be converted into amides in acceptable yields by in-situ activation with standard coupling reagents. Esterifications of hydroxy acids can also be achieved by treatment of the acid with excess alcohol under acidic reaction conditions [9, 10] (Scheme 7.2).

There have been few reports only of *N*-acylations with unprotected amino acids (Scheme 7.3). Such reactions will only yield substantial amounts of the desired product if the (unprotected) amino group in the acylating reagent is difficult to acylate. The examples in Scheme 7.3 show that reaction conditions for performing such transformations with success can sometimes be found; for large-scale or industrial preparations, in particular, such “protective-group-free” shortcuts should always be considered.

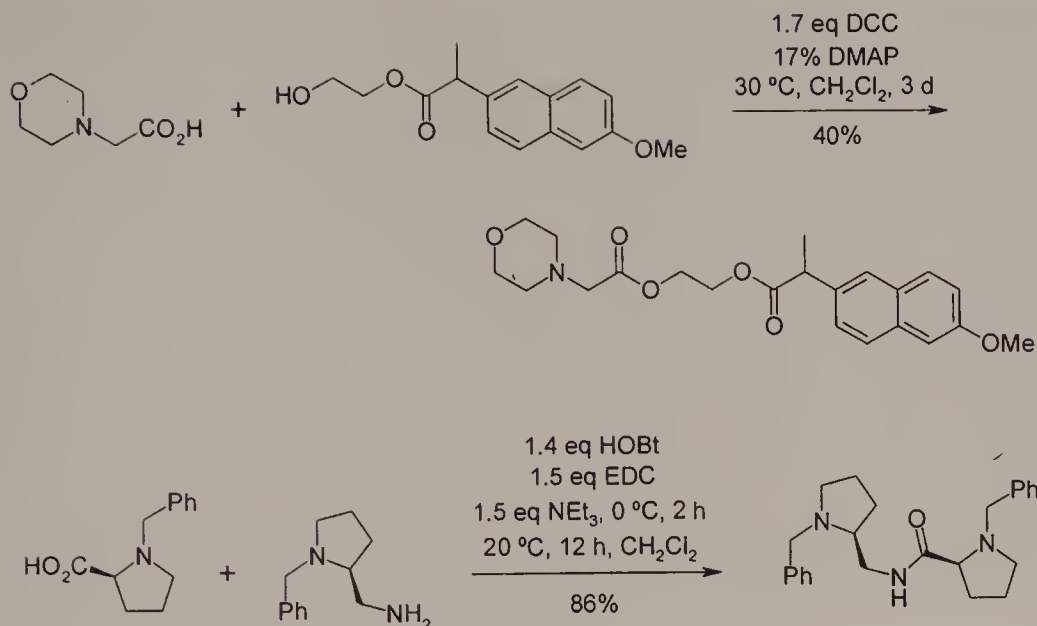


Scheme 7.2. Acylations with unprotected hydroxy acids [10–14].



Scheme 7.3. Acylations with unprotected amino acids [15–19].

Another problem posed by unprotected amino acids is that most are insoluble in organic solvents. Their conversion into an acylating reagent will, therefore, either not proceed or will proceed more slowly than usual, and a careful optimization of the reaction conditions might be required. Successful examples of such reactions are shown in Scheme 7.4. Problems resulting from low solubility of unprotected amino acids can be avoided by silylation or by conversion into esters in a separate step and by using these esters as acylating agents.



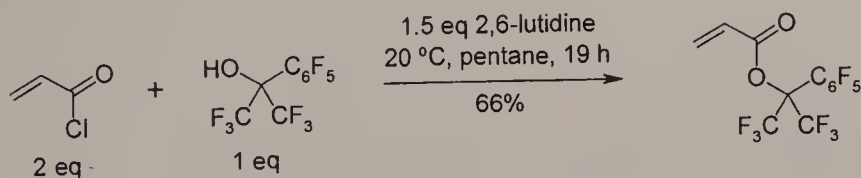
Scheme 7.4. Acylations with dialkylamino acids [20, 21].

7.1.3

Carboxylic Acids with Additional Electrophilic Groups

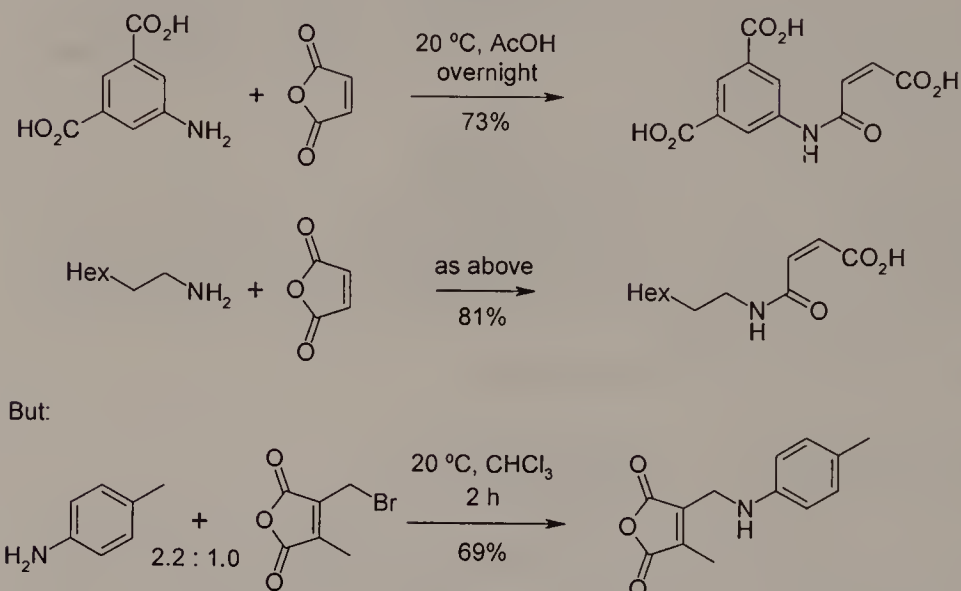
Carboxylic acids with strongly electron-withdrawing groups, for example trifluoroacetic or 2,4,6-trinitrobenzoic acid [22], are readily converted into esters or amides. The products can, however, be unusually sensitive toward attack by nucleophiles and can readily undergo hydrolysis, transesterification, or transamidation. 2,4,6-Tris(trifluoromethyl)benzoic acid has been reported to undergo conversion into the acyl chloride or esters only with difficulty [23].

Acrylic acid esters can polymerize readily; this must be taken into account during their preparation. Thus, attempts to prepare pentafluorophenyl acrylate from acryloyl chloride in the presence of pyridine led to extensive polymerization of the product [24]. This polymerization can be prevented by using the less nucleophilic 2,6-dimethylpyridine as base and diethyl ether or pentane instead of THF as solvent (Scheme 7.5). Esterifications of acrylic acid under acidic conditions should be conducted in the presence of small amounts of hydroquinone as radical scavenger. Acrylic acid derivatives can also be prepared by acylation with a propionic acid with a leaving group at C-3 followed by β -elimination.



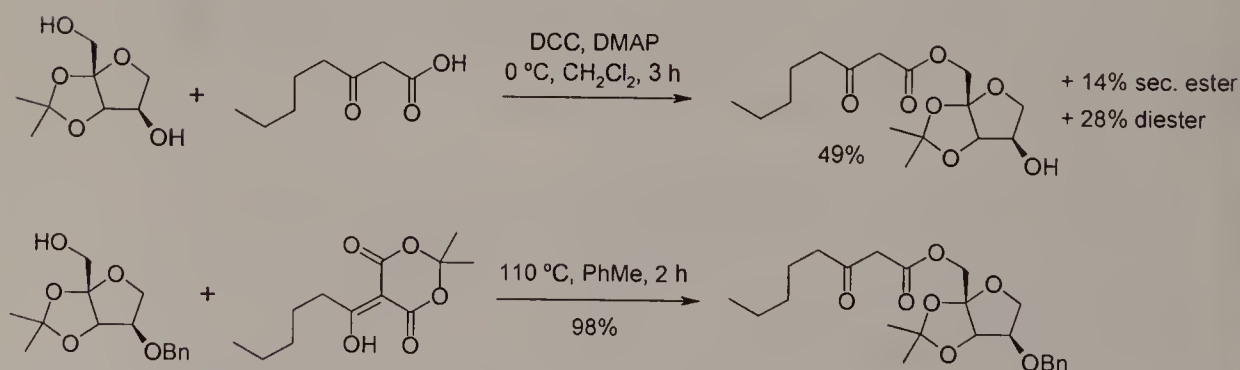
Scheme 7.5. Preparation of an acrylate [24].

Acrylic and related acid derivatives are good Michael acceptors, and will quickly react with amines or thiols if these are present in excess. Nevertheless, because acylations are usually much faster than Michael additions, acylation of these nucleophiles, even under basic conditions, can be performed with high yields. Similarly, acylating agents containing a functional group able to alkylate nucleophiles will usually act as acylating agents. Only with unreactive acylating functionalities will alkylation become the main reaction pathway (Scheme 7.6).



Scheme 7.6. Reactivity of acylating agents containing an alkylating functional group [25, 26].

β -Keto acids and 2-alkyl- or 2-arylmalonic acids readily decarboxylate, and acylations with these proceed satisfactorily only at low temperatures. An alternative to direct acylation with β -keto acids is thermolysis of acyl Meldrum's acid (to generate an acylketene) in the presence of a nucleophile (Scheme 7.7). Esters of β -keto acids can also be conveniently prepared from other keto esters by transesterification [27, 28].



Scheme 7.7. Esterification with β -keto acids [29].

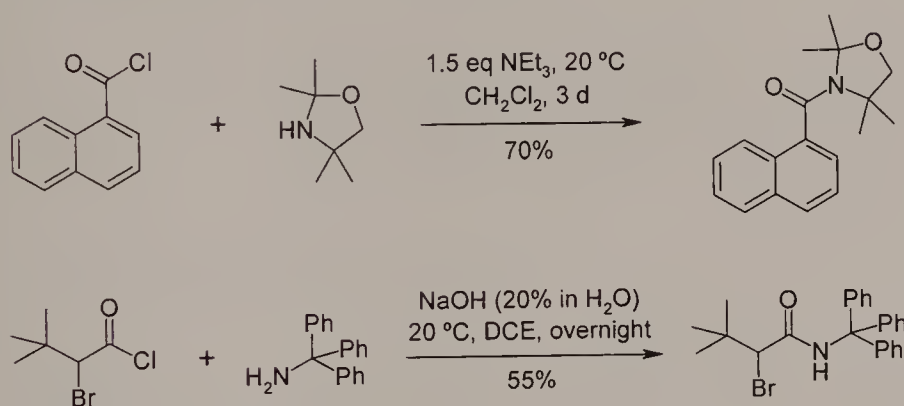
7.2

Problematic Amines

7.2.1

Sterically or Electronically Deactivated Amines

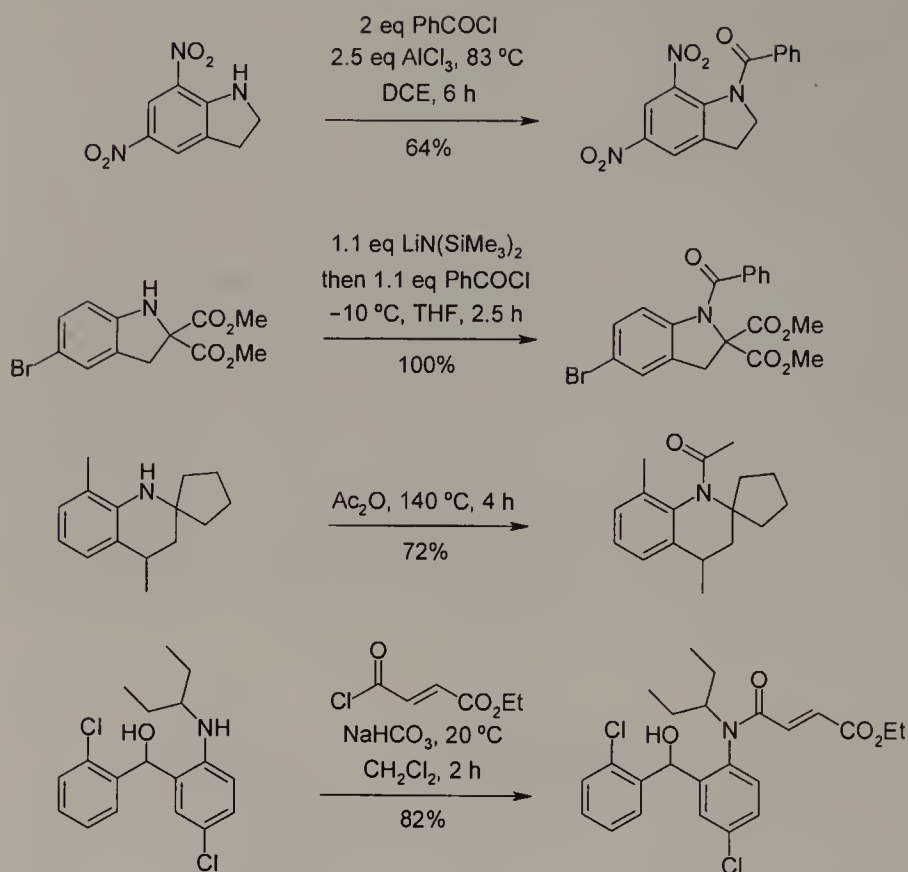
Most aliphatic and aromatic amines can be acylated in high yields with a suitable carboxylic acid derivative, even in the presence of water or alcohols. Problems can arise, however, if the amine is sterically demanding or if its nucleophilicity is reduced by electron-withdrawing groups. In such instances highly reactive acylating agents, for example ketenes, acyl halides, or anhydrides, might be required and the acylation will have to be conducted under anhydrous conditions. Nucleophilic catalysts, for example DMAP, can, furthermore, be used to enhance the rate of difficult acylations. Some sterically hindered amines, for example *N*-alkyl-*N*-trityl amines, cannot even be acylated intermolecularly with ketenes, although examples of intramolecular acylations have been reported [30]. Examples of the acylation of sterically demanding amines are shown in Scheme 7.8.



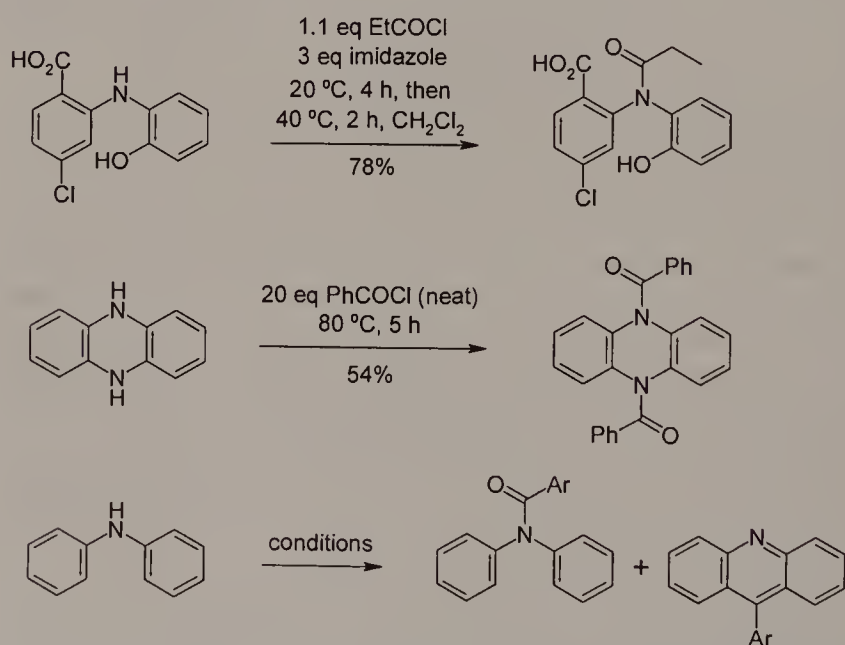
Scheme 7.8. Acylation of sterically demanding amines [31, 32].

Anilines are less basic and less nucleophilic than aliphatic amines, and their conversion to anilides might require strong acylating agents. On the other hand, because of their low basicity, acylation can be performed in the absence of an additional base or even under acidic reaction conditions. Anilines substituted with electron-withdrawing groups, and sterically demanding anilines, are particularly difficult to acylate (Scheme 7.9). If satisfactory conditions for acylating a given aniline cannot be found, its nucleophilicity (and basicity) can be enhanced by deprotonation with a strong base. Activated acids with α hydrogen (R_2CHCOX) will, however, be converted into ketenes by most metalated anilines.

Diarylamines will also usually require strong acylating agents to undergo acylation. If Lewis acids such as $ZnCl_2$ are used as catalysts the formation of an acridine can compete with *N*-acylation (Berntsen acridine synthesis; last reaction, Scheme 7.10).



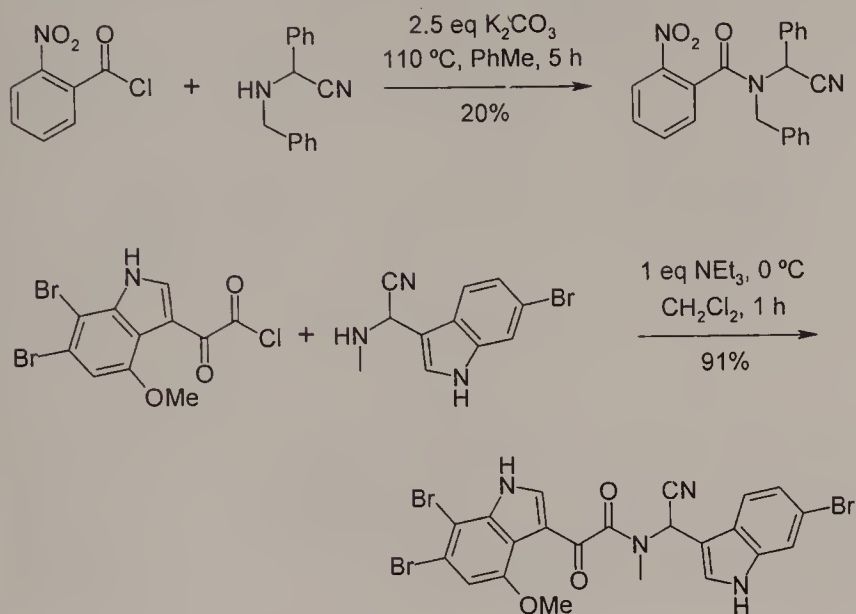
Scheme 7.9. Acylation of sterically or electronically deactivated anilines [33–36].



5 eq PhCO₂H, 4 eq ZnCl₂, microwaves (210 °C), 5 min 0 : 100 (37% yield; Ar = Ph)
 5 eq ArCO₂H, 4 eq ZnCl₂, microwaves (210 °C), 10 min 100 : 1 (23% yield)
 (Ar = 2,6-(MeO)₂C₆H₃)

Scheme 7.10. Acylation of diarylamines [37–39].

Another class of problematic amines are α -amino nitriles, which are readily accessible from ketones, amines, and cyanide. Like α -amino acids, these amines are electronically deactivated and less basic and nucleophilic than purely aliphatic amines, and are therefore difficult to acylate. Some α -amino nitriles or the corresponding acylated derivatives can, furthermore, decompose into imines and cyanide if reaction temperatures are too high or if the bases used are too strong (Scheme 7.11).

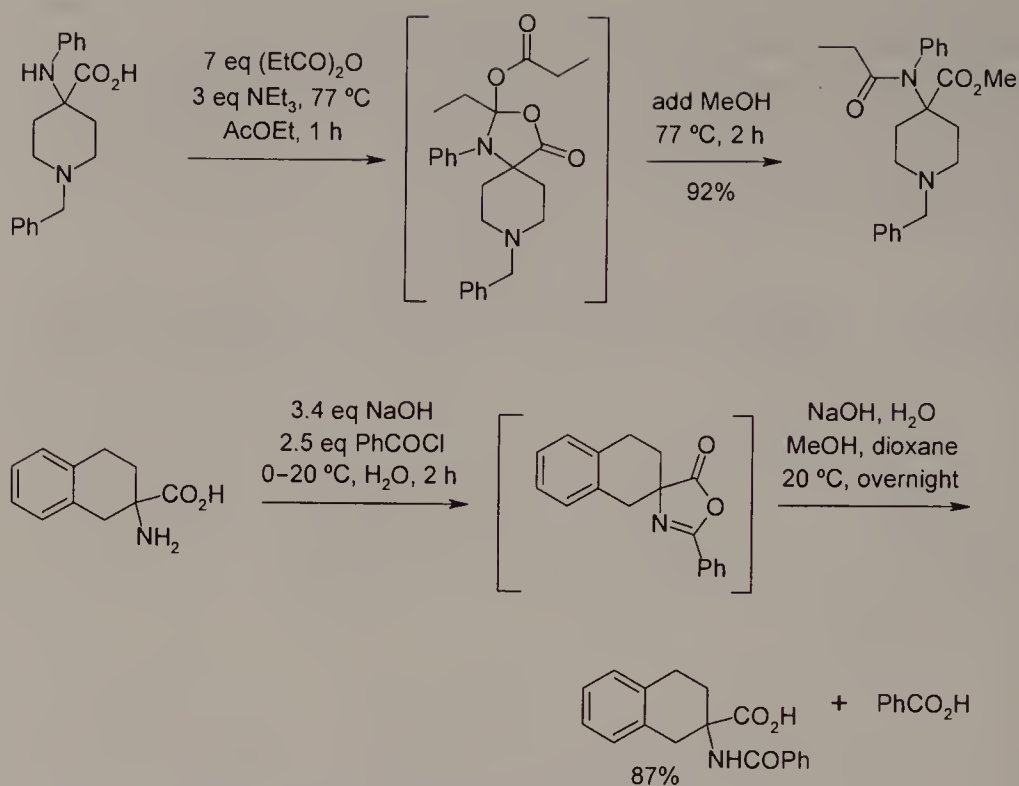


Scheme 7.11. Acylation of α -amino nitriles [40, 41].

7.2.2

Amino Acids

As mentioned above, unprotected amino acids are often insoluble in aprotic solvents, which can render their *N*-acylation difficult. If Schotten–Baumann conditions are applicable, these will usually give the best results. The direct acylation of unprotected amino acids is, however, hampered by another problem: the formation of mixed anhydrides from the amino carboxylate and the added acylating agent. These anhydrides can react with the amine to yield unwanted oligomers of the amino acid, or lead to other unexpected reactions. In Scheme 7.12 two examples of such reactions have been sketched. These examples show that carboxylates react with acyl halides at similar rates as with amines, leading in these instances to excessive consumption of acyl chloride and to the formation of product mixtures if only one equivalent of acylating agent is used. For this reason more than two equivalents of acylating agent will be required for complete acylation of the amino group. Use of a large excess of acylating agent will, however, only be practicable if the *N*-acylamino acid can be readily separated from the hydrolyzed acylating agent (which is also an acid).

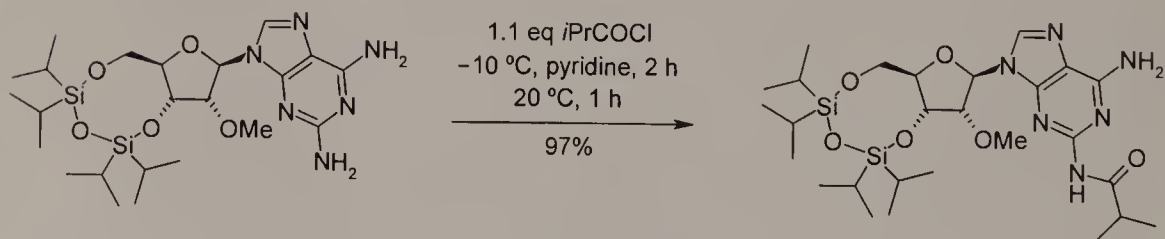


Scheme 7.12. Acylation of unprotected amino acids [42, 43].

7.2.3

Amines with Additional Nucleophilic Groups

Unsymmetric diamines can sometimes be acylated selectively at one amino group only, if one of the amino groups is sterically or electronically deactivated. If the difference in reactivity is only small, acylating agents of low reactivity will usually be required. Some polyamino heteroarenes can be monoacylated or monoalkylated with astonishingly high regioselectivity (Scheme 7.13), which is, however, difficult to predict.



Scheme 7.13. Regioselective acylation of a 2,6-diaminopurine [44].

Amino alcohols or aminophenols can be acylated selectively either at the amino group or at the hydroxyl group. Under slightly basic or neutral reaction conditions most acylating reagents will acylate amino groups faster than hydroxyl groups, and amides will be the main products. Strongly basic conditions, however, under which the amino alcoholate is formed, or acidic reaction conditions will usually lead to the formation of amino esters (Scheme 7.17). Most amino esters with a primary or secondary amino group will be stable as ammonium salts only, and will rearrange to amides under neutral or basic conditions, especially if the amino group is in close proximity to the alkoxycarbonyl group, as is the case for 2-aminoethyl esters or 2-aminophenyl esters.

7.3

Problematic Alcohols

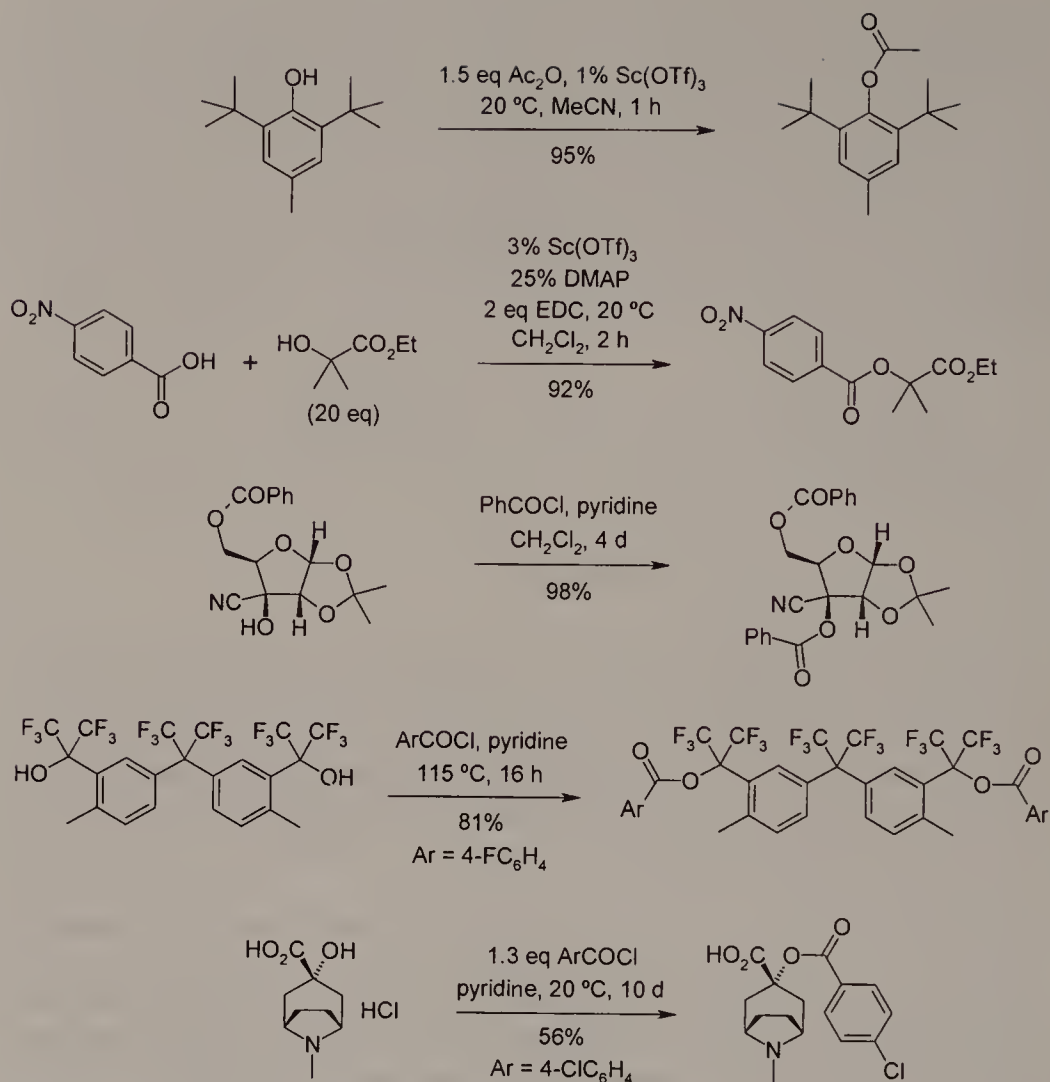
7.3.1

Sterically Deactivated and Base-labile Alcohols

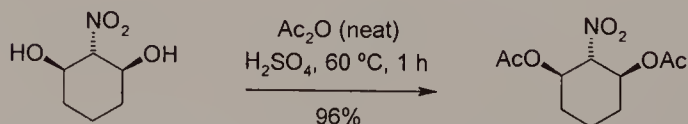
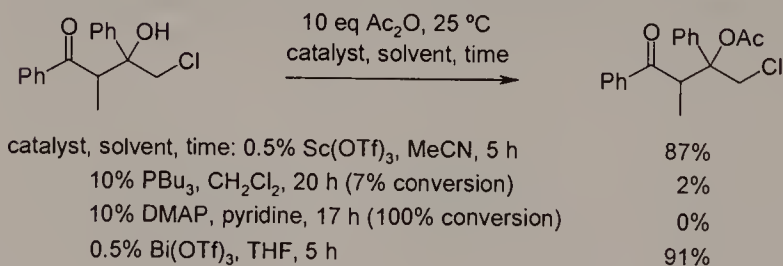
Alcohols can be converted into esters under both acidic or basic reaction conditions, and numerous methods have been developed which will be suitable for most alcohols. Problems can, however, arise if the alcohol is sterically hindered. Strongly acidic alcohols or phenols can usually be readily converted into esters [45], but these will be reactive acylating reagents themselves, and may be hydrolyzed during aqueous work-up. (This can sometimes be avoided by performing the work-up with $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$.)

Examples of the acylation of sterically demanding alcohols are given in Scheme 7.14. These reactions often proceed only slowly, and conditions suitable for most primary or secondary alcohols will fail with tertiary alcohols [46–48]. Trityl esters and similar compounds are difficult to prepare by acylation of the corresponding alcohols, but are readily accessible via *O*-alkylation of carboxylates.

If the hydroxyl group of an alcohol is β to an electron-withdrawing group, the resulting esters can undergo facile β -elimination. Such alcohols are difficult to acylate under basic reaction conditions but might undergo clean esterification in the presence of acids (Scheme 7.15).



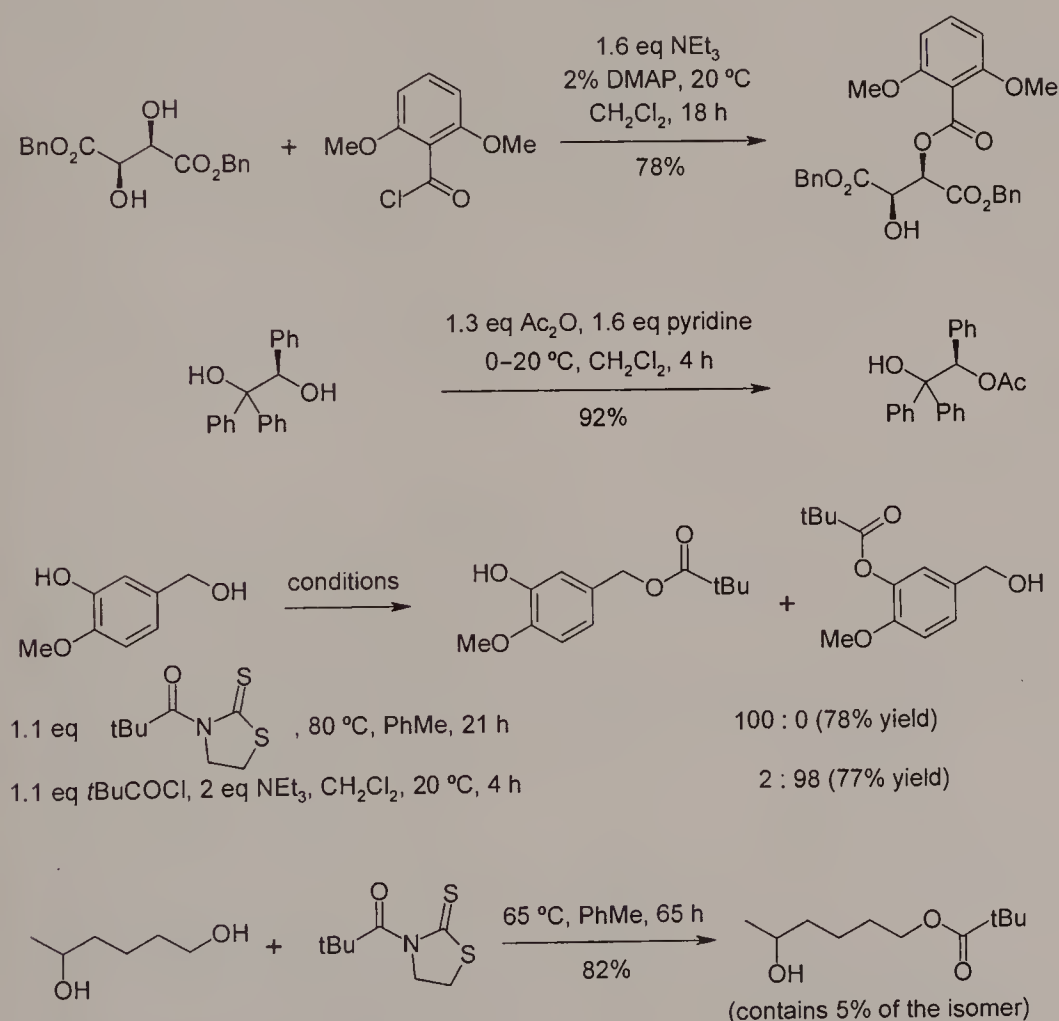
Scheme 7.14. Acylation of sterically demanding alcohols [49–53].

Scheme 7.15. Acylation of alcohols with electron-withdrawing groups in the β position [54, 55].

7.3.2

Alcohols with Additional Nucleophilic Groups

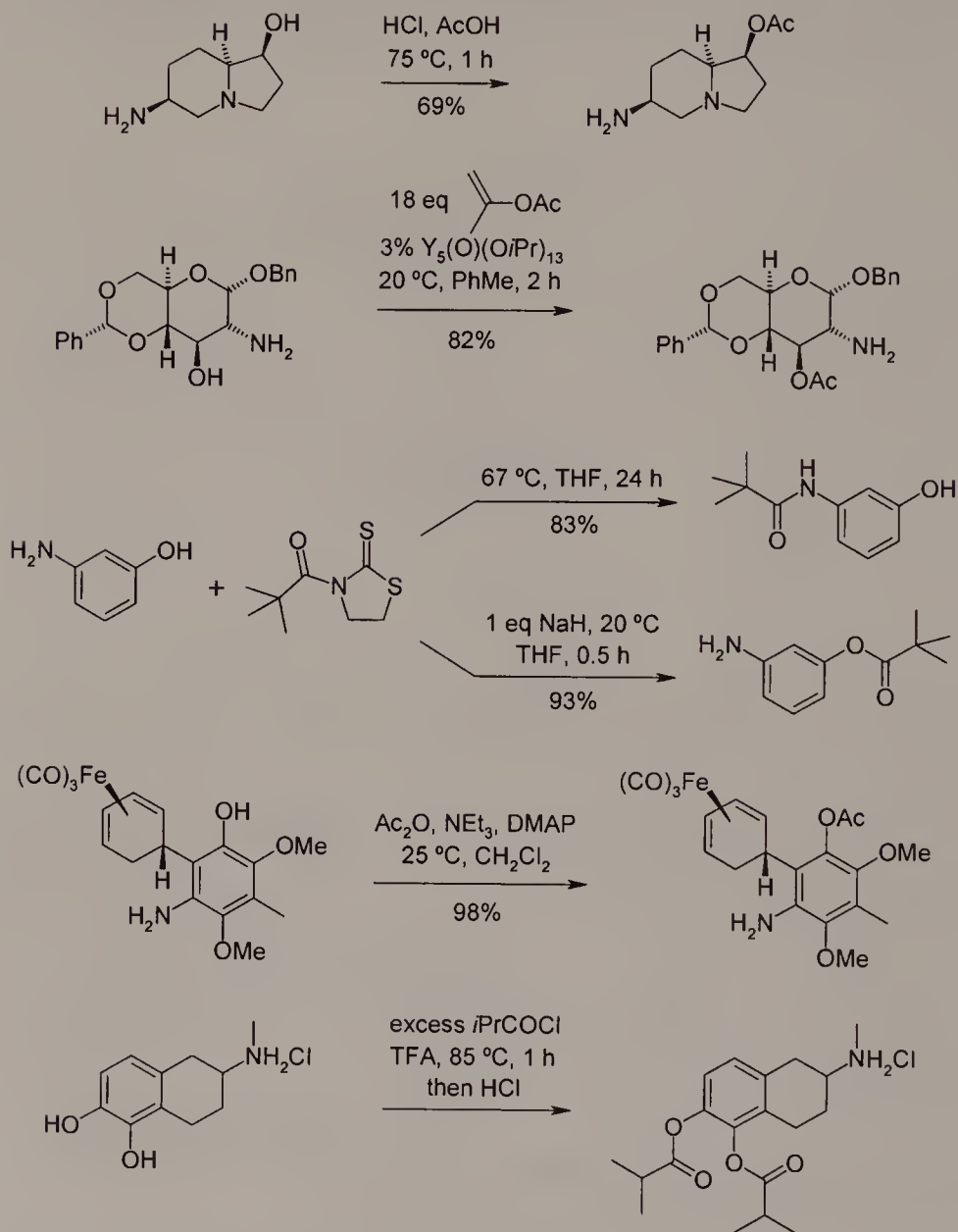
Unsymmetric polyols can be monoacylated selectively with acylating agents of moderate reactivity. For 1,2-diols the reactivity of the monoacylated product may be sufficiently lowered to prevent the formation of substantial amounts of diacylated product (first reaction, Scheme 7.16; see also Section 10.3). If the two hydroxyl groups are farther apart, however, selective monoacylations will require different nucleophilicity of both hydroxyl groups and an acylating reagent of low reactivity. If the hydroxyl groups are of different acidity, addition of a base can promote the esterification of the most acidic hydroxyl group (third example, Scheme 7.16). Polyols can also be partially protected against acylation by transient complexation with boron or tin derivatives [56].



Scheme 7.16. Selective monoacylation of diols [10, 57, 58].

Amino alcohols can be esterified, without simultaneous acylation of the amino group, by treatment with acids or acid anhydrides under acidic reaction conditions (Scheme 7.17) [59]. Reaction temperatures which are too high should be avoided, since these can lead to the acylation of ammonium salts to yield amides. Esters of 2-aminoethanols are stable only as ammonium salts, and conversion to the free amine will usually lead to migration of the acyl group (Section 3.3).

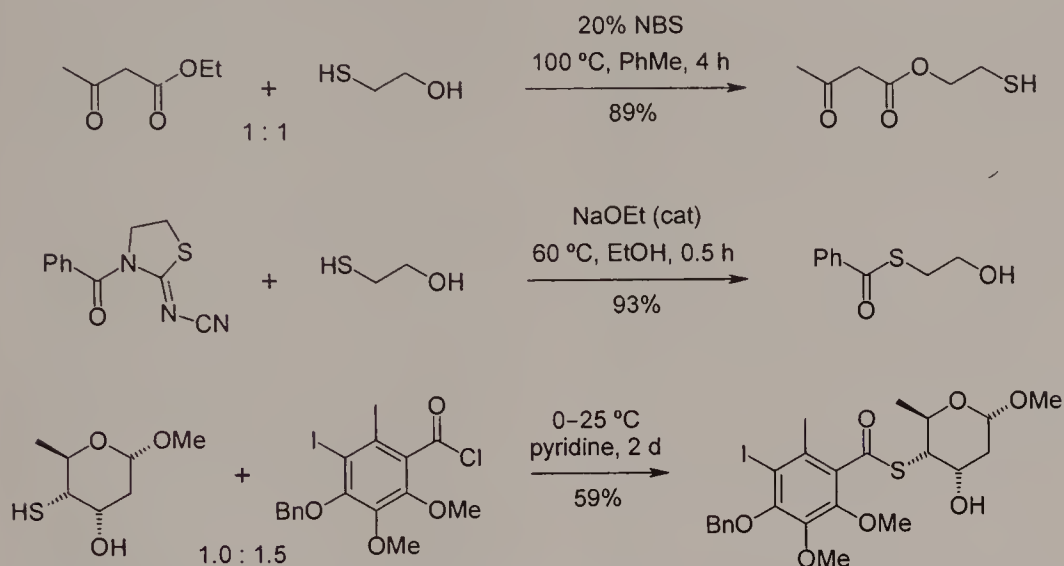
Aminophenols can be selectively esterified by deprotonation of the hydroxyl group followed by treatment with an acylating reagent of low reactivity (Scheme 7.17). Treatment with a strong acylating agent under acidic conditions will also result in clean esterification. In the presence of weak bases the regioselectivity of the acyla-



Scheme 7.17. Acylation of amino alcohols [60–63].

tion of aminophenols seems to depend on the type of acylating reagent chosen and on the specific reaction conditions.

Mercaptoalcohols can also be acylated with high regioselectivity. Under neutral or acidic reaction conditions acylation of the hydroxyl group predominates [27, 64–66] whereas basic reaction conditions favor acylation of the mercapto group (Scheme 7.18).



Scheme 7.18. Acylation of mercaptoalcohols [27, 67, 68].

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8

Palladium-catalyzed C–C Bond Formation

8.1

Introduction

The development in recent decades of numerous different Pd-catalyzed C–C bond-forming reactions has had a huge impact on synthetic organic chemistry [1–10]. Several classes of compounds, for example unsymmetrical biaryls or substituted polyenes, which were difficult if not impossible to synthesize in the 1950s, can now be readily prepared under mild conditions with high regio- and stereoselectivity via Pd-catalyzed cross-coupling reactions. The compatibility of Pd-catalysis with many functional groups and protic solvents, together with its broad scope, has secured a central role for this chemistry in organic synthesis.

The most important Pd-catalyzed C–C bond-forming reactions proceed according to the mechanisms outlined in Schemes 8.3 and 8.6. In these reactions a Pd(0) complex, which can be generated in situ by reduction of Pd(II), undergoes oxidative addition to an organic halide or sulfonate to yield an organopalladium(II) complex. This reaction is rapid with aryl or vinyl halides but proceeds more slowly with alkyl halides [9]. The reactivity decreases in the order $\text{RI} > \text{ROTf} \approx \text{RBr} \gg \text{RCl} \gg \text{RF}$ [11], and electron-poor aryl or vinyl halides react with Pd(0) complexes faster than electron-rich halides. The resulting organopalladium(II) complex can react with alkenes or a variety of organometallic compounds, forming the C–C bond and regenerating the catalytically active Pd(0) complex.

8.2

Chemical Properties of Organopalladium Compounds

The synthetically most important Pd-catalyzed C–C bond-forming reactions proceed via intermediate square planar organopalladium(II) complexes of the type PdRL_3 , in which the ligands L are usually halide or phosphine ligands. Organopalladium(II) complexes are rather stable organometallic compounds which can be readily prepared and isolated [12–14]. Complexes such as PdArL_2X with L representing phosphines or amines and X being a halogen do not usually react with water, and Pd-mediated C–C bond-forming reactions can be conducted in the presence of water

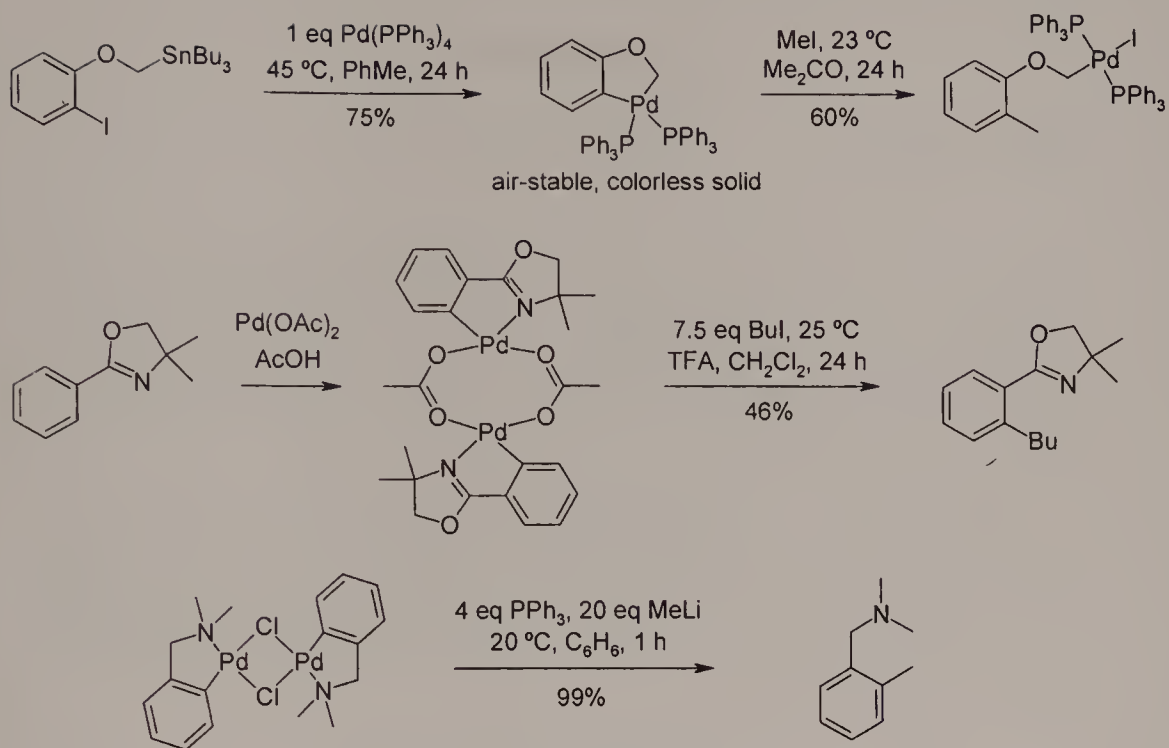
or in water alone [15–20]. Water may even be beneficial for some types of Pd-catalyzed reaction [21]. Organopalladium complexes such as PdArL_2X react with water only if L or X are very weak ligands (e.g. acetone [22]). These weak ligands can be displaced by water, and in the resulting complexes hydrolysis of the Pd–C bond can occur to yield a hydrocarbon.

The products of the thermolysis of $\text{PdAr(Hal)(PAr}_3)_2$ depend on the substitution pattern of the aryl groups, on the halide, on the solvent, and on the temperature chosen. Heating of $\text{PdAr(Hal)(PAr}_3)_2$, in the absence of other reagents, to temperatures above 50 °C leads to the reversible migration of aryl groups from palladium to phosphorus via intermediate formation of tetraarylphosphonium salts [11, 23, 24] (see Section 8.6). This migration proceeds more readily with electron-rich Pd-bound aryl groups [25]. Strong heating yields phosphonium salts, phosphines, biaryls Ar–Ar, reduced arenes ArH (the Ar group originating from both Pd-bound and phosphorus-bound aryl groups), and metallic palladium [11, 26], probably via homolytic Pd–C bond fission [27]. Heating in the presence of phosphines can lead to the reductive elimination of aryl halides [28].

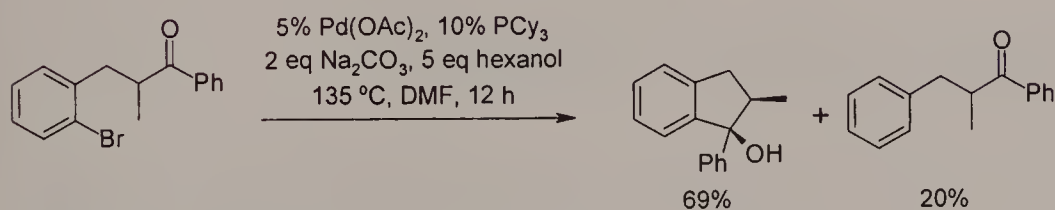
Complexes such as PdArL_2X are usually stable in air, but treatment with strong oxidants leads to cleavage of the Pd–C bond to yield phenols [29, 30]. Carbon monoxide cleanly converts organopalladium(II) complexes into acyl complexes (L_3PdCOR) [31, 32].

The metal-bound carbon atom in organopalladium(II) complexes can formally react either as an electrophile or as a nucleophile. Treatment of arylpalladium(II) complexes with alkyl halides, for example, yields products of homo- or cross-coupling, possibly via intermediate formation of hexacoordinated Pd(IV) complexes [31, 33] (Scheme 8.1). Treatment of the same type of complex with alkyl Grignard reagents or other carbon nucleophiles, on the other hand, also yields the corresponding alkyl arenes via nucleophilic displacement of a ligand followed by reductive elimination (Scheme 8.1).

Organopalladium complexes do usually not transfer a formal carbanion to aldehydes or ketones, but intramolecular Barbier-type reactions of this kind have been observed (Scheme 8.2).



Scheme 8.1. Reaction of arylpalladium(II) complexes with electrophilic and nucleophilic alkylating reagents [34–36].



Scheme 8.2. Palladium-mediated Barbier-type cyclization of a bromoaryl ketone [37].

8.3

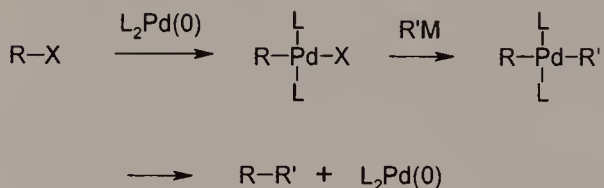
Mechanisms of Pd-catalyzed C–C Bond Formation

8.3.1

Cross-coupling

For Pd-catalyzed cross-coupling reactions the organopalladium complex is generated from an organic electrophile RX and a $Pd(0)$ complex in the presence of a carbon nucleophile. Not only organic halides but also sulfonium salts [38], iodonium salts [39], diazonium salts [40], or thiol esters (to yield acylpalladium complexes) [41] can be used as electrophiles. With allylic electrophiles (allyl halides, esters, or carbonates, or strained allylic ethers and related compounds) $Pd-\eta^3-\pi$ -allyl complexes are formed; these react as soft, electrophilic allylating reagents.

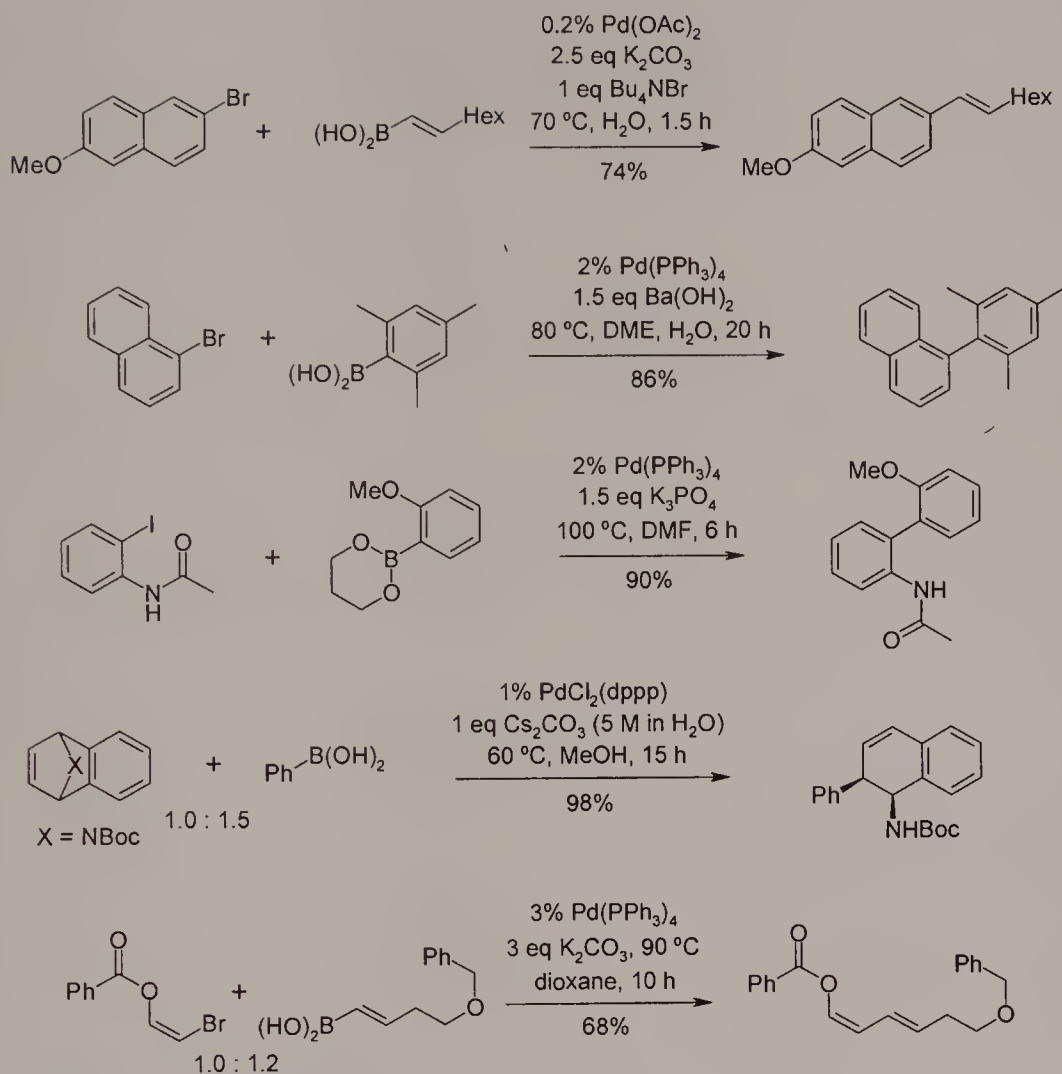
Organopalladium complexes formed by oxidative insertion of $Pd(0)$ into $C-X$ bonds can undergo ligand exchange with other organometallic reagents $R'M$ or with compounds with nucleophilic carbon (enolates, phenols, electron-rich heteroarenes) to yield diorganypalladium(II) complexes (Scheme 8.3). These may undergo reductive elimination to yield the cross-coupled product $R-R'$ and the catalytically active $Pd(0)$ complex (Scheme 8.3) [42].



Scheme 8.3. Simplified mechanism of Pd-catalyzed cross-coupling reactions. $R, R' =$ aryl, vinyl, alkynyl, allyl, benzyl, alkyl, acyl; $M = MgX, ZnX, B(OR)_2, BR_2, SnR_3$.

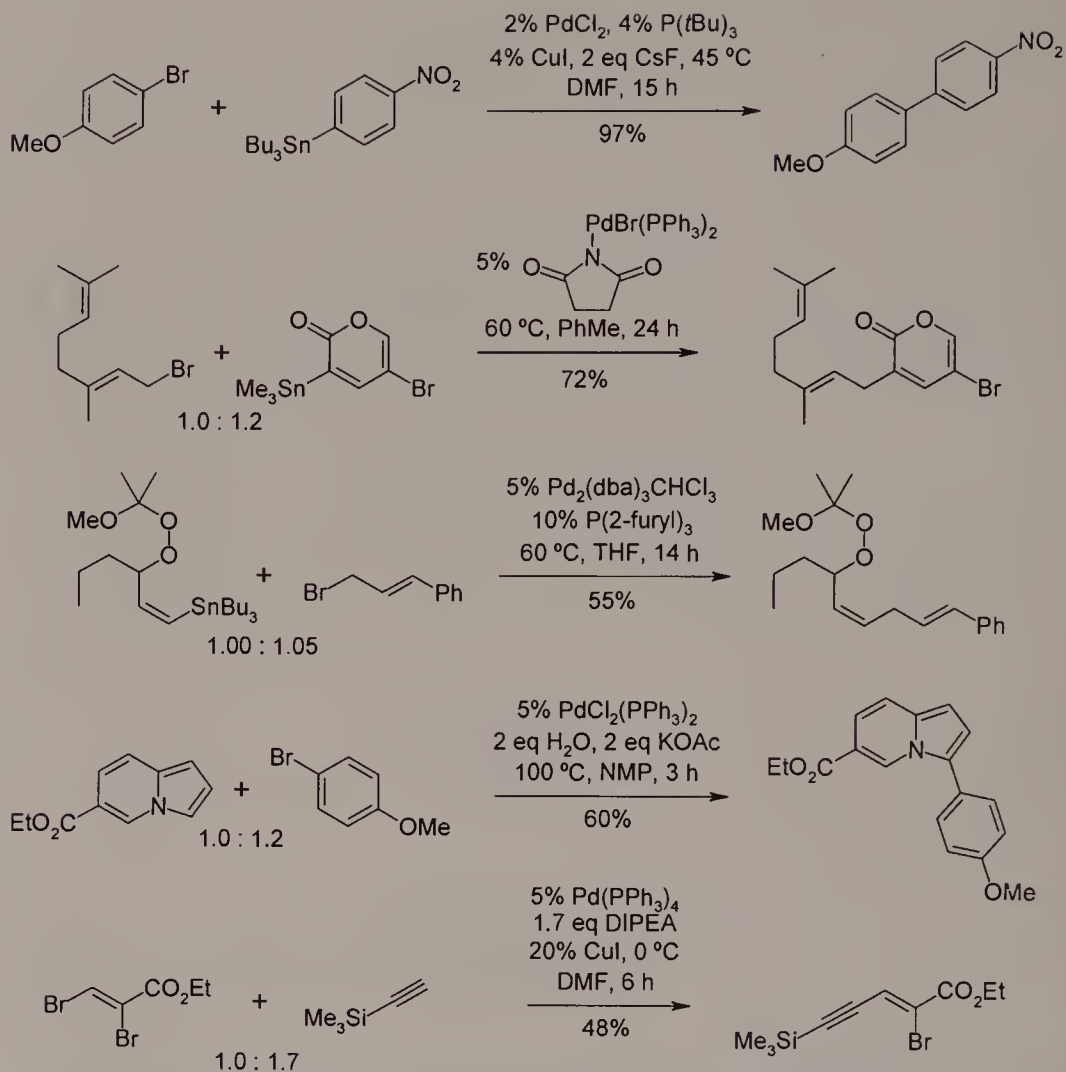
The synthetically most exploited cross-coupling variants are those in which the organometallic components are organoboron (Suzuki reaction), organotin (Stille reaction), organozinc (Negishi reaction), or alkynylcopper derivatives (Sonogashira reaction). The advantages of these reagents, if compared with the more polar organolithium or Grignard reagents (which also undergo Pd-mediated cross-coupling reactions) are their low reactivity toward most functional groups, their stability, and the consequent simplicity of their handling. Other nucleophilic reagents which can displace the leaving group X from complexes $PdRL_2X$ include cyanide [43], enolates [3, 44–51], phenols [52–54], indoles [55], indolizines (Scheme 8.5) [56], pyrroles, furans, thiophenes, imidazoles, thiazoles, and related compounds [57–62]. With most of these reagents a new $Pd-C$ bond is presumably formed on displacement of the ligand X .

Aryl-bound functional groups which are tolerated in Pd-mediated arylations include *ortho*-alkynyl [63], *ortho*-vinyl [64], *ortho*-nitro [65], and *ortho*-formyl groups [66]. Some examples of Pd-mediated cross-coupling reactions are depicted in Schemes 8.4 and 8.5, to illustrate the required conditions and scope of these reactions.



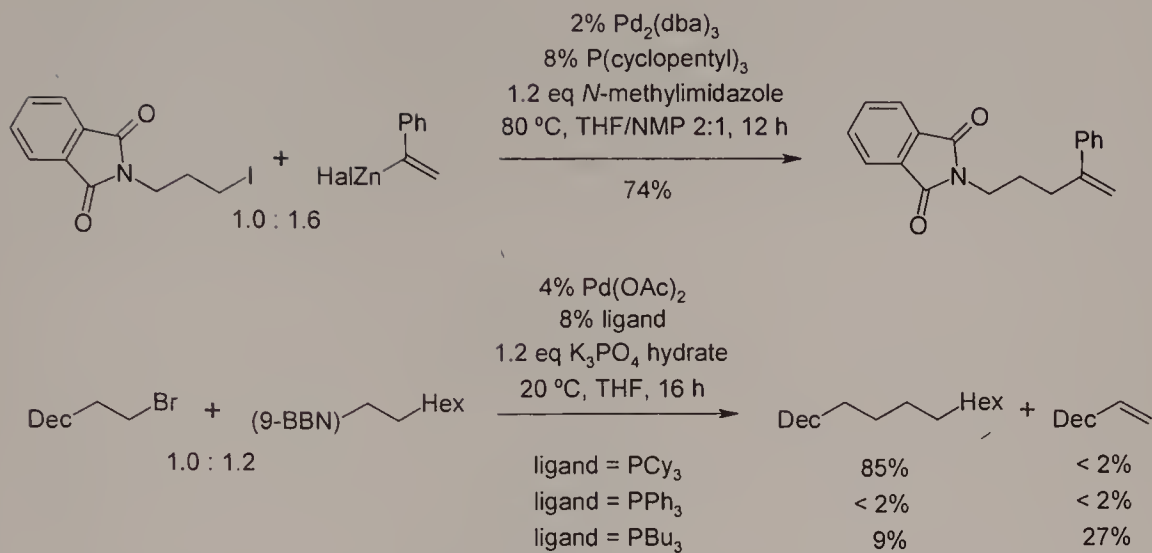
Scheme 8.4. Palladium-catalyzed cross-coupling reactions of boron derivatives [18, 66–68].

Organometallic reagents of low nucleophilicity, for example nitroaryl stannanes [69], undergo transmetalation only slowly; this can lead to low yields of cross-coupling products [69]. Catalytic amounts of CsF and CuI, together with a palladium source and a phosphine can bring about cross-coupling of such unreactive stannanes (first reaction, Scheme 8.5) [69].



Scheme 8.5. Palladium-catalyzed cross-coupling reactions of stannanes and other carbon nucleophiles with aryl, allyl, and vinyl bromides [56, 69–72].

Alkylpalladium complexes generated by oxidative addition of Pd(0) to alkyl halides with a β hydrogen can undergo β -elimination to yield an alkene and a Pd-hydrido complex (as in the Heck reaction; Scheme 8.7). Nevertheless, this process is relatively slow compared with transmetalations and reductive eliminations, and simple alkyl halides or tosylates with β hydrogen can be cross-coupled with carbon nucleophiles under optimized conditions if the nucleophile is sufficiently reactive [9, 73–75] (Scheme 8.6).

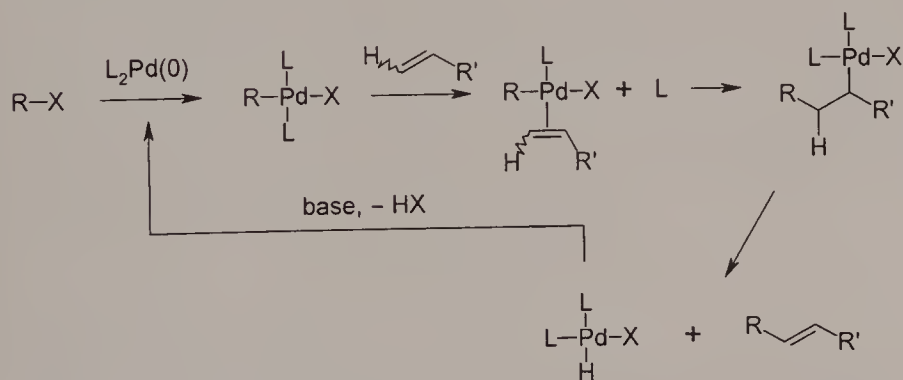


Scheme 8.6. Alkyl halides with β hydrogen in palladium-mediated cross-couplings [76, 77].

8.3.2

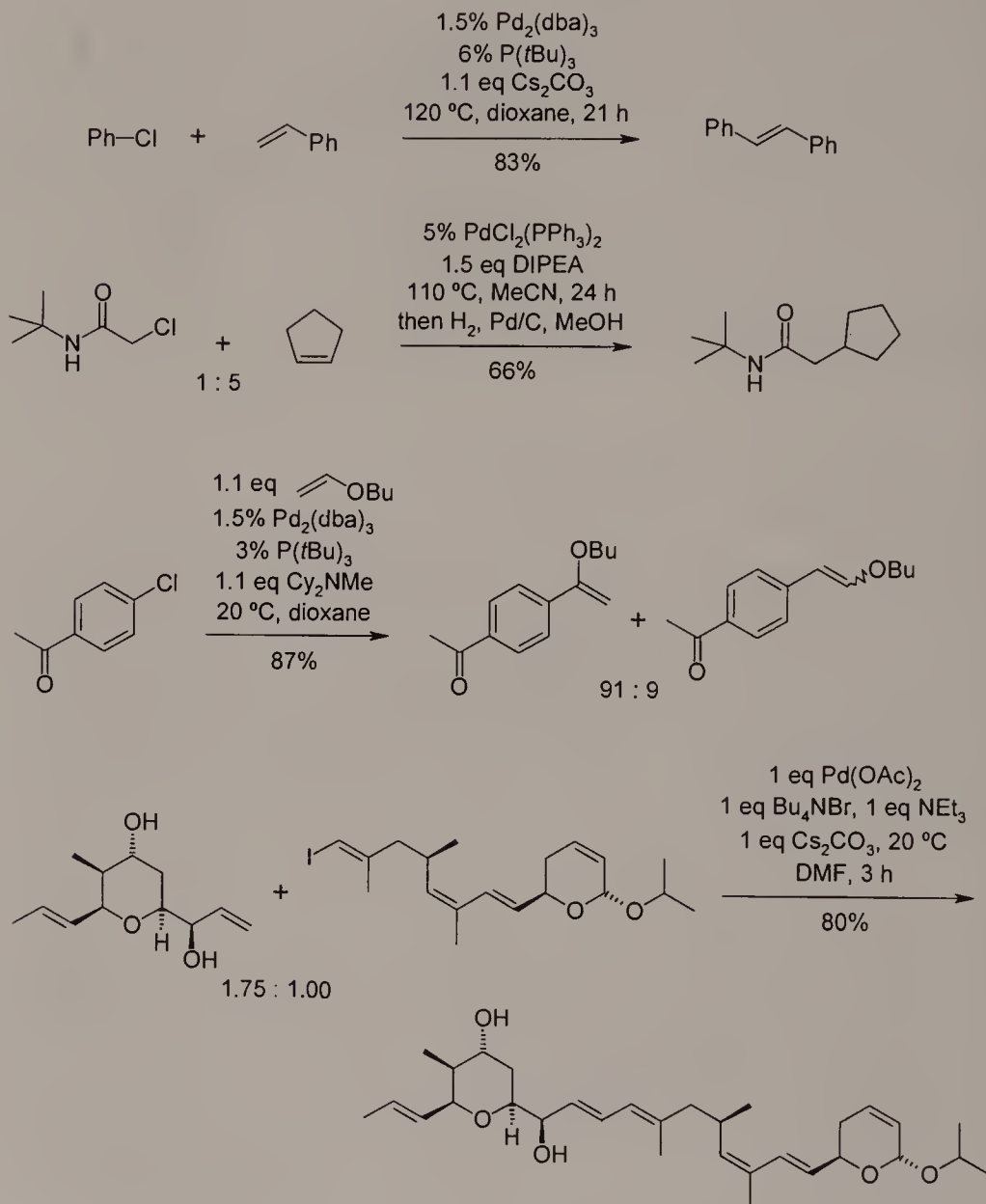
The Heck Reaction

If the initial organopalladium complex is formed in the presence of an alkene, transfer of the organyl group to the alkene can occur (Heck reaction, Scheme 8.7) [5, 78]. Electron-deficient and electron-rich alkenes and even some arenes [79] can be used. In the last step of this process a Pd-hydrido complex is formed by β -hydride elimination, leading to the formation of the C–C double bond. In the presence of bases the hydrido complex eliminates HX, regenerating the catalytically active Pd(0) complex (Scheme 8.7).



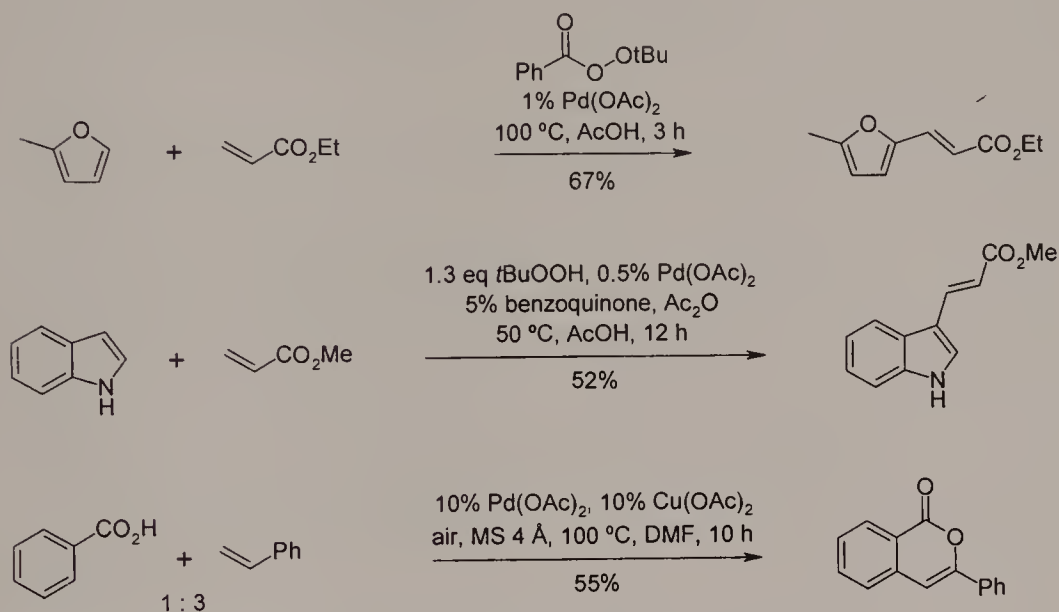
Scheme 8.7. Mechanism of the Heck reaction.

Representative examples of Heck reactions are depicted in Scheme 8.8. Terminal alkenes react faster than internal alkenes, and the formation of mixtures of products resulting from further arylation or vinylation of the initial product is therefore only observed when a large excess of halide and long reaction times are employed. Electron-poor alkenes usually react more rapidly than electron-rich alkenes, and the new C–C bond is usually formed at the most electron-deficient carbon atom.



Scheme 8.8. Examples of Heck reactions [80–84].

Direct palladation of C–H bonds can be achieved by treatment of, for example, electron-rich arenes with Pd(II) salts (see also Section 8.11). After cross-coupling via reductive elimination the resulting Pd(0) must be reoxidized to Pd(II) if Pd-catalysis is the aim [85]. Reoxidation of Pd(0) with Cu or Ag salts (as in the Wacker process) is not always well suited for C–C bond-forming reactions [86], but other oxidants, for example peroxides, have been used with success (Scheme 8.9). The required presence of oxidants in the reaction mixture limits the scope of these reactions to oxidation-resistant starting materials.



Scheme 8.9. Formation of C–C bonds via intermediate palladation of C–H bonds [86–88].

The large number of highly diverse examples of high-yielding Pd-catalyzed organic reactions might give the non-specialist the impression that almost any conceivable transformation might work in the presence of a suitable Pd catalyst. This is, of course, not true, and even the most robust Pd-catalyzed processes have their limitations. Some of these will be discussed in the following sections. The most important unwanted processes which can compete with Pd(0)-catalyzed C–C bond formation include homocoupling or reduction of the halide and homocoupling, C-protonation, or oxidation of the organometallic reagent.

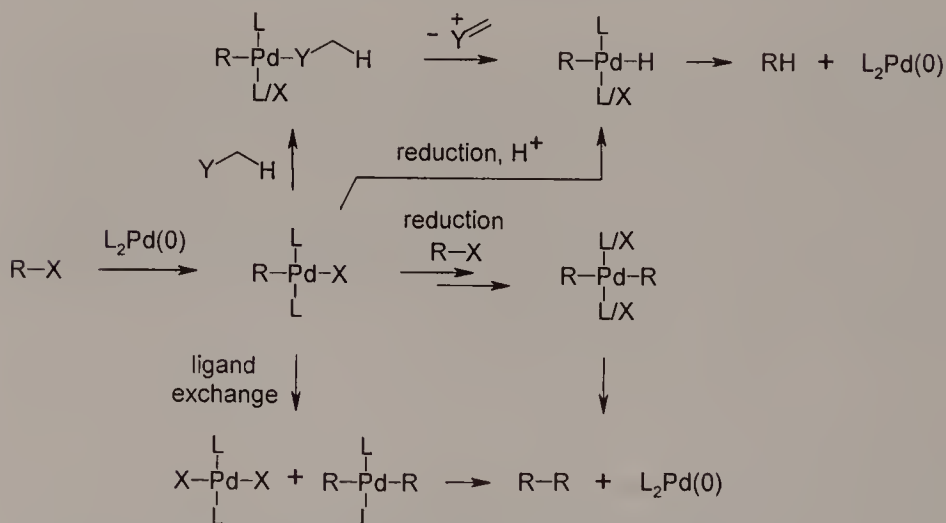
8.4

Homocoupling and Reduction of the Organyl Halide

As mentioned in Section 8.2, organopalladium(II) complexes can react with organyl halides to yield products of cross-coupling. The formation of large amounts of symmetric biaryls as a result of homocoupling of the aryl halide is often observed during

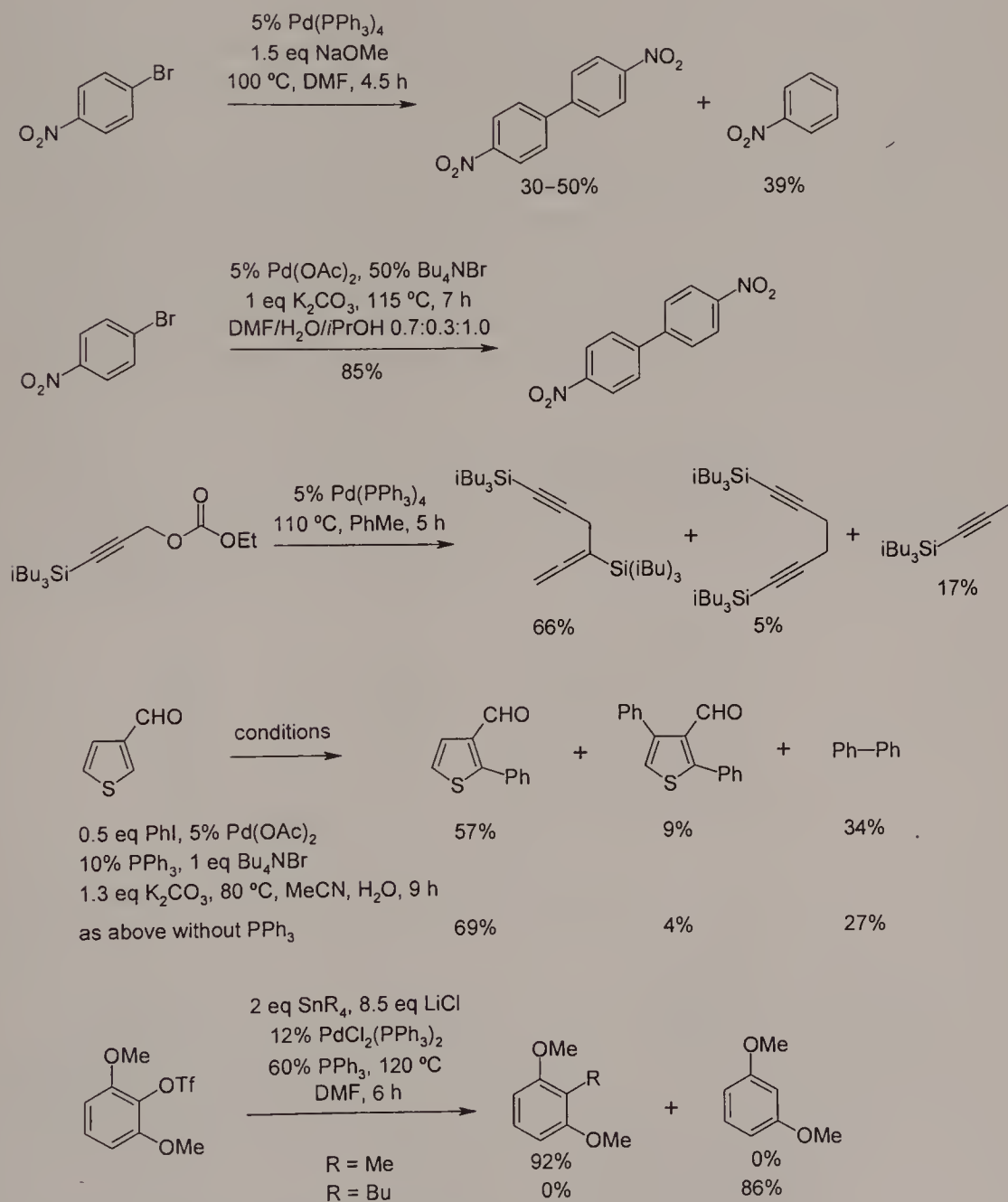
the coupling of aryl halides with weak nucleophiles or unreactive alkenes. This reaction may proceed via transient formation of Pd(IV) complexes. Another possible mechanism of this homocoupling is reduction of the intermediate organopalladium(II) complex to a Pd(0) complex which then undergoes a second oxidative addition to the halide to yield a diorganylpalladium(II) complex (Scheme 8.10) [89]. Alternatively, the initially formed Pd(II) complex can undergo ligand exchange with itself to yield diorganylpalladium(II) complexes and complexes without organyl groups [90]. This process will compete most efficiently with Stille and Suzuki cross-couplings if the stannane or boronic acid is electron-deficient, sterically hindered, or otherwise unreactive and undergoes transmetalation only slowly. Benzylic halides and 2-halopyridines are particularly prone to undergo homocoupling (and reduction) [62, 91, 92].

Reduction of the halide to a hydrocarbon is another common side reaction of Pd-mediated cross-couplings. This hydrodehalogenation can proceed via reductive elimination from a hydrido complex PdRL_2H , which can be formed from the initial product of oxidative addition (PdRL_2X) by ligand exchange with an alkoxide, an amine, or an organometallic reagent containing β hydrogen, followed by β -hydride elimination (and formation of a carbonyl compound [93, 94], an imine [1], or an alkene [36], respectively). Hydrodehalogenation is, therefore, often observed in palladium-catalyzed reactions of aryl halides with alcoholates [95] or amines [96], but can be largely suppressed by use of sterically demanding phosphines, which accelerate reductive elimination of the arylamine from aryl(amido)palladium(II) complexes at the expense of β -hydride elimination [1, 97]. Alternative routes to hydrido complexes include the reduction of Pd(II) complexes to Pd(0) complexes, followed by protonation [98] (Scheme 8.10). It has been observed that arenes are formed during the reduction of a Pd(II) catalyst precursor to Pd(0) in the presence of aryl halides [97], but the precise mechanism of this process remains unknown.



Scheme 8.10. Possible mechanisms of the Pd-catalyzed reduction and homocoupling of organic halides. X = halide, triflate; Y = R_2C^- , NHR , O^- .

Reducing agents which have been used to promote the Pd-mediated homocoupling of organyl halides include hydroquinone [99], zinc powder [15, 100, 101], magnesium [101], tetra(dimethylamino)ethene [102], tertiary aliphatic amines [103–105], and aliphatic alcohols [104, 106]. However, as mentioned above, homocoupling can also proceed in the absence of reducing agents [107]. As illustrated by the examples illustrated in Scheme 8.11, the reaction conditions for homocouplings do not differ

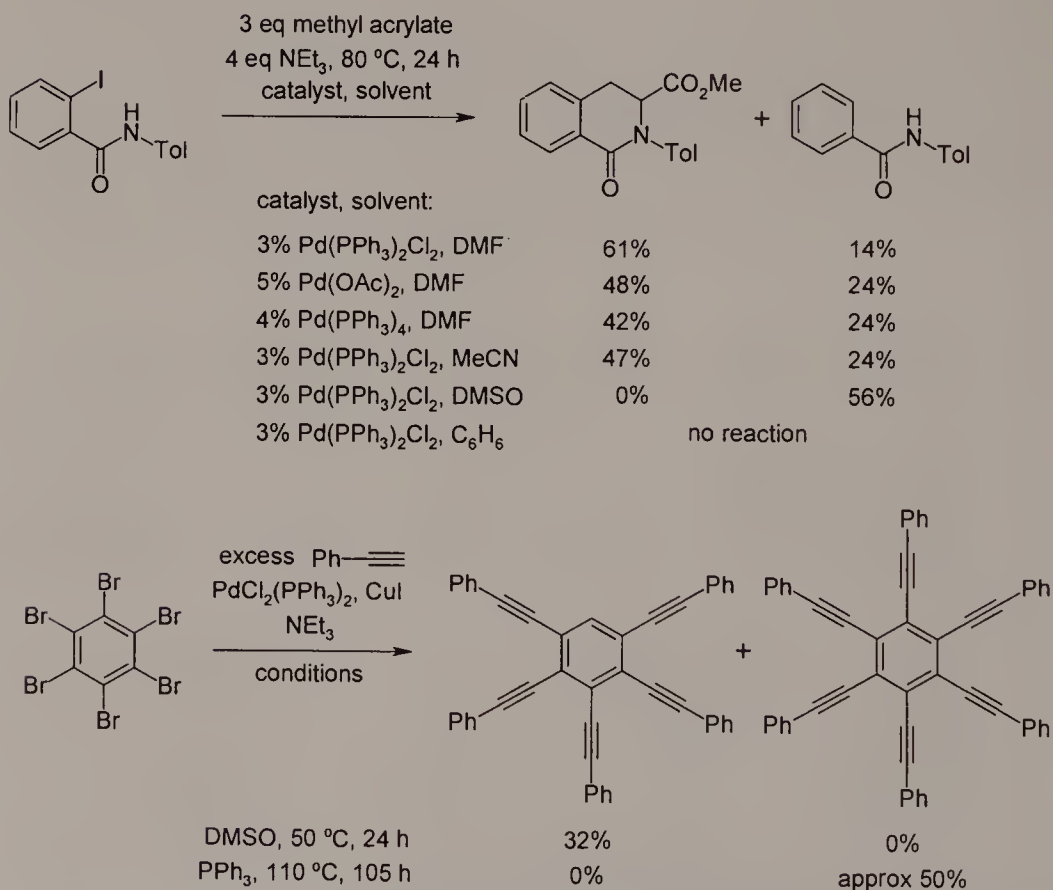


Scheme 8.11. Palladium-catalyzed homocoupling and reduction of organyl halides, carbonates, and triflates [57, 94, 104, 108, 109].

much from those used for Heck reactions or some cross-couplings, and homocoupling can therefore compete with these.

Reduction of the starting halide to a hydrocarbon should, at least in theory, be suppressible by strong ligands (e.g. chelating diphosphines), which will not be readily displaced by alcoholates or amines. Reduction should proceed swiftly if only weak, readily displaceable ligands are present in the reaction mixture [80], together with efficient reducing agents such as amines or alcoholates with α hydrogen.

The amount and type of base chosen can also have an impact on the extent of homocoupling and reduction of aryl halides in the presence of Pd(0). KO t Bu has been reported to increase the rate of homocoupling [46], whereas NaH can bring about quick reduction of some aryl halides [46, 47]. Higher reaction temperatures can lead to larger amounts of biaryls and to less hydrodehalogenation [15]. In the absence of strong reducing reagents or bases clean homocoupling of aryl halides without any reduction can occasionally be achieved [89] (Scheme 8.11). As illustrated by the examples depicted in Scheme 8.12, the amount of reduced product can also depend on the solvent. Reduction and homocoupling of the halide can, of course, also be suppressed by adding to the reaction mixture an efficient transmetalating reagent, a reactive alkene, or another reagent which can react quickly with the initially formed product of oxidative addition before it is converted to a hydrido com-



Scheme 8.12. Palladium-catalyzed reduction of organyl halides [112, 113].

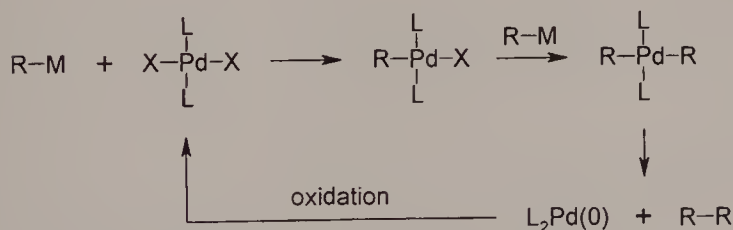
plex. Thus, Heck or Sonogashira reactions are usually performed in the presence of amines, and even preformed complexes of palladium with aliphatic amines can be used as catalysts for Suzuki couplings, with no reduction of the halide being observed [110]. Similarly, carbon monoxide reacts much more rapidly with organopalladium complexes than do hydrogen or other reducing agents [111], and aryl or vinyl halides can be cleanly converted into aldehydes by treatment with mixtures of carbon monoxide and hydrogen without competing hydrodehalogenation [32].

8.5

Homocoupling and Oxidation of the Carbon Nucleophile

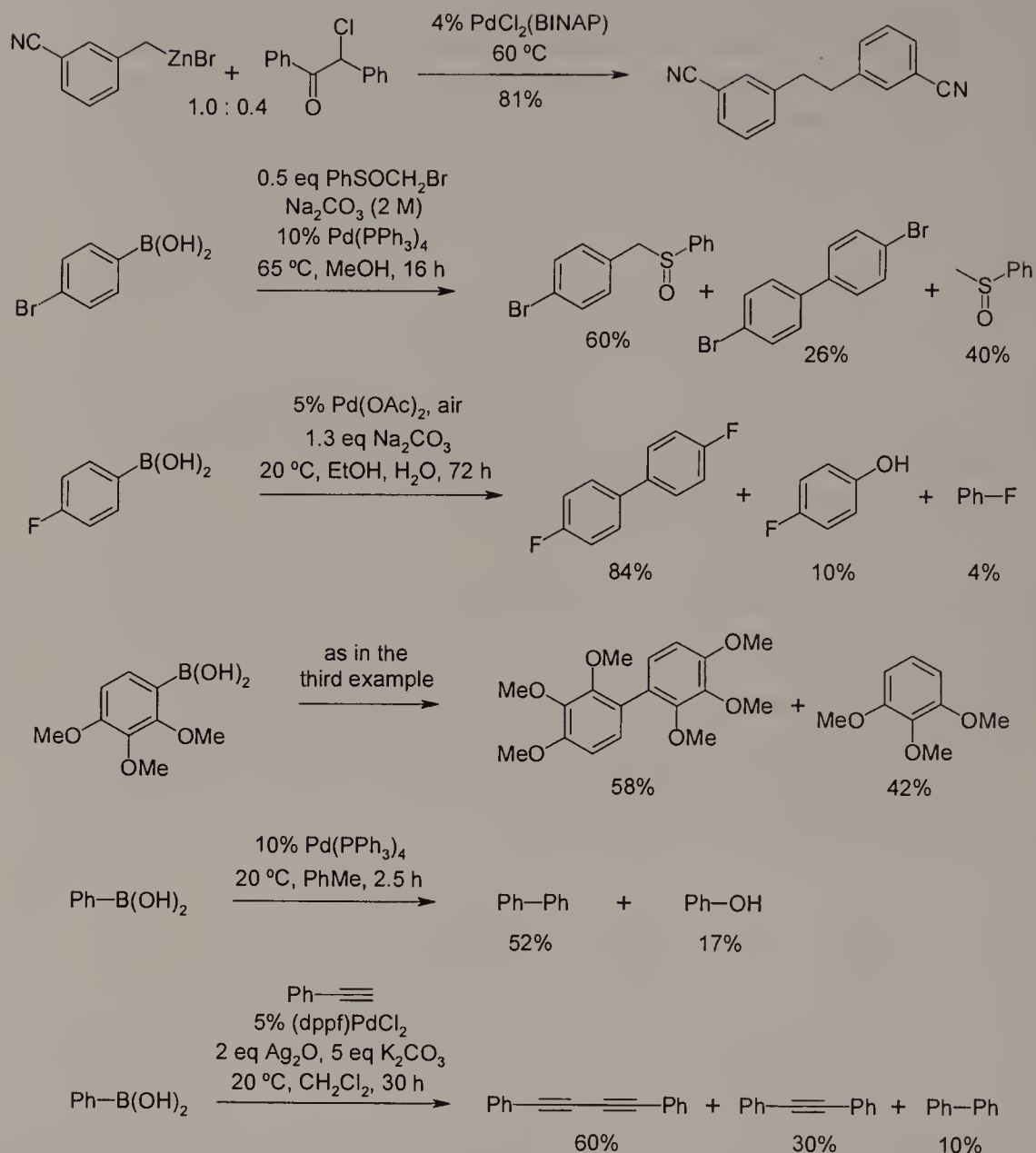
Most transition metal-catalyzed cross-coupling reactions also yield small quantities of the product of homocoupling of the nucleophilic reactant [16, 114, 115]. In particular terminal alkynes [116, 117] or metalated terminal alkynes [118] readily dimerize to the corresponding 1,3-butadiynes (Scheme 8.14).

Homocoupling of the carbon nucleophiles might proceed by the mechanism shown in Scheme 8.13. Stannanes or boronic acids, for instance, can sequentially displace either halides or organyl groups from Pd(II) complexes to yield new diorganypalladium(II) complexes [67, 101, 116], which can undergo reductive elimination to yield a hydrocarbon and Pd(0). In the presence of an oxidant, a Pd(II) complex can be regenerated and homocoupling of the stannane or boronic acid will proceed with catalytic amounts of Pd [119, 120]. For arylboronic acids the type of base chosen can affect the extent of homocoupling: with NaOH and NEt₃ significantly more symmetric biaryl is sometimes formed than with CsF, K₃PO₄, or Na₂CO₃ as bases [16]. The reason for this behavior is not well understood.



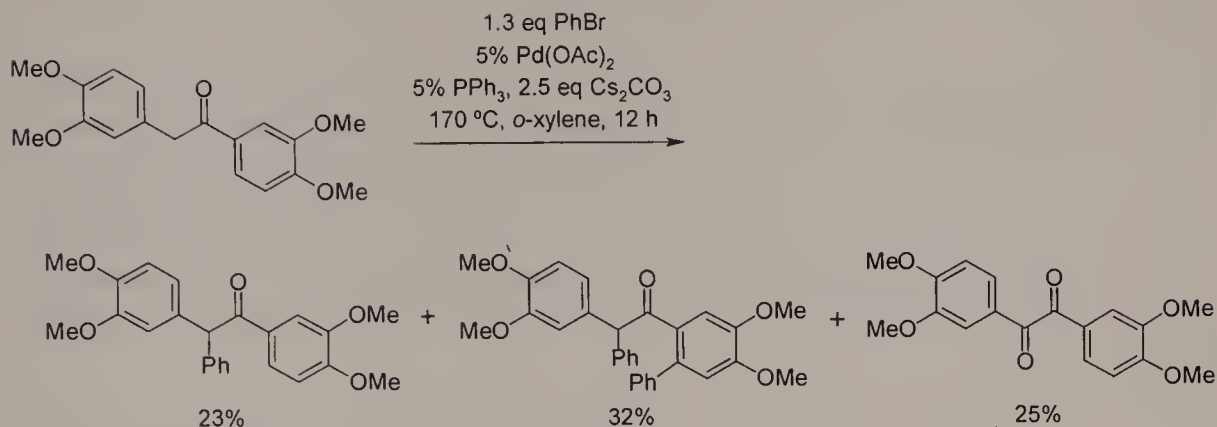
Scheme 8.13. Possible mechanism of the homocoupling of the organometallic component of Pd-mediated cross-couplings [119, 121].

Numerous examples of unwanted or deliberate Pd-mediated homocoupling of organometallic reagents have been reported (Scheme 8.14) [38, 122, 123]. Suitable oxidants include α -halo ketones [116, 124, 125] (which can, therefore, not be used as electrophilic component in cross-coupling reactions), oxygen [120, 124, 126], 1,2-diiodoethene [127], 2,3-dibromopropionic acid esters [119], and CuCl₂ [128].



Scheme 8.14. Palladium-mediated homocoupling of carbon nucleophiles [117, 120, 121, 125, 129].

Occasionally hydroxylation of the carbon nucleophile is observed during Pd-catalyzed C–C bond formation (Scheme 8.15; third reaction in Scheme 8.14 [121]). These reactions may in some instances proceed by a mechanism analogous to the Wacker reaction [130], or to the hydroxylation of organometallic compounds or boranes by peroxides or air (Section 3.5).

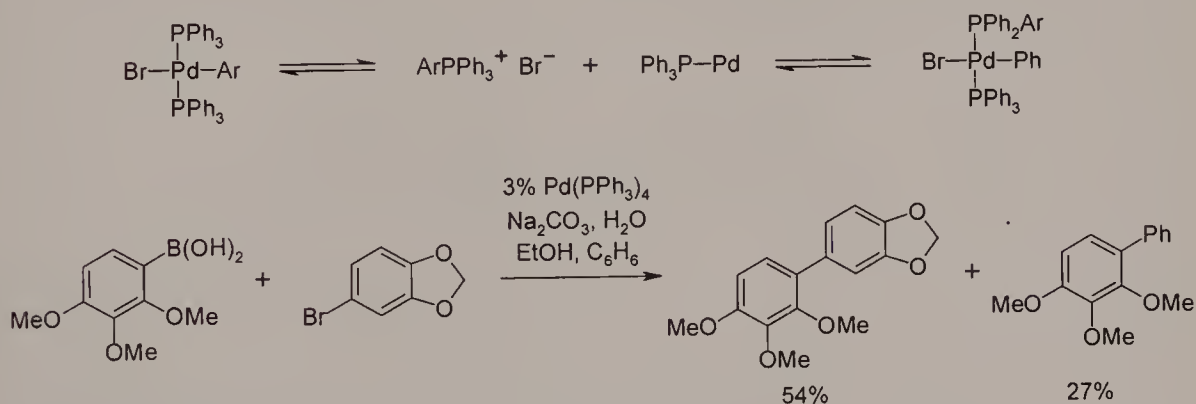


Scheme 8.15. Oxidation of a carbon nucleophile during Pd-catalyzed cross-coupling [48].

8.6

Transfer of Aryl Groups from the Phosphine Ligand

During arylations of carbon nucleophiles with aryl halides in the presence of palladium triarylphosphine complexes products containing the aryl group of the phosphine can result (Scheme 8.16). These reactions proceed via reversible arylation of the Pd-bound phosphine, which occurs at temperatures above 50 °C, particularly readily in the presence of iodide [11] (see Section 8.2). Electron-deficient aryl groups usually migrate less readily than electron-rich groups [23, 25].



Scheme 8.16. Aryl group exchange between phosphines and palladium [11, 131].

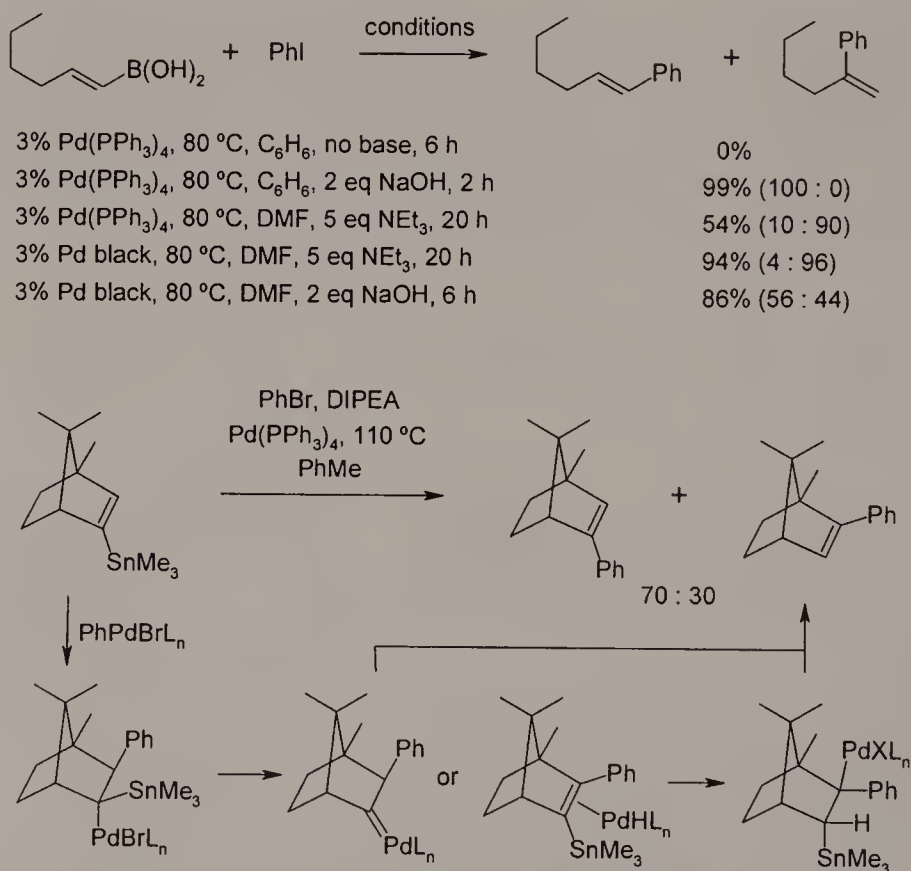
This unwanted side reaction can be suppressed by keeping the amount of catalyst as small as possible, by using sterically demanding trialkyl phosphine ligands, by conducting the reaction in solvents of low polarity, such as CH₂Cl₂ (instead of THF or DMF), or by using phosphine-free catalysts [23, 38, 62, 132–134].

8.7

ipso- vs *cine*-Substitution at Vinylboron and Vinyltin Derivatives

Cross-coupling reactions with vinylboronic acids can yield either the normal product (*ipso*-substitution of boron) or a regioisomer formed via a Heck-type reaction (*cine*-substitution; Scheme 8.17) [135]. Formation of the normal product (1-phenylhexene in Scheme 8.17) requires a base capable of binding to the boronic acid, thereby increasing the nucleophilicity of the boron-bound carbon atom (typically ROM, MOH, M_2CO_3 , M_3PO_4 , where M = alkali metal [136]). Products of *cine*-substitution result when tertiary amines are used as bases, i.e. under Heck-type reaction conditions.

Similarly, vinylstannanes can also yield products of *cine*-substitution (Scheme 8.17), specially if tin and an electron-withdrawing or aryl group are bound to the same carbon atom [40, 137–141]. It has been suggested that formation of these products proceeds via intermediate formation of a palladium carbene complex [138, 140] or via reversible β -hydride elimination [141], and can be avoided by addition of Cu(I) salts [142], which increase the rate of Stille coupling, or by protecting vinylic C–H groups by transient silylation [143].

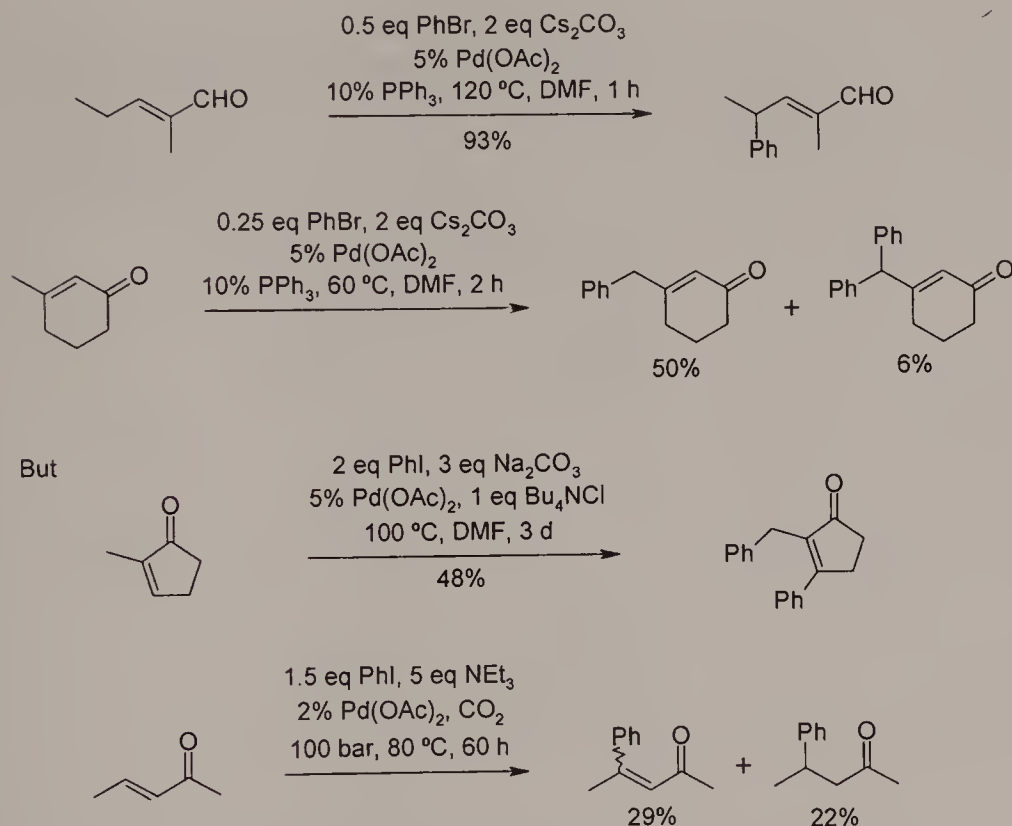


Scheme 8.17. Regioselectivity of cross-coupling reactions with vinylboronic acids and vinylstannanes [9, 144].

8.8

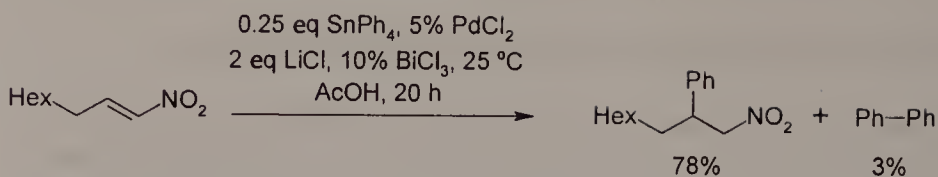
Allylic Arylation and Hydrogenation as Side Reactions of the Heck Reaction

Alkenes substituted with electron-withdrawing groups and with an allylic, acidified C–H group can react with organopalladium complexes under basic conditions either as carbon nucleophiles (cross-coupling) or as alkenes (Heck reaction). Highly substituted alkenes will undergo Heck reaction only slowly, so that their reaction as carbon nucleophiles might become the main reaction pathway (first two reactions, Scheme 8.18). Few examples of such reactions have been reported, however, and, as illustrated by the last two examples in Scheme 8.18, not all enones or enals react this way.



Scheme 8.18. Heck reaction vs allylic arylation [145–147].

Aliphatic amines can be readily oxidized by Pd(II) to imines or iminium salts and hydrido complexes. The latter can transfer hydrogen to alkenes, leading to the formation of alkanes as byproducts of the Heck reaction (last example, Scheme 8.18). Such reactions can be avoided by using alkali carbonates as base instead of aliphatic amines [148]. Treatment of stannanes or organoboron derivatives with electron-deficient alkenes under acidic reaction conditions can also lead to formal products of Michael addition instead of the products of a Heck-type reaction [149, 150] (Scheme 8.19).

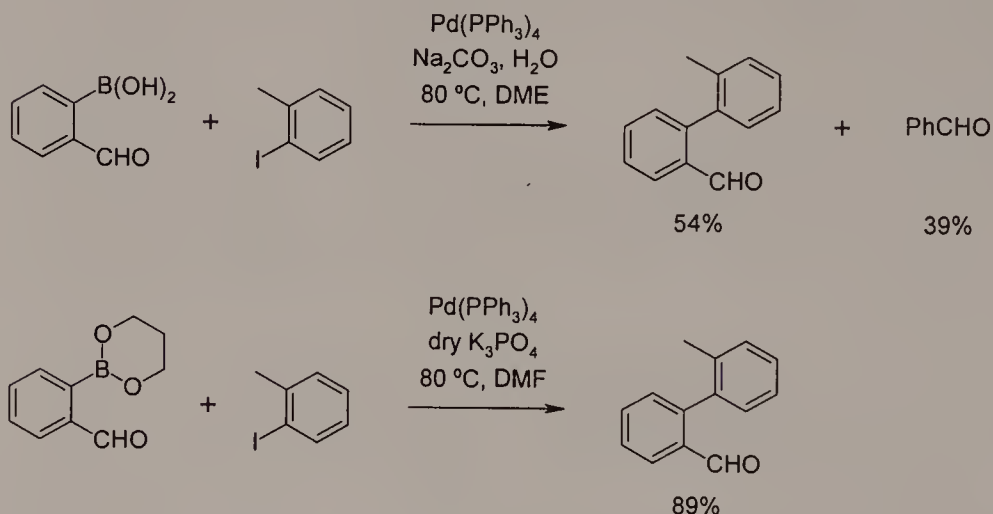


Scheme 8.19. Arylation of electron-poor alkenes under acidic reaction conditions [150].

8.9

Protodemetalation of the Carbon Nucleophile

Boranes and, to a lesser extent, boronic acids can undergo slow hydrolysis (protodeboration) in the presence of protic solvents. This unwanted reaction can become predominant if a cross-coupling reaction only proceeds slowly (e.g. with electron-rich, sterically demanding, or unreactive halides; Scheme 8.20; see also Scheme 8.14) or if the boron derivative is particularly sensitive, for example 2-formylphenylboronic acid. In such instances the reaction should be performed under anhydrous conditions in an aprotic solvent with a boronic acid ester [151] or a stannane.



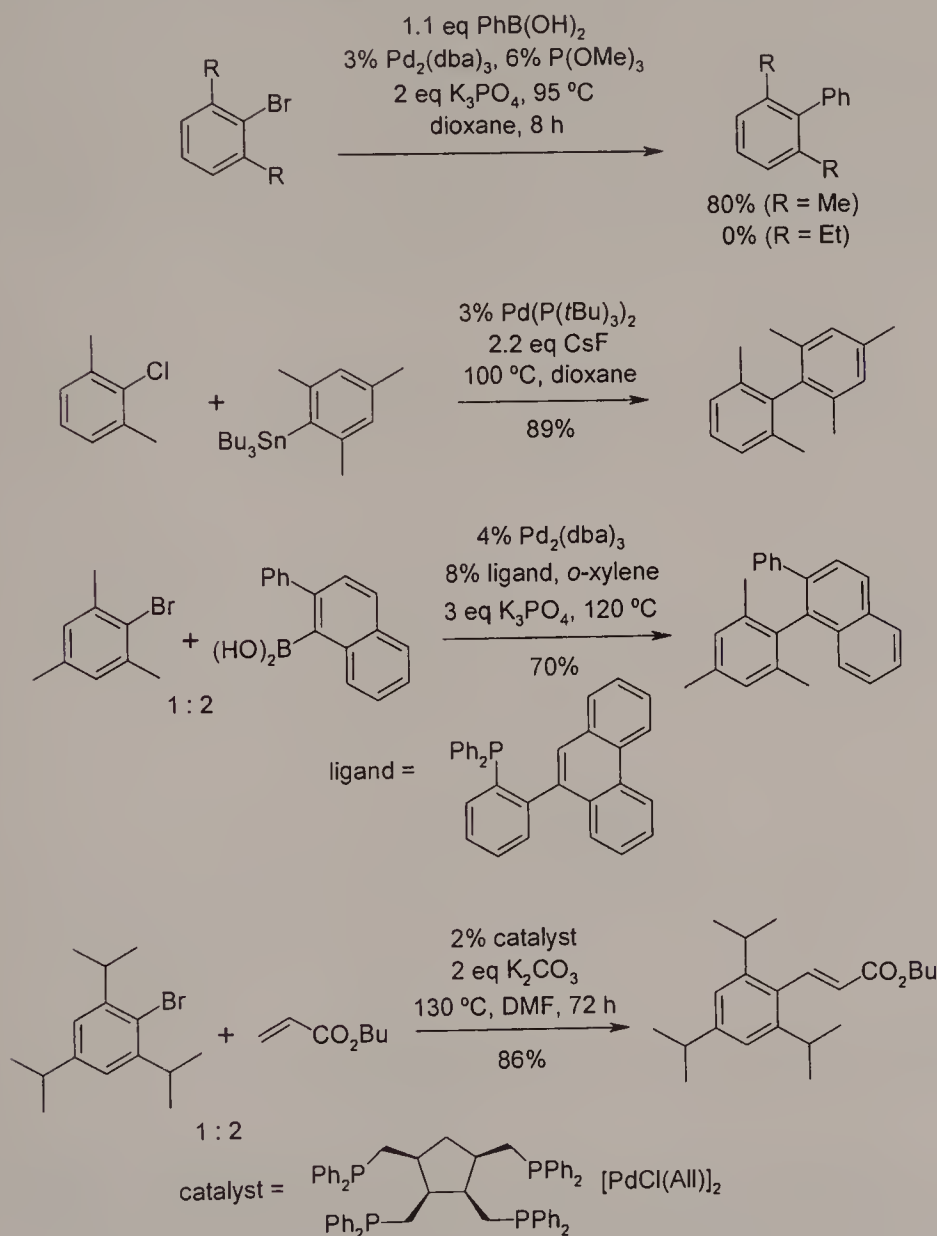
Scheme 8.20. Protodeboration of boronic acids in the presence of water [66].

8.10

Sterically Hindered Substrates

Cross-couplings of 2,6-disubstituted aryl halides, stannanes, or boronic acids proceed less readily than with sterically less demanding starting materials and might require a careful optimization of the reaction conditions (Scheme 8.21) [109]. Reduction or hydrolysis to the corresponding arenes will usually compete effectively with these slow cross-couplings, which should therefore be conducted under anhydrous conditions and in the absence of reducing agents. It has been found that sterically

demanding phosphines are particularly well suited to Suzuki or Stille couplings of sterically demanding starting materials. Thus, neither the coupling of mesitylboronic acid and iodomesitylene with $\text{Pd}(\text{PPh}_3)_4$ [66, 151] nor the coupling of mesitylmagnesium bromide and 2-chloro-*m*-xylene or bromomesitylene with 1,3-(2-mesityl)imidazol-2-ylidene Pd complexes [115] yield the desired 2,6,2',6'-tetrasubstituted biaryls. Compounds of this type can, however, be prepared by using sterically demanding phosphines as ligands (Scheme 8.21). Heck reactions with sterically demanding aryl halides can, similarly, also be performed successfully with the aid of sterically demanding phosphines (last example, Scheme 8.21).



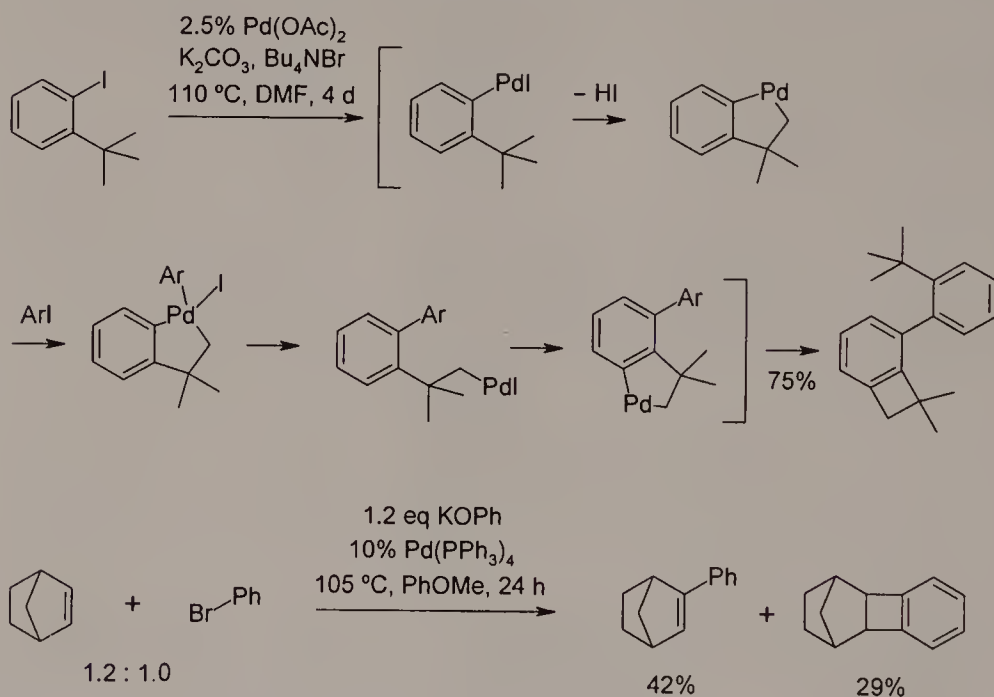
Scheme 8.21. Palladium-mediated C–C bond formation with sterically demanding substrates [152–155].

8.11

Cyclometalation

In transition metal complexes of suitable geometry the metal may undergo intramolecular oxidative insertion into C–H bonds. Intermediates of Pd-catalyzed C–C bond formation can also undergo such cyclometalations to yield “palladacycles”. This can give rise to unexpected products or, if the palladacycles are too stable, the catalyst will be consumed and no further reaction will occur. At high temperatures reductive elimination from such complexes can occur to yield cyclic products.

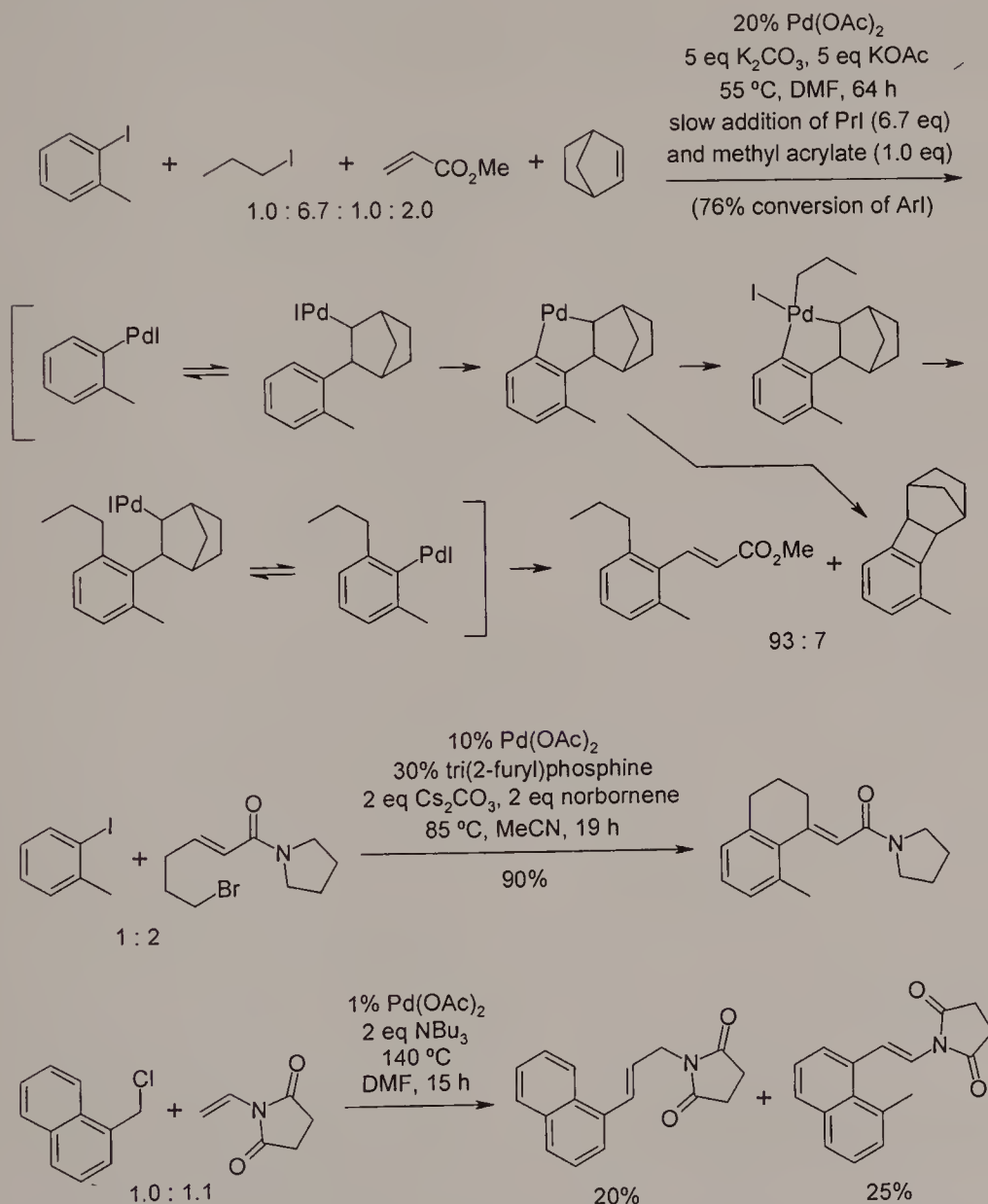
In the first example sketched in Scheme 8.22 a palladacycle is formed by intramolecular insertion of Pd into a methyl C–H group after intermolecular oxidative addition to the C–I group. The resulting intermediate does not undergo reductive elimination to yield a benzocyclobutene, probably because it is less strained than the final intermediate of this process. First after cross-coupling with a second aryl iodide followed by a second cyclometalation the resulting palladacycle undergoes reductive elimination to yield a benzocyclobutene. Similarly, Heck reactions with norbornene can also give rise to cyclobutanes (second reaction, Scheme 8.22).



Scheme 8.22. Cyclopalladation during Pd-mediated homocoupling of aryl iodides [156] and Heck reaction with norbornene [157]. Ar = 2-(*t*Bu)C₆H₄.

Other intermediates which can undergo similar cyclometalations include (2-methoxyphenyl)palladium [158, 159] and (1-naphthylmethyl)palladium complexes (Scheme 8.23) [160]. Cyclometalation is usually promoted by high temperatures, and if these are necessary the yield of cross-coupling reactions with substrates prone to undergo cyclopalladation (for example 2-bromoanisole) can drop dramatically [43].

Another example of transient formation of a palladacycle is the Pd-mediated *ortho*-alkylation and *ipso*-vinylation of aryl iodides depicted in Scheme 8.23. In this multicomponent reaction the ability of norbornene to undergo reversible arylation and palladacycle formation is exploited. This reaction also illustrates that aryl halides undergo oxidative addition to Pd faster than do alkyl halides, and that aryl–alkyl bond-formation by reductive elimination also proceeds faster than alkyl–alkyl bond-formation. The large excess of alkyl iodide used in these reactions prevents the formation of biaryls. Benzocyclobutenes can also be formed in this reaction, in particular when the alkyl group on the aryl iodide is sterically demanding or when a secondary alkyl iodide is used [161].

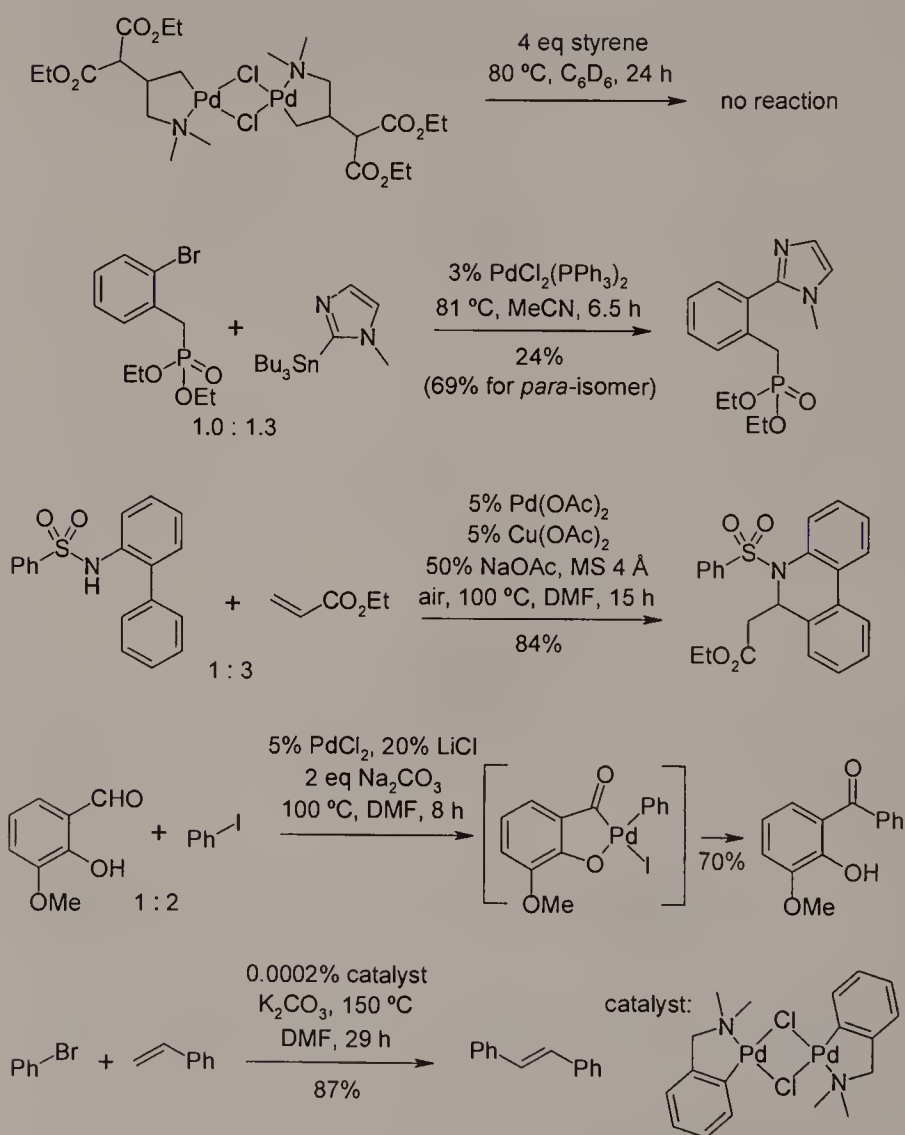


Scheme 8.23. Palladium-mediated C–C bond formation via cyclopalladation [160–162].

8.12

Chelate Formation

Organic compounds can react with Pd salts to form stable chelates via oxidative C–H insertion and simultaneous bond formation with a further coordination site in the molecule, for example an aliphatic amine, a hydrazone, a carboxylate, a phenolate, a phosphine, or a thioether [13, 14, 51, 163]. Such cyclic complexes can be significantly more stable than related, non-cyclic organopalladium complexes, and might no longer undergo cross-coupling or Heck reactions under the usual conditions [164]. For instance, although Heck reactions can usually be performed with internal alkenes [165], only terminal alkenes or allene react intermolecularly with isolated 2-(aminomethyl)arylpalladium complexes [166, 167]. 3-(Dialkylamino)propylpalladium complexes are even less reactive (Scheme 8.24) [168], and five-mem-



Scheme 8.24. Reactions involving Pd-chelates [51, 88, 174–176].

bered Pd-chelates with sulfur or phosphorus ligands are unreactive towards alkenes [166, 169]. Accordingly, aryl halides with strongly chelating *ortho*-substituents will undergo transition metal-catalyzed C–C bond formation only sluggishly or not at all (Scheme 8.24). Some palladacycles or Pd-chelates are even sufficiently stable to be useful catalysts for cross-coupling or Heck reactions, and can be recovered unchanged because they do not undergo cross-coupling during these reactions (Scheme 8.24) [78, 170–172]. 2-(Hydroxymethyl)aryl halides or 2-(acylamino)aryl halides have, however, been used with success in Pd-mediated cross-coupling reactions [66, 173]. Similarly, in the third example in Scheme 8.24 the intermediate sulfonylamino chelate is sufficiently labile to undergo Heck reaction with ethyl acrylate.

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9

Cyclizations

9.1

Introduction

Cyclic compounds are mainly prepared from non-cyclic starting materials either by cycloaddition reactions or by cyclization. Whereas in cycloadditions the ring size of the product is determined by the reaction mechanism of a given cycloaddition, cyclizations enable the use of most bond-forming reactions and, in principle, enable access to any ring size. Certain rings, however, are more difficult to prepare than others, and because oligomerization competes with all cyclizations, slow cyclizations will have a detrimental effect on the yield of cyclic products. In this section some of the critical structural considerations for successful cyclizations will be presented and examples of difficult cyclizations will be discussed.

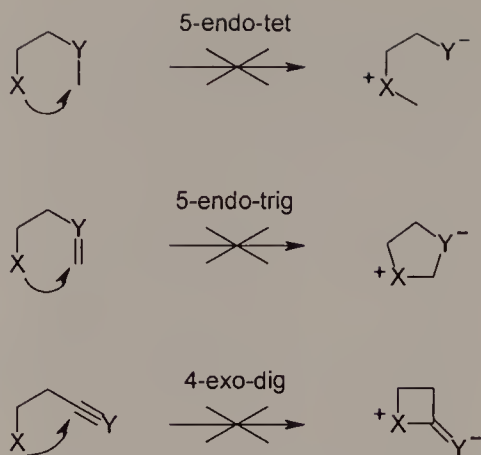
9.2

Baldwin's Cyclization Rules

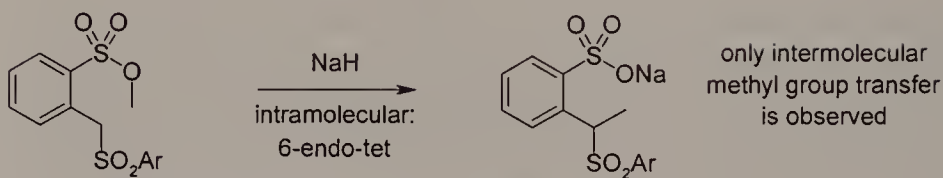
In the 1970s J.E. Baldwin proposed a set of qualitative generalizations for the probability of formation of cyclic compounds, based on the favored trajectories for the approach of one reactant to another [1–5]. Cyclizations were organized according to the ring size formed, whether the breaking bond is located in (endo) or outside (exo) the newly formed ring, and the hybridization of the (mostly uncharged) carbon atom with the highest *s* character involved in bond formation (tet, trig, or dig for sp^3 -, sp^2 -, or sp -hybridized carbon, respectively). Baldwin's rules state that 3 to 6-endo-tet, 3 to 5-endo-trig, and 3 and 4-exo-dig processes are unfavorable, whereas all remaining cyclizations are allowed (Scheme 9.1).

These rules do not apply strictly, but provide useful guidelines for synthesis design. The rules are generally not applicable to electrocyclic reactions or to substrates containing non-second-period elements (e.g. P or S), because their longer bond lengths imply different geometric constraints.

An example of a forbidden 6-endo-tet process would be the intramolecular alkylation of a carbanion via a six-membered transition state (Scheme 9.2). Because such an alkylation would proceed via the S_N2 mechanism and would require a linear



Scheme 9.1. Unfavorable processes according to Baldwin's rules.

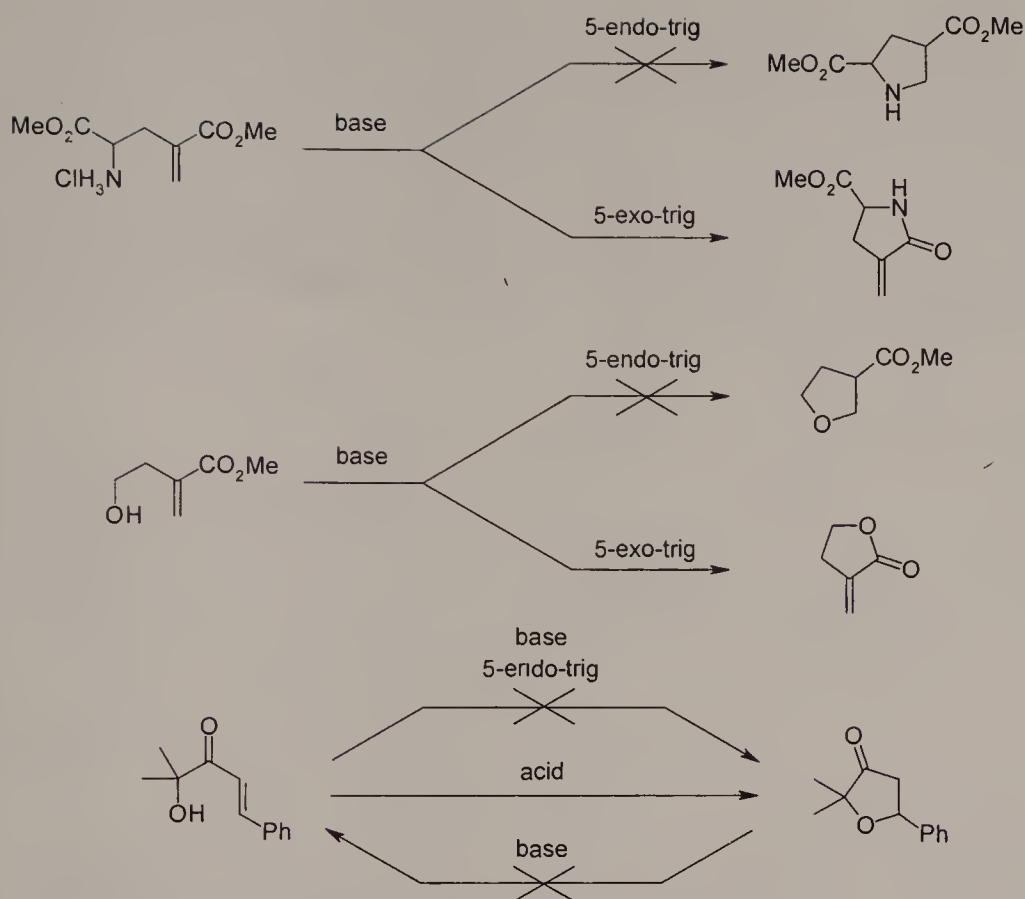


Scheme 9.2. Methylation of a metalated sulfone [6].

arrangement of the incoming nucleophile (the carbanion), the central carbon, and the leaving group, it cannot occur intramolecularly in rings with fewer than approximately nine atoms. The reaction sketched in Scheme 9.2 was shown by Eschenmoser to proceed exclusively intermolecularly.

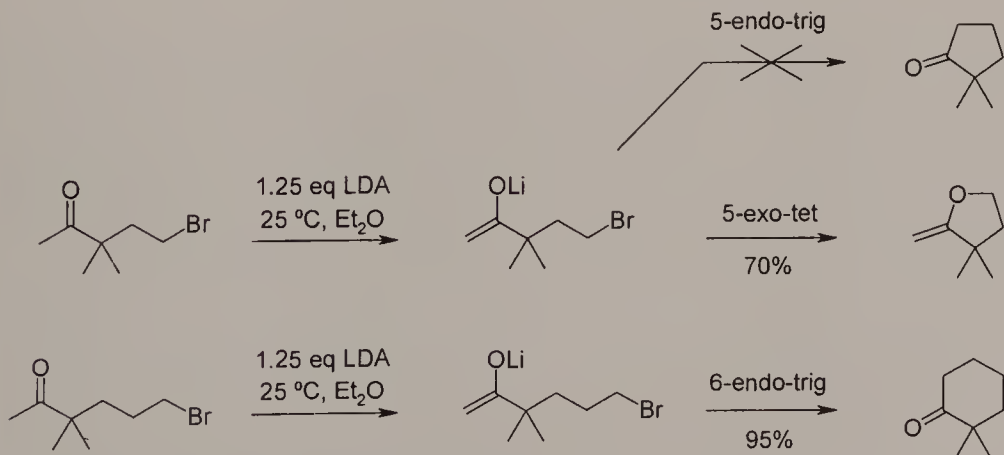
Further unfavorable processes are 3 to 5-endo-trig cyclizations (Scheme 9.3). Although Michael additions of amines or alcohols to acrylates are usually faster than reaction of these nucleophiles with esters, 2-(2-amino/hydroxy)ethylacrylates do not undergo intramolecular Michael additions to yield pyrrolidines or furans, but yield lactams or lactones instead. The reason for this is that the nucleophilic functional groups cannot approach the π^* orbital of the alkene sufficiently without undue generation of strain [7]. Interestingly, the reverse reactions (e.g. the base-induced scission of 3-methoxycarbonylfuran) do not proceed either. Similarly, the hydroxy ketone shown in Scheme 9.3 (third example) does not cyclize on treatment with bases, and the expected furanone, which can be prepared by acid-catalyzed cyclization of the hydroxy ketone, does not undergo ring opening on treatment with bases, because the energy barrier between these two compounds is too high. That the acid-catalyzed cyclization proceeds smoothly might be because of the reduced double bond character and increased flexibility of the alkene in the protonated hydroxy ketone [3, 8].

Another type of cyclization which follows Baldwin's rules is the intramolecular alkylation of enolates. Cyclopentanones cannot usually be prepared this way because the electrophilic carbon atom cannot approach the nucleophilic carbon atom sufficiently (Scheme 9.4). If the C–C double bond of the enolate remains exocyclic,



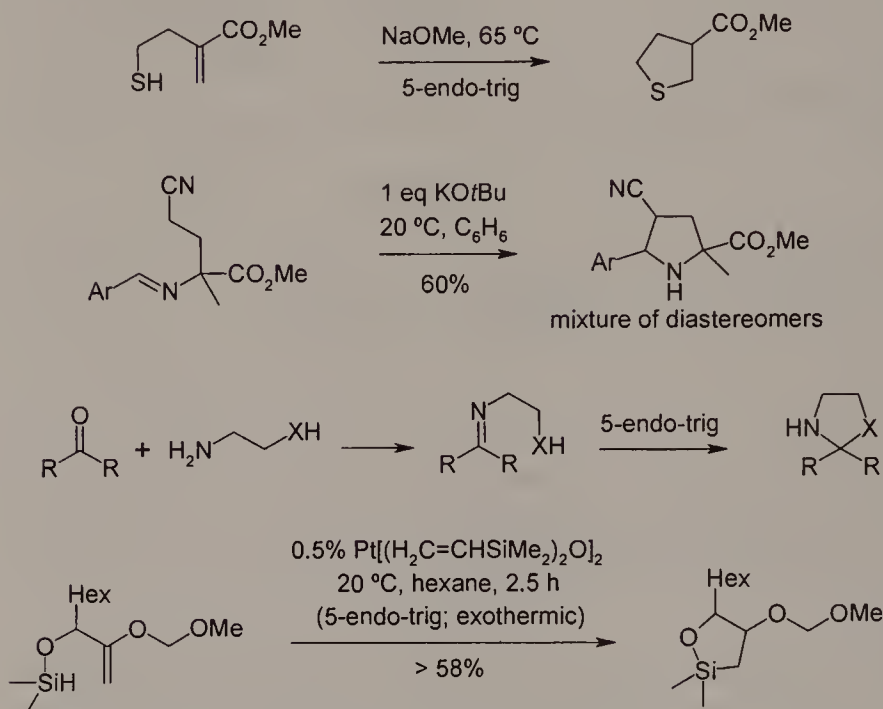
Scheme 9.3. Examples of allowed and forbidden cyclizations according to Baldwin's rules [2, 5].

however, cyclization proceeds smoothly to yield a cyclic enol ether. Because 6-endo-trig cyclization is usually favored, cyclohexanones can be formed by intramolecular C-alkylation of enolates.



Scheme 9.4. Cyclization of haloalkyl ketones [9].

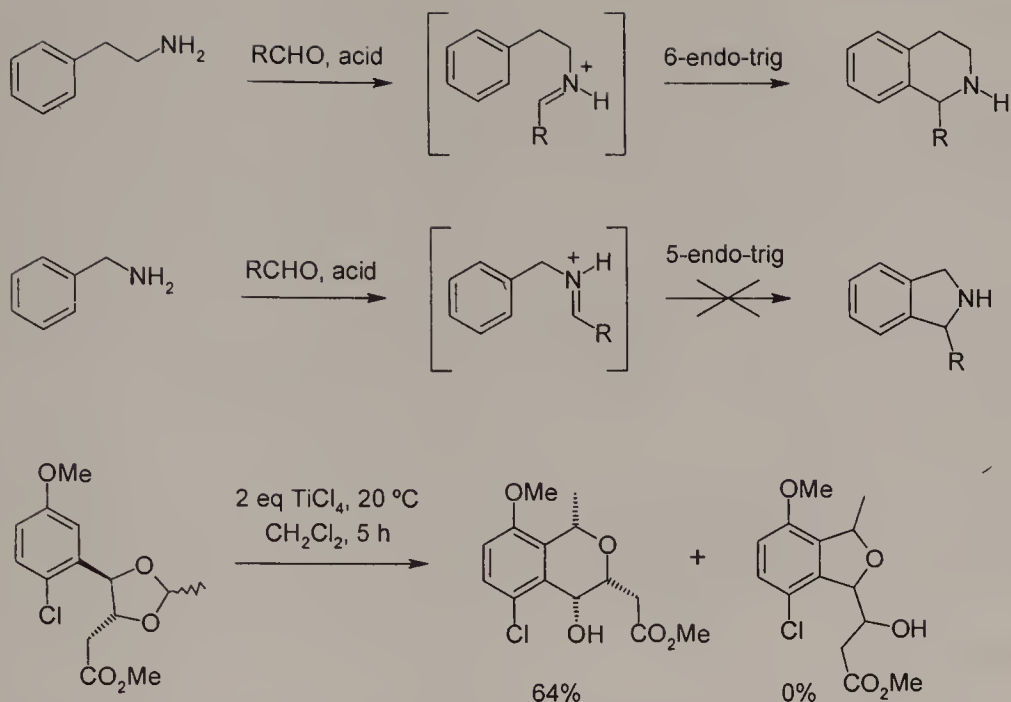
Examples of “forbidden” 5-endo-trig cyclizations which proceed anyway are shown in Scheme 9.5. Thiols do undergo 5-endo-trig cyclizations, because C–S bonds (1.82 Å) are substantially longer than C–N (1.47 Å) or C–O bonds (1.43 Å). Moreover, the intramolecular addition of carbon nucleophiles to imines to yield pyrrolidines [10, 11] or the easy conversion of aldehydes or ketones into five-membered cyclic aminals also involve an unfavorable 5-endo-trig cyclization [12], and suggest that Baldwin’s rules are not applicable to cyclizations involving imines. The C–Si bond (1.88 Å) is also sufficiently long to enable 5-endo-trig cyclizations to proceed smoothly (last reaction, Scheme 9.5).



Scheme 9.5. Examples of forbidden cyclizations according to Baldwin’s rules [2, 5, 10, 13]. Ar = 4-MeOC₆H₄; X = O, S, NH.

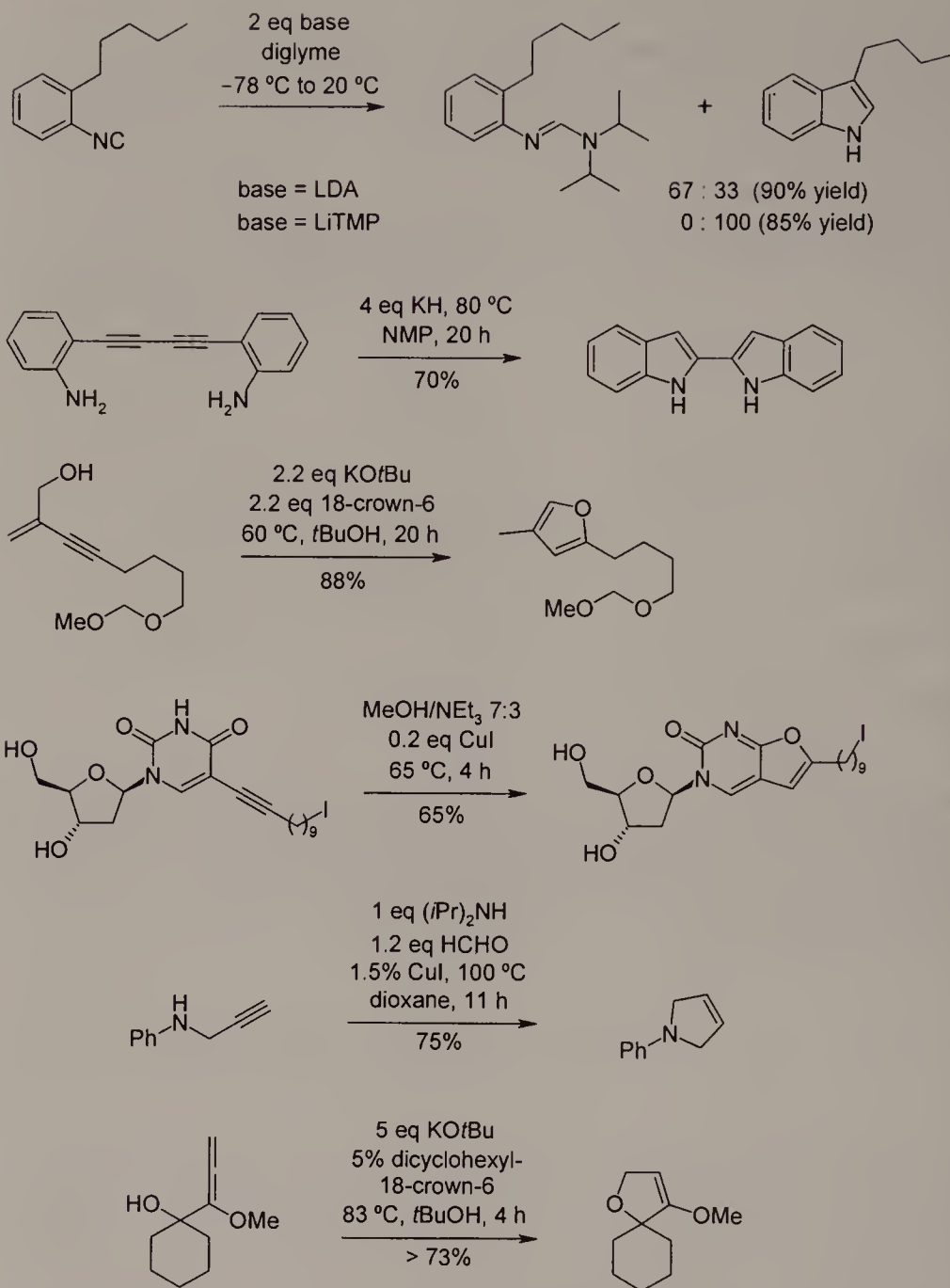
Whereas 5-endo-trig processes are unfavorable, 6-endo-trig cyclizations are allowed. For this reason the reaction conditions used for several well-known preparations of six-membered rings cannot be used to prepare the corresponding five-membered rings. For example, treatment of phenethylamines with aldehydes and acid yields tetrahydroisochinolines (Pictet–Spengler synthesis), but treatment of benzylamines under these conditions does not yield dihydroisoindoles (Scheme 9.6).

It might, at first glance, come as a surprise that, despite the ban on 5-endo-trig cyclizations, 5-endo-dig cyclizations are allowed. A possible reason for this observation is that intramolecular nucleophilic or electrophilic attack at an alkyne can proceed with the substrate in a flat conformation, because two orthogonal π^* (or π) orbitals are available. Similarly, hydroxymethyl allenes cyclize on treatment with a base (Scheme 9.7), because the terminal π^* orbital of the allene and the hydroxymethyl group can readily achieve a synperiplanar orientation. Intramolecular



Scheme 9.6. Formation of heterocycles by 6-endo-trig cyclization [14].

nucleophilic attack at the C–C double bond in a homoallylic alcohol or amine, on the other hand, requires an out-of-plane approach of the nucleophile to the alkene, with a significant build-up of strain and thus a high barrier of activation. The cyclization of 3-butyne-1-ols or alkynylamines can, alternatively, also be catalyzed by a variety of transition metals [15, 16].

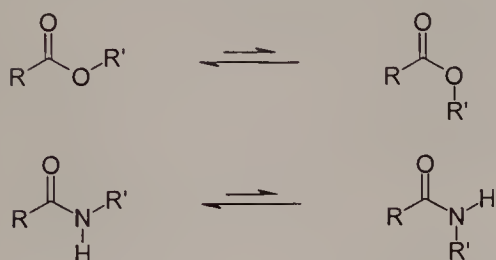


Scheme 9.7. Examples of 5-endo-dig cyclizations [17–21] and 5-endo-trig cyclizations of allenes [22].

9.3

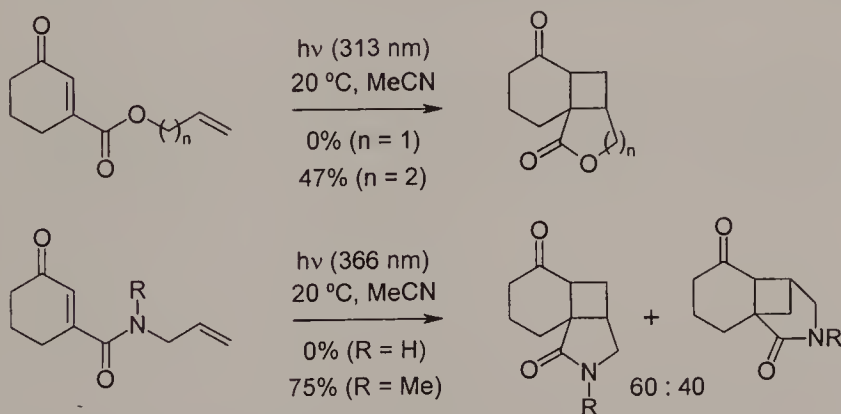
Structural Features of the Chain

Cyclizations will only proceed if the substrate has or can readily attain a conformation in which the two reacting groups are in close proximity. Hence, substrates of low flexibility must already have the correct arrangement of functional groups to enable their reaction. Such preorganization can significantly enhance the rate of cyclizations, and even promote reactions which would not take place intermolecularly (Section 3.3). On the other hand, if the conformation required for cyclization is energetically unfavorable, the cyclization will not proceed, even if the two functional groups would readily react intermolecularly. Not only alkenes, but also oximes, *N*-monosubstituted amides ($RCONHR'$), or esters, for example, are flat and have a high barrier of rotation for the interconversion of *Z* and *E* conformers [23]. Because the *Z* conformation is preferred by amides and esters [24] (Scheme 9.8), cyclizations of amides or esters to yield lactams or lactones, respectively, do not always proceed smoothly. Catalysis by acids may in some cases facilitate the required change of conformation of amides [25, 26].



Scheme 9.8. Preferred conformations of esters and amides.

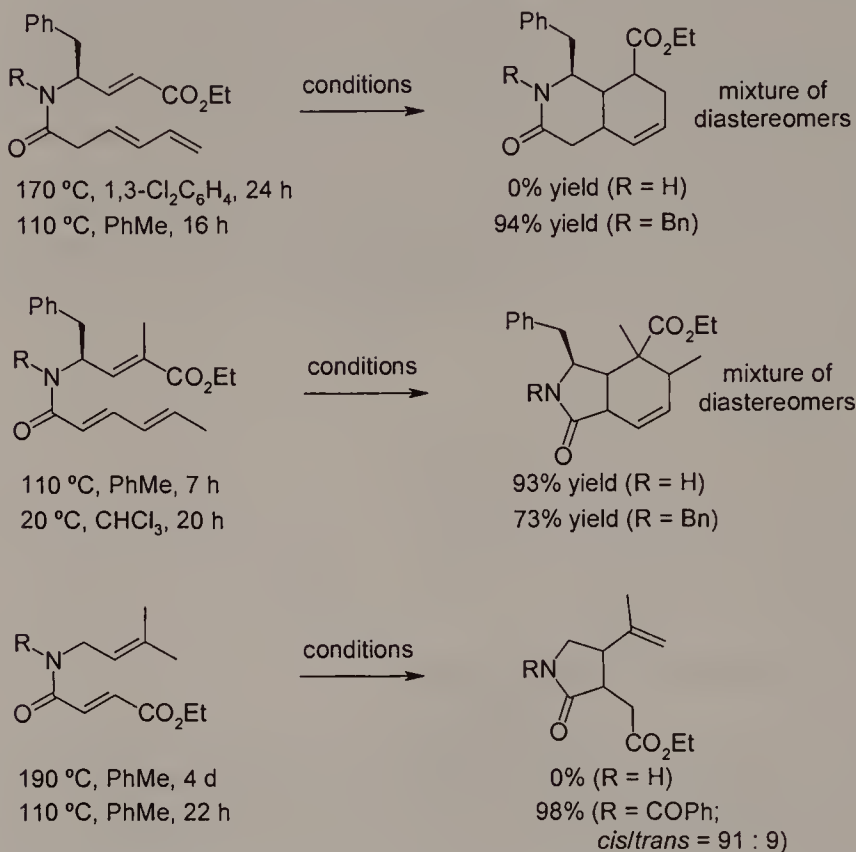
Some examples of photolytic intramolecular $[2 + 2]$ cycloadditions which lead to the formation of lactones and lactams are sketched in Scheme 9.9. The allyl ester and *N*-monosubstituted amide do not undergo cyclization, probably because of the high energy of the required *E* conformers. Cyclization of the homoallyl ester does,



Scheme 9.9. Formation of lactones and lactams by intramolecular $[2 + 2]$ cycloaddition [27].

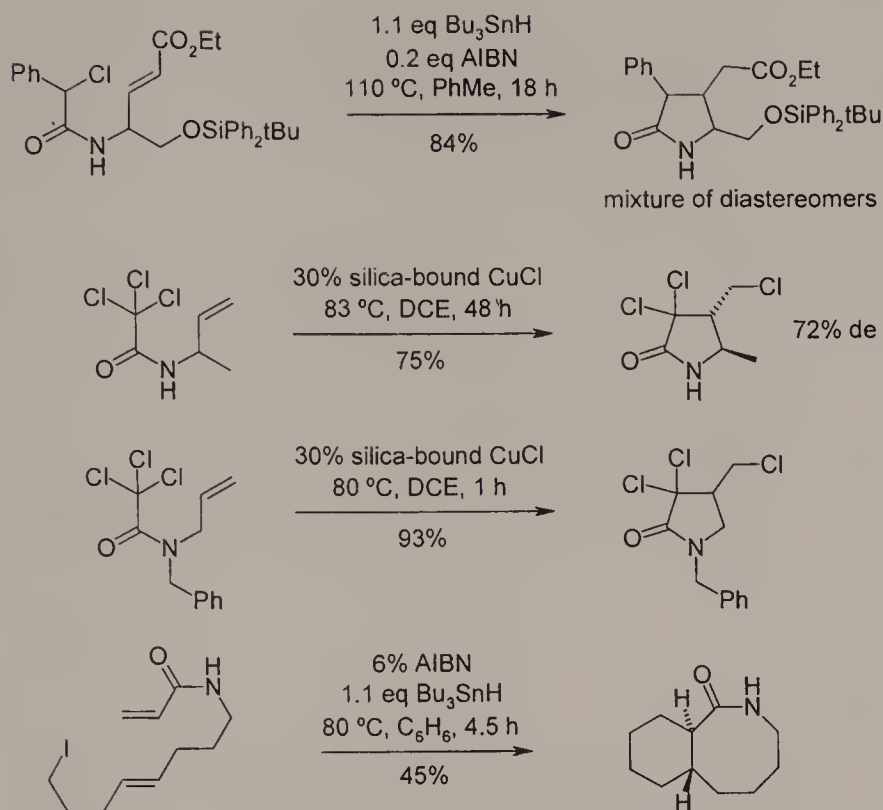
however, proceed well because of the higher flexibility of this substrate. For the *N*-allyl-*N*-methyleamide both possible conformations have similar energy and will be equally populated; cyclization also proceeds smoothly in this case.

Similarly, only *N*-substituted lactams are formed readily by intramolecular Diels–Alder or ene reactions (Scheme 9.10). Lactams without a substituent on the nitrogen can either not be prepared, or require higher reaction temperatures or longer reaction times than the preparation of similar, *N*-substituted lactams.



Scheme 9.10. Formation of lactams by intramolecular Diels–Alder and ene reaction [25, 28]

Cyclizations proceeding via radicals are, apparently, better suited to the preparation of *N*-unsubstituted lactams (Scheme 9.11). Nevertheless, in this type of cyclization also the formation of *N*-substituted lactams proceeds more rapidly and more cleanly.

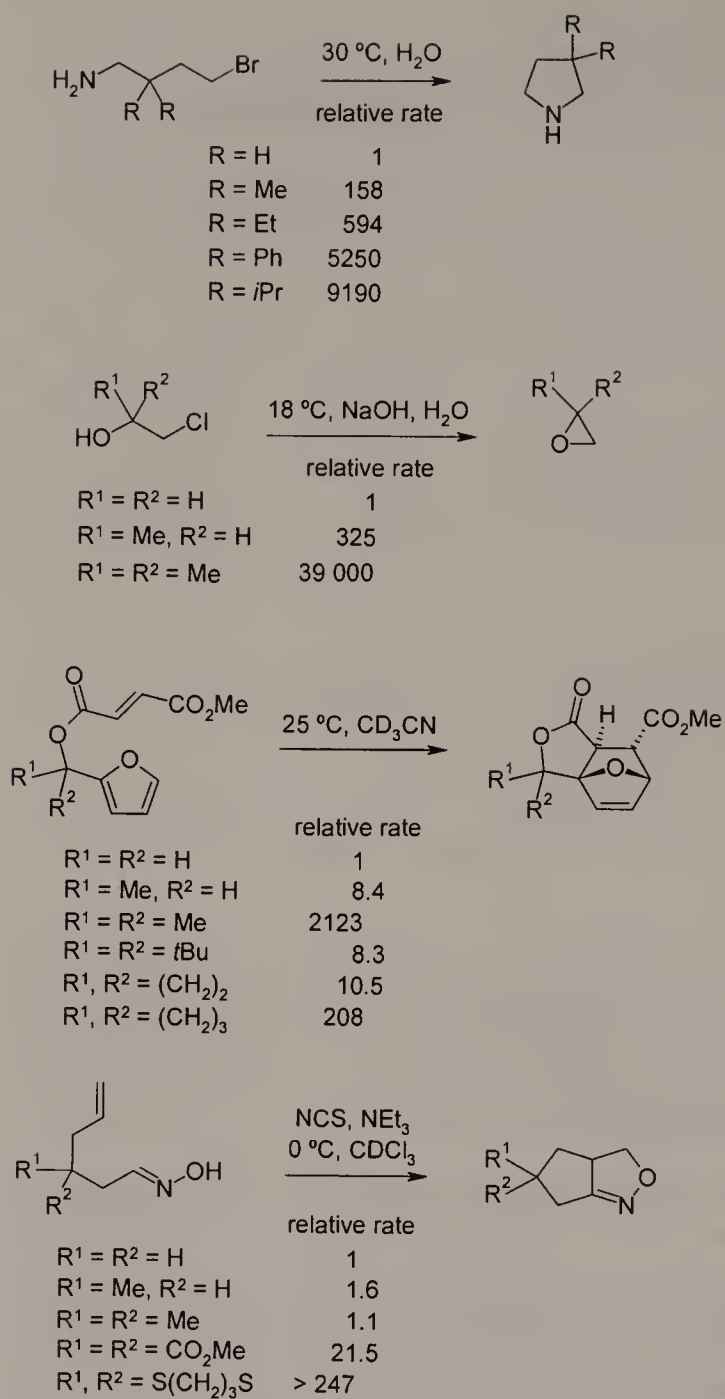


Scheme 9.11. Formation of lactams by intramolecular addition of radicals to C–C double bonds [29–31].

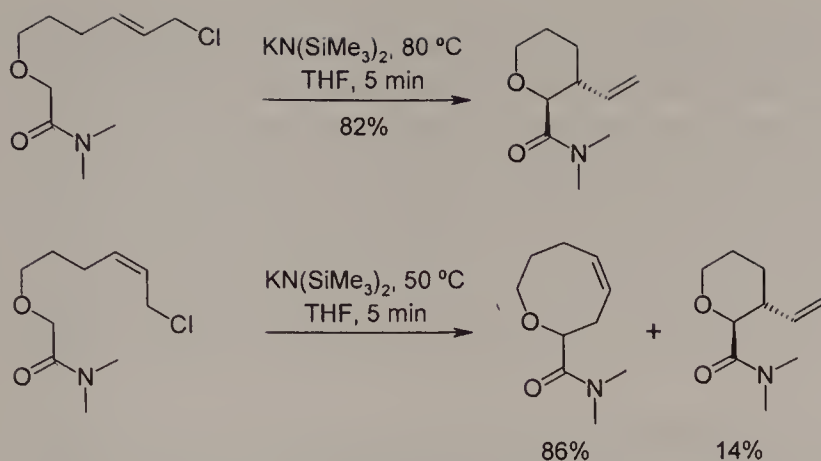
Alkylene chains with geminal dialkyl substitution have been shown to cyclize more readily than the corresponding unsubstituted compounds (Scheme 9.12). This effect can be used to achieve cyclization which might not occur without geminal disubstitution (see, e.g., Scheme 9.21) [32]. The magnitude of this effect is, however, highly dependent on the type of reaction and product, as illustrated by the examples in Scheme 9.12.

Two possible reasons for this effect have been suggested – angle compression at the substituted carbon and “the reactive rotamer effect” [34], i.e. facilitation, by the two alkyl groups, of the generation of an energy-rich conformation suitable for promoting the cyclization. The two last examples of the intramolecular Diels–Alder reaction in Scheme 9.12 indicate that angle compression does not have a decisive effect on reaction rate enhancement in this system, because in these two instances (1,1-disubstituted cyclopropane and cyclobutane) angle enlargement rather than angle compression will occur [34].

Cyclizations proceeding by intramolecular $\text{S}_{\text{N}}2$ reactions are usually irreversible, and will, therefore, not necessarily yield the thermodynamically most stable product but that which is formed most quickly. Scheme 9.13 depicts a cyclization in which the outcome depends on the configuration of the starting alkene. Interestingly, the *cis* isomer gives mainly rise to a strained, eight-membered ether even though a path to the less strained tetrahydropyran is, in principle, accessible.



Scheme 9.12. Promotion of cyclizations by geminal disubstitution in the chain [33–36].



Scheme 9.13. Configuration-dependent cyclization of a chloroalkenyloxy acetamide [37].

9.4 Ring Size

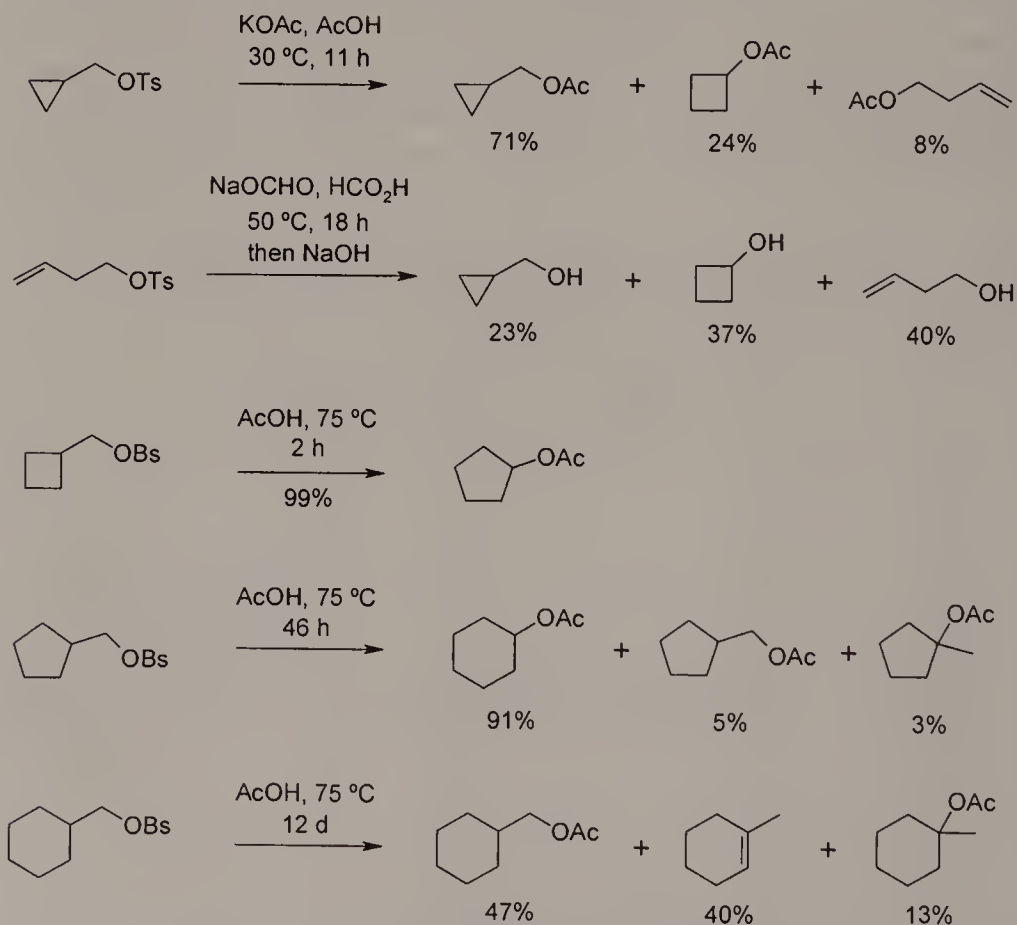
Comparison of the heats of combustion of cycloalkanes (Table 9.1) shows that cyclopropane, cyclobutane, and cyclononane yield more energy per methylene group than the other cycloalkanes. This can be attributed to strain resulting from bond-angle distortion (Baeyer strain), eclipsed conformations (Pitzer strain), and transannular, repulsive van der Waals interactions. Common (five- and six-membered) rings and large (more than twelve-membered) rings have little or no strain. This

Table 9.1. Heats of combustion (ΔH_c , kcal mol⁻¹) in the gas phase of n -membered cycloalkanes per methylene group, and enthalpies (ΔH_{cy}° , kcal mol⁻¹) and entropies (ΔS_{cy}° , cal mol⁻¹ K⁻¹) for the cyclization $\text{H}(\text{CH}_2)_n\text{H} \rightarrow \text{cyclo}-(\text{CH}_2)_n + \text{H}_2$ [42, 43].

n	$-\Delta H_c$	$-\Delta H_c + \Delta H_c(\text{C}_6\text{H}_{12})$	ΔH_{cy}°	$-\Delta S_{cy}^\circ$
3	166.3	8.9	37.6	7.7
4	163.9	6.5	37.1	10.9
5	158.7	1.3	16.7	13.3
6	157.4	0.0	7.9	21.2
7	158.3	0.9	16.6	19.8
8	158.6	1.2	20.1	19.0
9	158.8	1.4	17.8	
10	158.6	1.2	22.8	
11	158.4	1.0	21.9	
12	157.8	0.4	14.3	
13	157.7	0.3	15.6	
14	157.4	0.0	22.3	
15	157.5	0.1	12.3	
16	157.5	0.1	12.9	
17			7.1	

does, however, not mean that small rings or seven- to eleven-membered rings will always be more difficult to prepare than the other ring sizes. Cyclopropanes, for instance, are quite readily formed by cyclization because the reacting carbon atoms are already in close proximity and few bonds are required to assume a suitable conformation [38]. The entropy change during cyclopropane formation is, therefore, only small compared with those for formation of larger rings (Table 9.1). Very large rings, on the other hand, are difficult to prepare, despite their lack of strain, because the two functional groups which have to react with each other are far apart and unlikely to come into close proximity [39]. Macrocyclizations, therefore, often require high dilution or a template which can bring the two ends of the precursor together [40, 41].

The relative stability of cycloalkylmethyl carbocations is illustrated by the rearrangements illustrated in Scheme 9.14. Primary cycloalkylmethyl cations tend to undergo ring enlargement to yield secondary cycloalkyl cations if the resulting, larger cycloalkane is not significantly more strained than the starting cycloalkane. Thus, the cyclobutylmethyl cation rearranges cleanly to the cyclopentyl cation. Ring enlargement of the cyclopropylmethyl cation to a cyclobutyl cation or ring scission to the homoallyl cation are, however, not particularly favorable processes, because of the strong carbocation-stabilizing effect of the cyclopropyl group. The solvolysis of



Scheme 9.14. Rearrangement of cycloalkylmethyl carbocations [45–47].

cyclopropylmethyl derivatives usually gives mixtures of cyclopropylmethyl, cyclobutyl, and homoallyl derivatives [44], and some homoallyl cations can even cyclize to yield cyclopropane derivatives (second reaction, Scheme 9.14). That the cyclohexylmethyl cation does not undergo ring expansion to a cycloheptyl cation results from the stability of cyclohexane derivatives – hydride migration to yield a tertiary 1-methyl-1-cyclohexyl cation is the preferred reaction pathway in this instance (last example, Scheme 9.14).

9.4.1

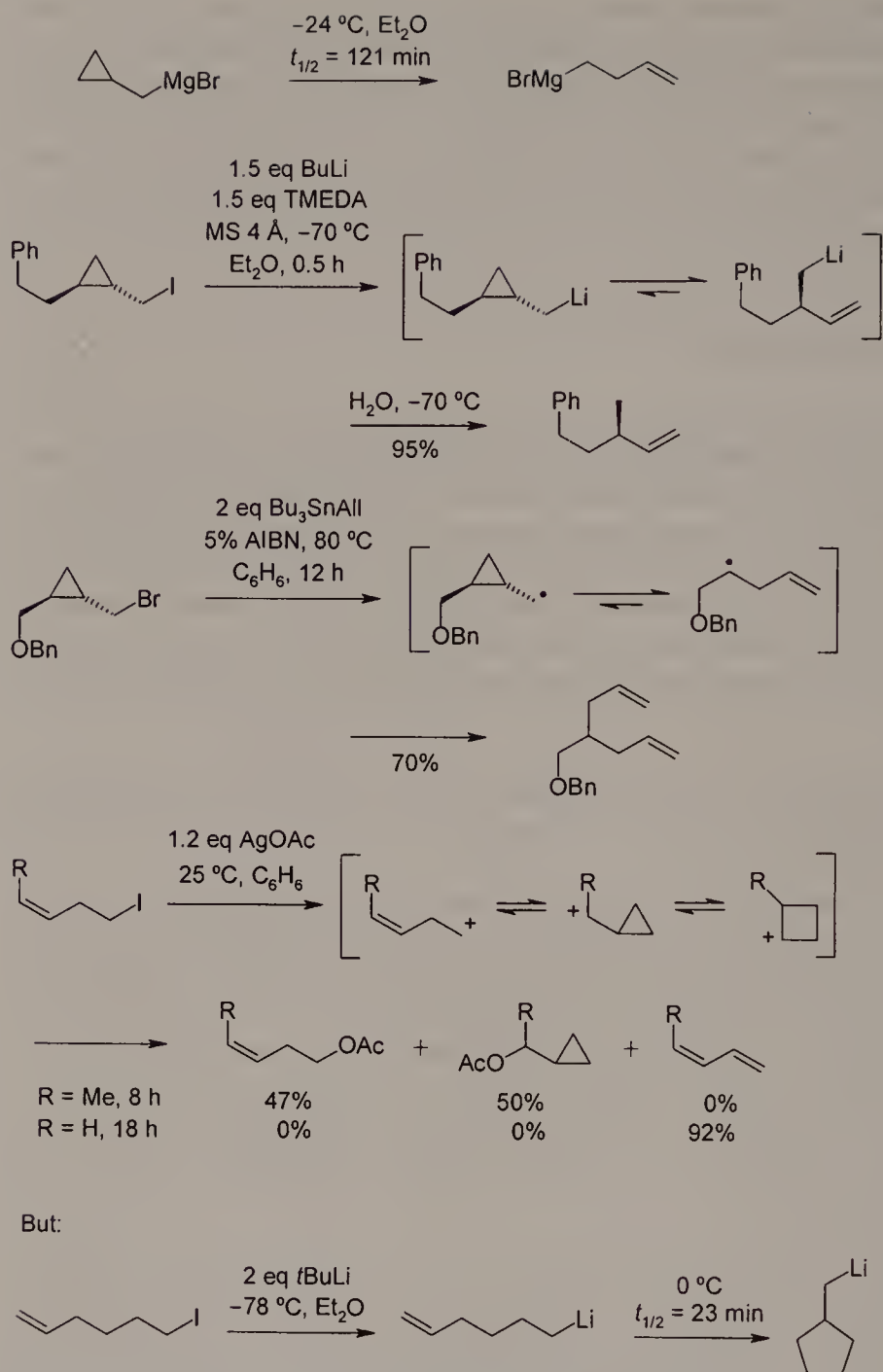
Formation of Cyclopropanes

The high strain energy of cyclopropane markedly affects its chemistry. As shown in Scheme 9.14, the cyclopropylmethyl carbocation is a relatively stable intermediate, which does not readily undergo ring expansion or ring scission. The cyclopropylmethyl radical [48] or cyclopropylmethyllithium [49] or -magnesium derivatives, on the other hand, tend to undergo rapid ring scission to the corresponding homoallylic intermediates [50], because the cyclopropyl group does not effectively stabilize either radicals or carbanions [51]. This behavior contrasts with the irreversible formation of cyclopentylmethyllithium from hexenyllithium (Scheme 9.15) or of other five- or six-membered rings from the corresponding alkenyllithium derivatives [52, 53].

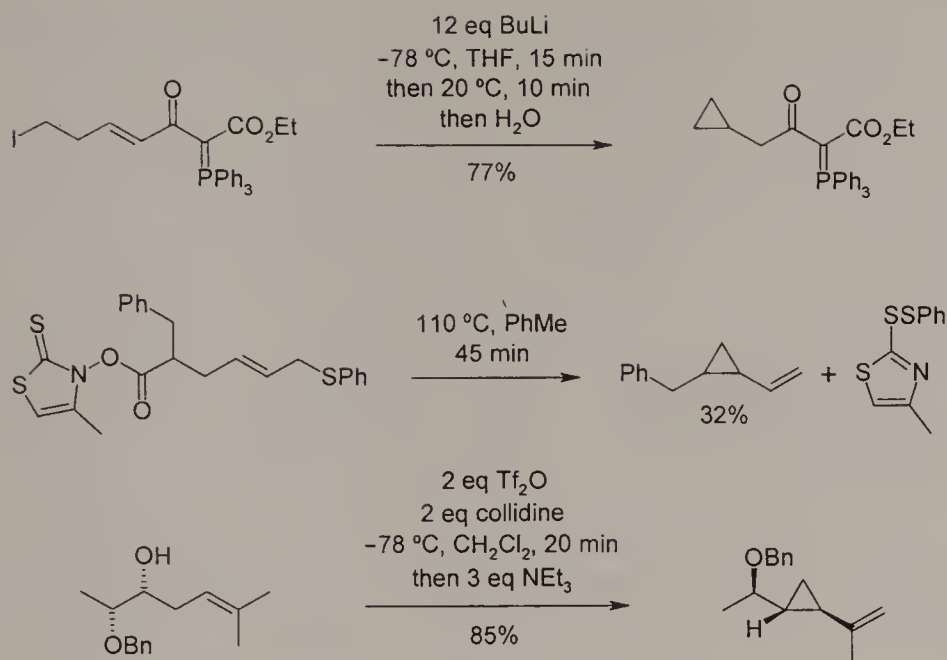
The cyclopropylmethyl Grignard reagent can only be trapped with electrophiles before rearrangement if the Grignard reagent is generated and treated with the electrophile at -75°C [54].

The facile ring scission of cyclopropylmethyl radicals or carbanions does not mean that cyclopropanes are kinetically unstable or synthetically inaccessible. Despite their high strain, cyclopropanes are not difficult to prepare by cyclization, and are sometimes even formed when reaction pathways to larger, less strained rings are available. The reason for this is the small entropy change which accompanies cyclopropane formation (Table 9.1) and the close proximity of the reacting centers [38]. This proximity of both reacting carbon atoms accelerates cyclizations to cyclopropanes significantly, and cyclization rates to cyclopropanes can be up to 1,000 times higher than the formation of cyclopentanes from homologous substrates [38] (Table 9.2).

Although the parent cyclopropylmethyl radical or lithium intermediates readily rearrange to homoallylic species, cyclopropanes can be prepared via similar intermediates if the corresponding cyclopropylmethyl derivatives are stabilized by suitable functional groups or trapped by an irreversible reaction (Scheme 9.16). Thus, 1-metallo-3-butenes cyclize readily to cyclopropanes if the double bond is substituted with an electron-withdrawing group [60], with an allylic leaving group [61], or is otherwise reactive towards nucleophiles [62]. Homoallyl radicals can cyclize irreversibly to cyclopropanes if the C–C double bond is substituted in the allylic position with a group with a weak bond to carbon, for example a phenylthio group [63]. Cyclopropanes can also be obtained in high yields by intramolecular addition of carbocations to alkenes (last reaction, Scheme 9.16).



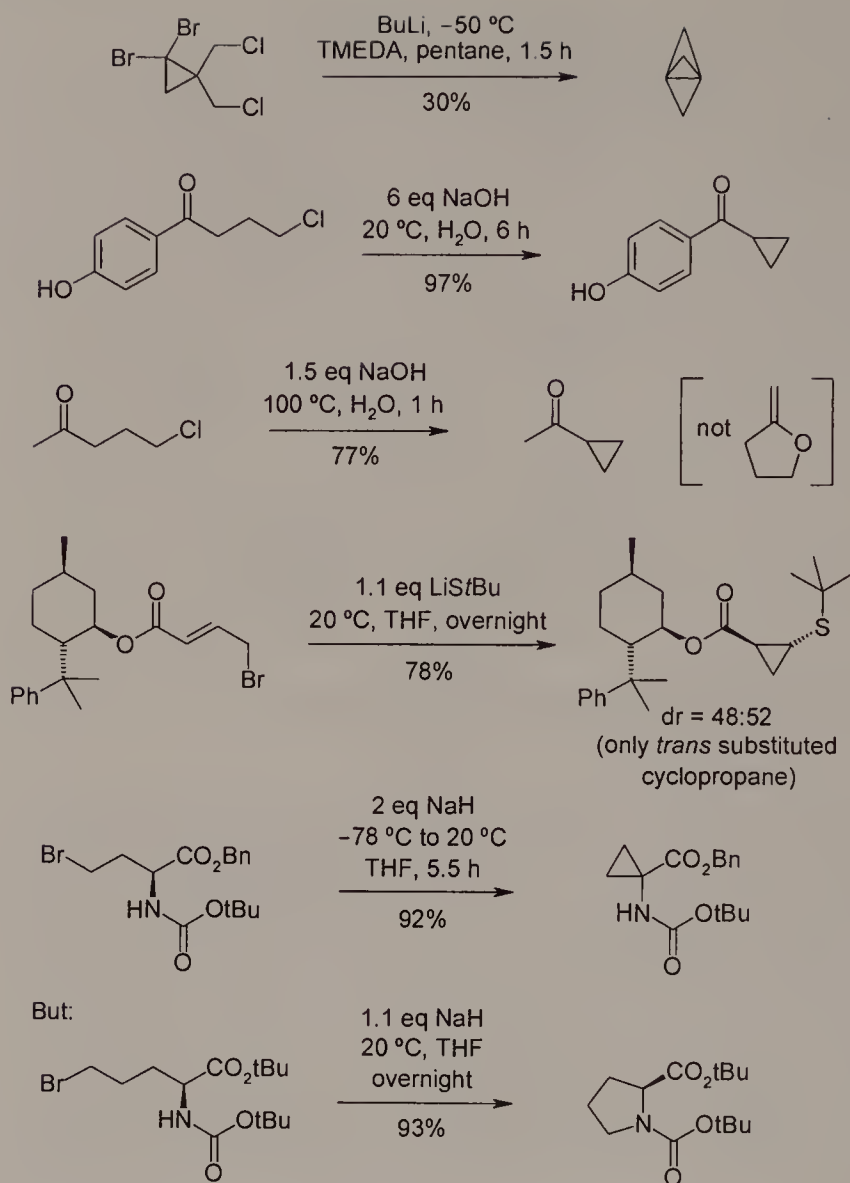
Scheme 9.15. Reactivity of cyclopropylmethyl carbanions, radicals, and carbocations [55–59].



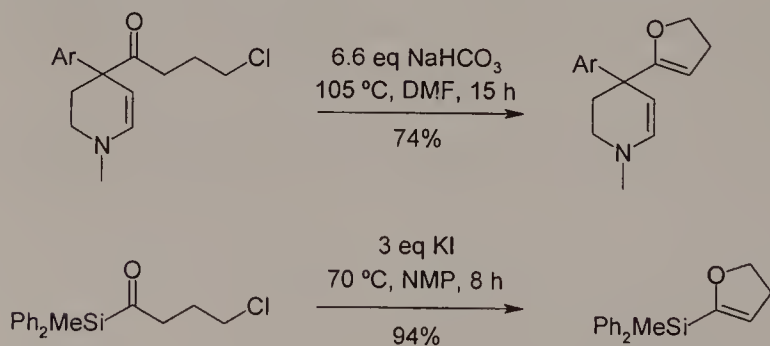
Scheme 9.16. Preparation of cyclopropanes by intramolecular addition of radicals, carbanions, or carbocations to C–C double bonds [63–65].

Examples of the preparation of cyclopropanes by intramolecular nucleophilic substitution are illustrated in Scheme 9.17. The first example is a synthesis of [1.1.1]propellane, which yields the product in acceptable yields, despite the high strain and poor stability of this compound [66]. The second and third examples illustrate the remarkable ease with which 3-halopropyl ketones cyclize to yield cyclopropanes instead of cyclic, five-membered enol ethers or ketones. Similarly, carbamates of 2-haloethylglycine esters do not undergo intramolecular *N*- or *O*-alkylation on treatment with bases, but yield cyclopropanes instead [67, 68]. Some nucleophiles can undergo Michael addition to 3-halomethyl acrylates faster than direct S_N2 reaction, to yield cyclopropanes by cyclization of the intermediate enolates (fourth example, Scheme 9.17) [69].

Because of the readiness with which cyclopropanes are formed from 3-halopropyl ketones, cyclization of the latter to dihydrofurans is difficult, and few examples of such cyclizations have been reported (Scheme 9.18). Acylsilanes, on the other hand, are more nucleophilic at oxygen than ketones, and readily undergo intramolecular *O*-alkylations [73–75].



Scheme 9.17. Preparation of cyclopropanes by intramolecular S_N2 reactions [66–68, 70–72].



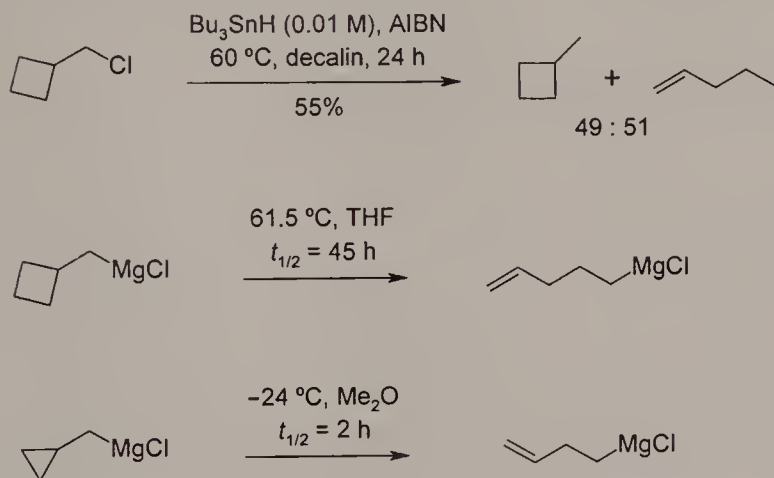
Scheme 9.18. Formation of dihydrofurans from 3-chloropropyl ketones and acylsilanes [74, 76]. Ar = 2,3-dimethoxyphenyl.

9.4.2

Formation of Cyclobutanes

Cyclobutanes are usually more difficult than cyclopropanes to prepare by cyclization. Although their ring strain is as high as that of cyclopropanes, more bonds must assume a suitable conformation for cyclobutane formation, resulting in a higher entropic barrier (Table 9.1).

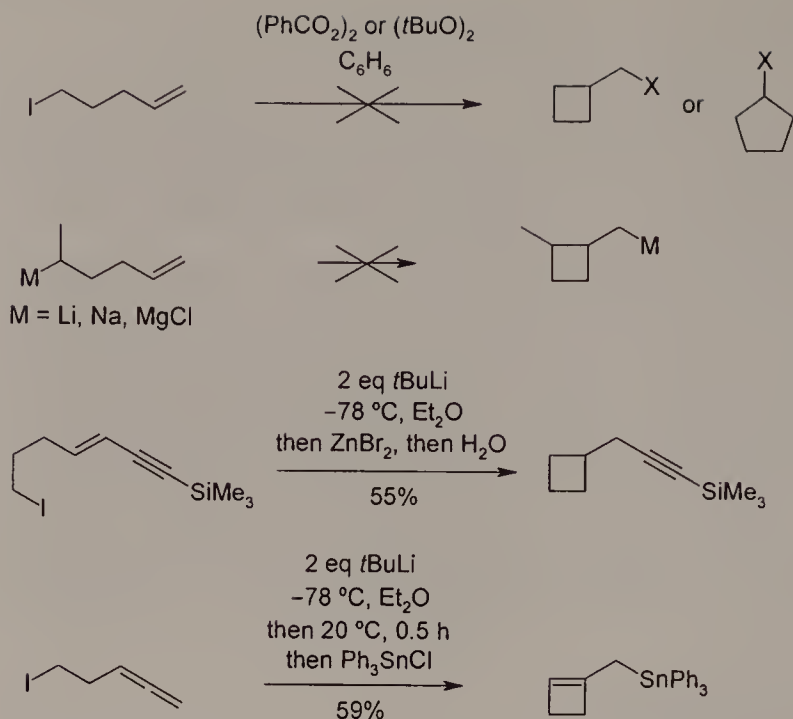
Ring scission of cyclobutylmethyl radicals or carbanions is significantly slower than that of the corresponding cyclopropylmethyl intermediates. Thus, rearrangement of the cyclopropylmethyl radical to the homoallyl radical is extremely rapid ($k = 1.3 \times 10^8 \text{ s}^{-1}$ at 25°C), and has often been used as a radical clock [48, 50, 77]. Ring scission of cyclobutylmethyl radicals, on the other hand, is approximately five orders of magnitude slower [78], and these radicals can therefore be trapped intermolecularly before ring opening has occurred (Scheme 9.19). Similarly, although cyclopropylmethyl Grignard reagents or organolithium compounds often rearrange even at low temperatures, the corresponding cyclobutyl derivatives are substantially more stable (Scheme 9.19).



Scheme 9.19. Reactivity of cyclobutylmethyl and cyclopropylmethyl carbanions [55, 79] and radicals [80].

Cyclobutanes can be formed by intramolecular addition of carbanions or radicals to C–C double bonds only if the latter are substituted with electron-withdrawing groups (see, e.g., Schemes 9.20 and 9.21) [81] or otherwise activated toward attack by nucleophiles. Activation by an alkynyl group or a cumulated double bond can be sufficient to promote cyclobutane formation (Scheme 9.20). Unactivated alkenes, however, do not usually undergo cyclization to cyclobutanes via intramolecular addition of carbanions or radicals.

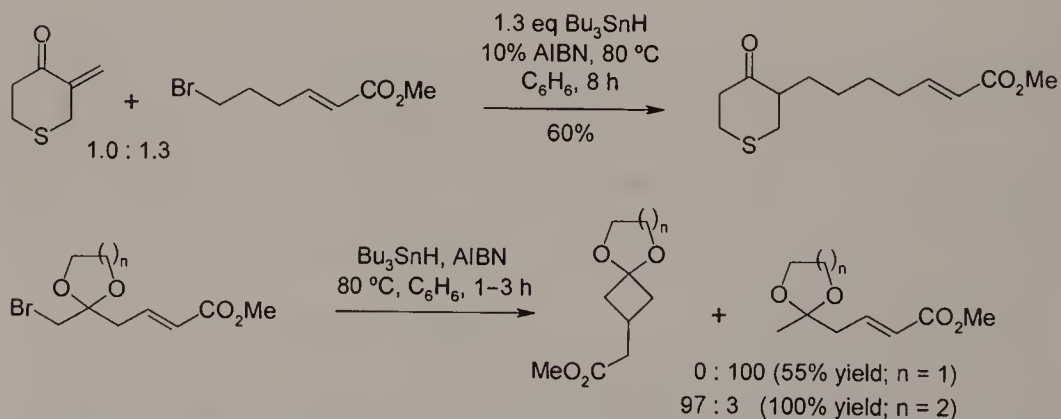
The fact that cyclobutanes are not readily formed is further illustrated by the reactions shown in Scheme 9.21. The radicals formed from the sketched (haloalkyl)acrylates or related (haloalkyl)acrylonitriles [85] can, in principle, cyclize to yield cyclobutane derivatives, but instead these intermediates react intermolecularly [86] or are



Scheme 9.20. Formation of cyclobutanes by intramolecular addition of organometallic reagents to C–C double bonds [60, 82–84].

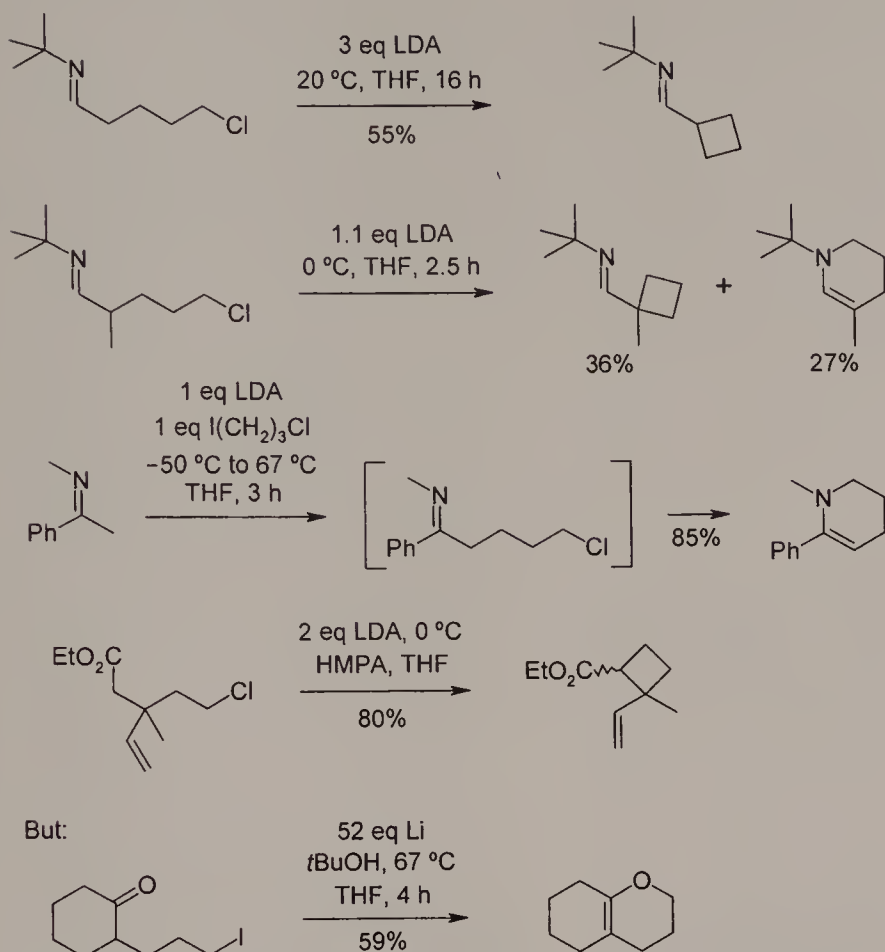
reduced before cyclization. Cyclobutane formation can sometimes be promoted by introduction of substituents at the chain [32, 85].

Intramolecular nucleophilic displacements are sometimes better suited to difficult cyclizations than additions to C–C multiple bonds, because nucleophilic substitutions are usually irreversible. Some metalated 4-halobutyl imines cyclize to yield cyclobutanes rather than six-membered cyclic enamines (Scheme 9.22). If alkoxides are used as bases, however, exclusive *N*-alkylation is observed. No examples could be found of the cyclization of 4-halobutyl ketones to cyclobutyl ketones, but 5-halopen-



Scheme 9.21. Reactions of 3-(3-bromopropyl)acrylates [32, 87].

tanoic esters and amides, 5,6-epoxynitriles [88, 89], and 2-(2,3-epoxy-1-propyl)malonates [90] do undergo intramolecular C-alkylation to yield cyclobutane derivatives (Scheme 9.22).



Scheme 9.22. Formation of cyclobutanes from enolates and metalated imines [91–94].

9.5 Heterocycles

The relative rates of formation of saturated heterocycles by intramolecular alkylation of the heteroatom do not correlate exactly with those of formation of carbocycles. For heterocycles, five-membered rings are usually formed faster than three-membered rings, whereas for carbocycles the opposite is observed (i.e. cyclopropanes are formed faster than cyclopentanes) (Table 9.2). For heterocycles and for carbocycles the formation of five-membered rings is faster than the formation of six-membered rings, and four-membered rings are usually formed more slowly than six-membered rings. The formation of five- and six-membered hetero- or carbocycles is usually highly favored over competing intermolecular reactions.

The relative rates given in Table 9.2 should be used as a rough guideline only, because small structural variations or different reaction conditions can alter the cyclization rates significantly.

Table 9.2. Relative rates of the reaction $\text{HNu}(\text{CH}_2)_n\text{X} \rightarrow \text{cyclo-Nu}(\text{CH}_2)_n + \text{HX}$ as a function of product ring size.

Ring size	HNu/X $\text{NH}_2/\text{Br}^{\text{a}}$	OH/Cl^{b}	PhS/Cl^{c}	$\text{CO}_2\text{H/Br}^{\text{d}}$	$\text{E}_2\text{CH/Cl}^{\text{e}}$
3	0.29	215	5.0	8.46×10^{-4}	125,000
4	3.98×10^{-3}	0.05	0.026	0.92	0.19
5	72.5	285	1.0	100	1,250
6	1.0	1.0		1.0	1.0
7	4.78×10^{-3}			3.73×10^{-3}	
8				3.85×10^{-5}	
9				4.23×10^{-5}	
10				1.31×10^{-4}	

a) H_2O , 25 °C [95, 96]

b) H_2O , NaOH , 30 °C [97]

c) rate of hydrolysis; H_2O , dioxane, 100 °C [98]

d) DMSO , 50 °C [36]

e) $\text{KO}t\text{Bu}$, $t\text{BuOH}$, 25 °C; $\text{E} = \text{CO}_2\text{Et}$ [99]

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10

Monofunctionalization of Symmetric Difunctional Substrates

10.1

Introduction

Many symmetric, difunctional organic compounds, for example diols, dihalides, diamines, or dicarboxylic acids, are commercially available, and the organic chemist is often tempted to base a synthetic strategy on the “desymmetrization” (i.e. monofunctionalization) of these, often attractively cheap, starting materials. Unfortunately, such monofunctionalization can quickly turn into a nightmare. Because unoptimized procedures will often yield product mixtures containing only small amounts of the desired product, its successful isolation will require perseverance and sometimes a good portion of luck. Therefore, before embarking in such ventures, alternative synthetic routes based on an unsymmetric starting material should always be seriously considered.

Difunctional compounds can be roughly divided into two groups – those in which chemical modification of one group significantly changes the reactivity of the other group and those in which no such change will occur. Monofunctionalization of the former can be easy and high-yielding whereas the second group will usually yield mixtures of starting material and the mono- and difunctionalized products when monofunctionalization is attempted. For instance, cyclic anhydrides such as succinic or glutaric anhydride are readily converted into monoesters or monoamides, because after acylation the remaining carboxyl group is no longer activated. Preparation of monoesters from other activated diacids (e.g. isophthalic acid dichloride) will, on the other hand, be more difficult, because the functional groups have little effect on each other. Similarly, Friedel–Crafts acylation of benzene leads to a strong decrease of electron density on the arene, which prevents further acylation. In Friedel–Crafts alkylations, however, no such deactivation occurs, and polyalkylated products will be obtained unless a large excess of arene is used.

Theoretical product ratios of monofunctionalized and difunctionalized product, as a function of the excess of difunctional reagent, for completely independent reactivity of both functional groups, are given in Table 10.1. These ratios show that purer monofunctionalized products will result when a large excess of difunctional reagent is used. The strategy of using a large excess of difunctional reagent will, however, be practicable only if this excess can be readily separated from the desired product.

Table 10.1. Theoretical product ratios of the reaction of a difunctional reagent A with a monofunctional reagent B ($A + B \rightarrow A + AB + AB_2$).

Starting material A/B	Products			
	A	AB	AB ₂	AB/AB ₂
1:2	0%	0%	100%	0
1:1.5	6%	38%	56%	0.7
1:1.33	11%	44%	44%	1
1:1	25%	50%	25%	2
1.5:1	44%	44%	11%	4
2:1	56%	38%	6%	6
3:1	69%	28%	3%	10
4:1	76.5%	22%	1.5%	14
5:1	81%	18%	1%	18

A further requisite for achieving the theoretical yield of monofunctional product is that both starting reagents are thoroughly mixed *before* extensive conversion to the products has occurred. If the reaction is rapid, it might proceed to completion as soon as the two reagents come into contact, and large amounts of difunctionalized product will result because the initially formed monofunctionalized product cannot diffuse away from the added reagent.

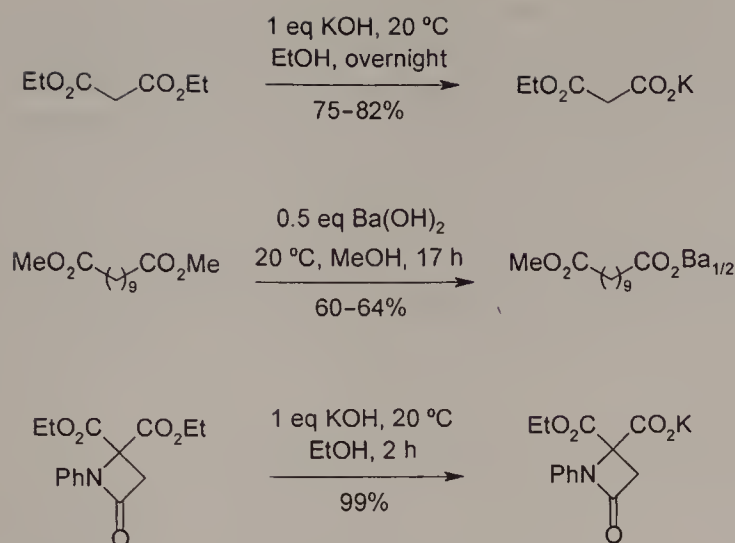
10.2

Monofunctionalization of Dicarboxylic Acids

Monoesters of symmetric dicarboxylic acids can be prepared either by monoesterification of a diacid [1] or by monosaponification of a diester. Dicarboxylic acids which can form five- or six-membered cyclic anhydrides are readily transformed into monoesters via these intermediates, but for diacids which cannot be converted into such cyclic anhydrides monosaponification of diesters seems to be more reliable than selective monoesterification. Monoesters or monoamides of succinic, maleic, glutaric, or related diacids can be rather unstable, because of the close proximity of a carboxyl group (see Section 3.3).

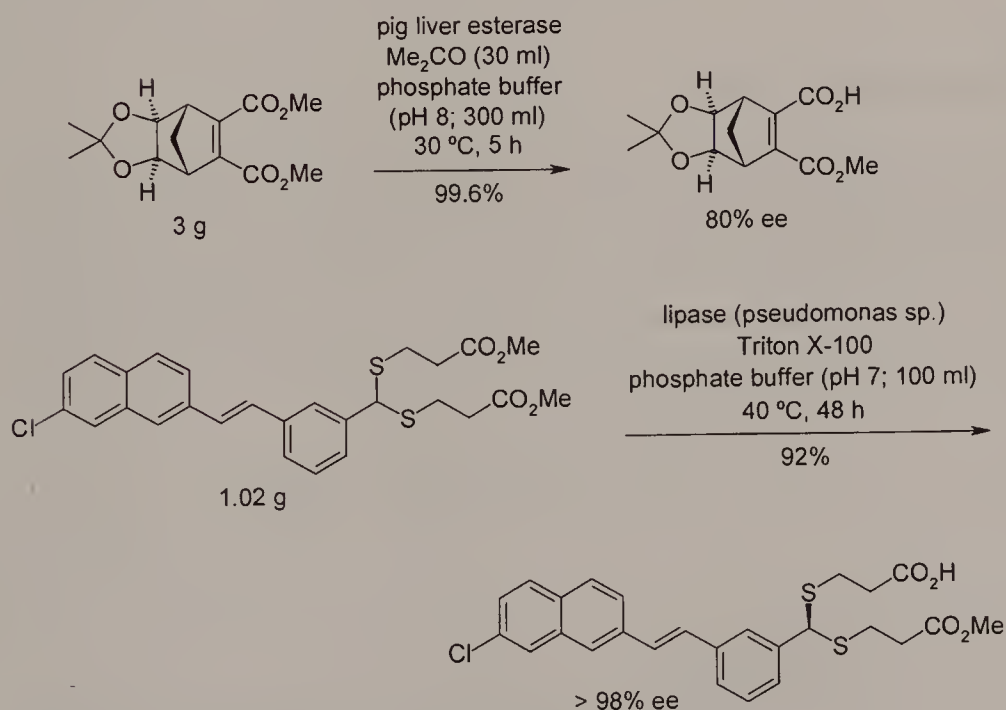
Diesters of α,ω -alkanedicarboxylic acids can be monosaponified by addition of one equivalent of hydroxide. Best results are obtained if conditions can be found under which the desired product precipitates from the reaction mixture. This is, for instance, observed for all the examples shown in Scheme 10.1. The products of monosaponification of malonic esters are significantly less electrophilic than the diesters, which leads to a highly selective reaction. This is, however, not so for the undecanoic diacid diester. With this compound precipitation of the monoester salt from the reaction mixture is presumably the main reason for the high yield obtained.

Symmetric diesters with enantiotopic alkoxy carbonyl groups can sometimes be monosaponified enantioselectively by use of esterases (Scheme 10.2) [5]. Enzymes



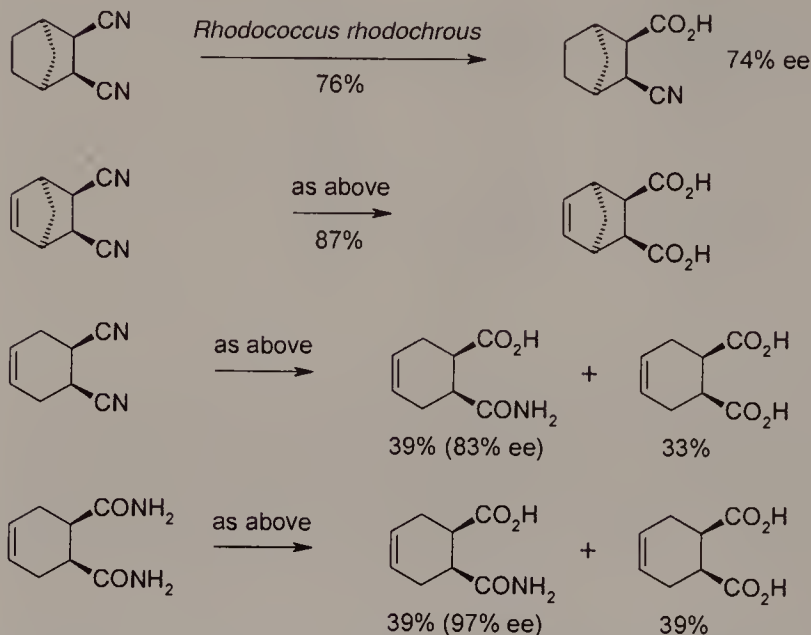
Scheme 10.1. Monosaponification of diesters [2–4].

are highly selective and can often discriminate between the diester and the monoester, even if the two functionalities are far apart from each other. This elegant method requires the diester to be soluble in water to some extent, because most enzymes require water as solvent to unfold their catalytic activity. Alternatively, addition of detergents might help to attain useful reaction rates [6]. A related strategy is the enzymatic monoesterification of symmetric dicarboxylic acids [7]. The main problem of these enzymatic reactions is that their outcome with a new substrate is difficult to predict and must always be established empirically.



Scheme 10.2. Enantioselective monosaponification of diesters [6, 8].

Dinitriles and diamides also can sometimes be partially hydrolyzed by use of enzymes. As with other enzymatic reactions, small structural modifications can substantially modify the suitability of a given substrate. Scheme 10.3 gives illustrative examples of the highly substrate-dependent hydrolysis of dinitriles and diamides by use of a microorganism.

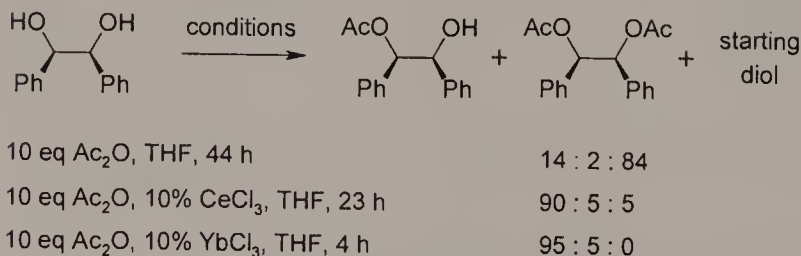


Scheme 10.3. Microorganism-mediated hydrolysis of dinitriles and diamides [9].

10.3

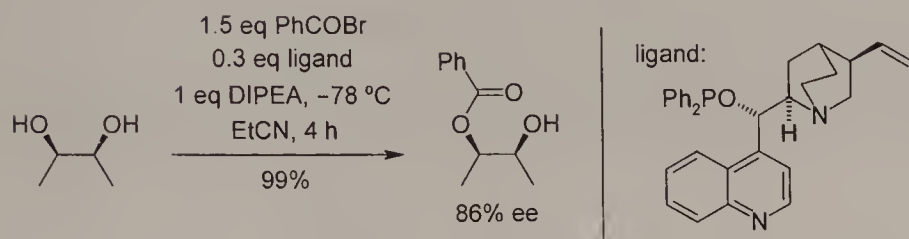
Monofunctionalization of Diols

The monoacylation of symmetrical diols has been extensively investigated, and several useful methods have been developed. 1,2-Diols can be monoacylated readily, presumably because the product is acylated more slowly than the starting diol (Scheme 10.4). A variety of catalysts, for example lanthanide salts [10, 11], zeolites [12, 13], and tin derivatives [14, 15] have been used to further improve the selectivity of this reaction. Orthoesters have also been successfully used as acylating agents for the monoacylation of 1,2-diols [16].



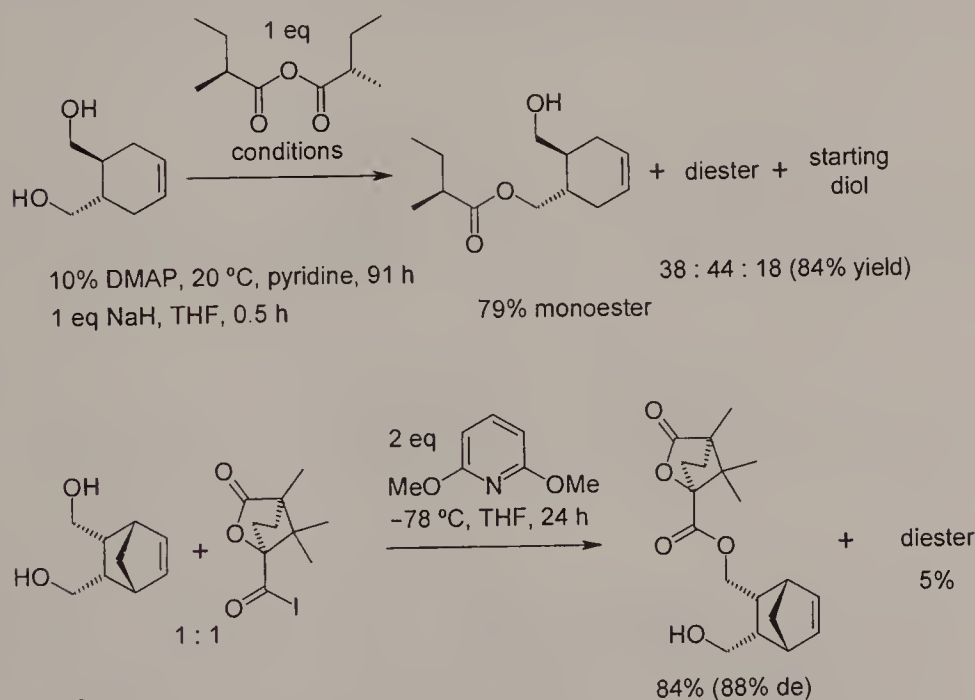
Scheme 10.4. Acetylation of *meso*-hydrobenzoin [11].

If the monoacylation of a diol with enantiotopic hydroxyl groups is performed in the presence of a chiral tertiary amine, a chiral diamine[17], or a chiral phosphine[18], the acylation can proceed with high enantioselectivity, as illustrated by the example shown in Scheme 10.5. These reactions require stoichiometric amounts of a tertiary amine (DIPEA or NEt_3), and the chiral tertiary amine must, therefore, be significantly more nucleophilic than DIPEA or NEt_3 , in order to react faster with the acylating agent to generate a chiral *N*-acyl ammonium salt. This salt is believed to be the intermediate which transfers the acyl group to the alcohol. Pyrrolidines, quinuclidines, or analogs of DMAP are usually much more nucleophilic than non-cyclic tertiary amines, and are therefore effective nucleophilic catalysts [19].



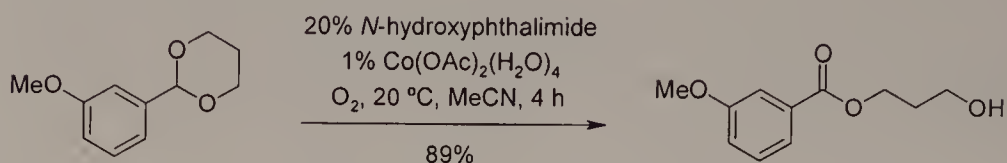
Scheme 10.5. Enantioselective monobenzoylation of a *meso*-1,2-diol [20].

Diols with more than two carbon atoms between the two hydroxyl groups may require more carefully controlled reaction conditions if a monoacylation is desired (Scheme 10.6). Suitable catalysts which promote the formation of monoacylated products include silica gel [21], zeolites [12], and tin(IV) derivatives [14, 22].



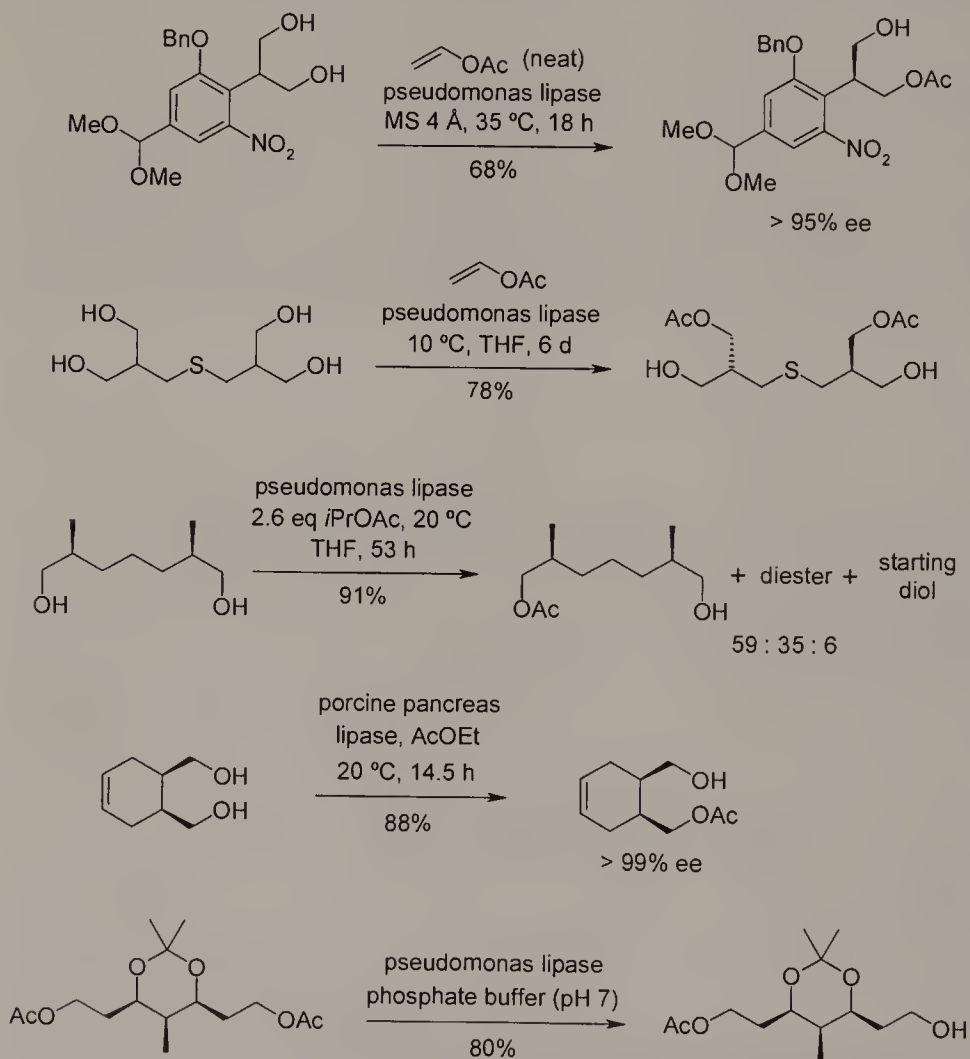
Scheme 10.6. Monoacylation of 1,4-diols [23, 24].

An alternative strategy for preparation of monoacylated 1,2- and 1,3-diols is oxidative cleavage of cyclic acetals prepared from a diol and an aliphatic or aromatic aldehyde (Scheme 10.7). For this purpose the required acetal does not need to be isolated, but can be generated in situ [25]. Acetals prepared from strongly electrophilic aldehydes, for example nitrobenzaldehydes, will, however, usually be difficult to oxidize (and to hydrolyze).



Scheme 10.7. Oxidative cleavage of acetals to yield monoacylated diols [26].

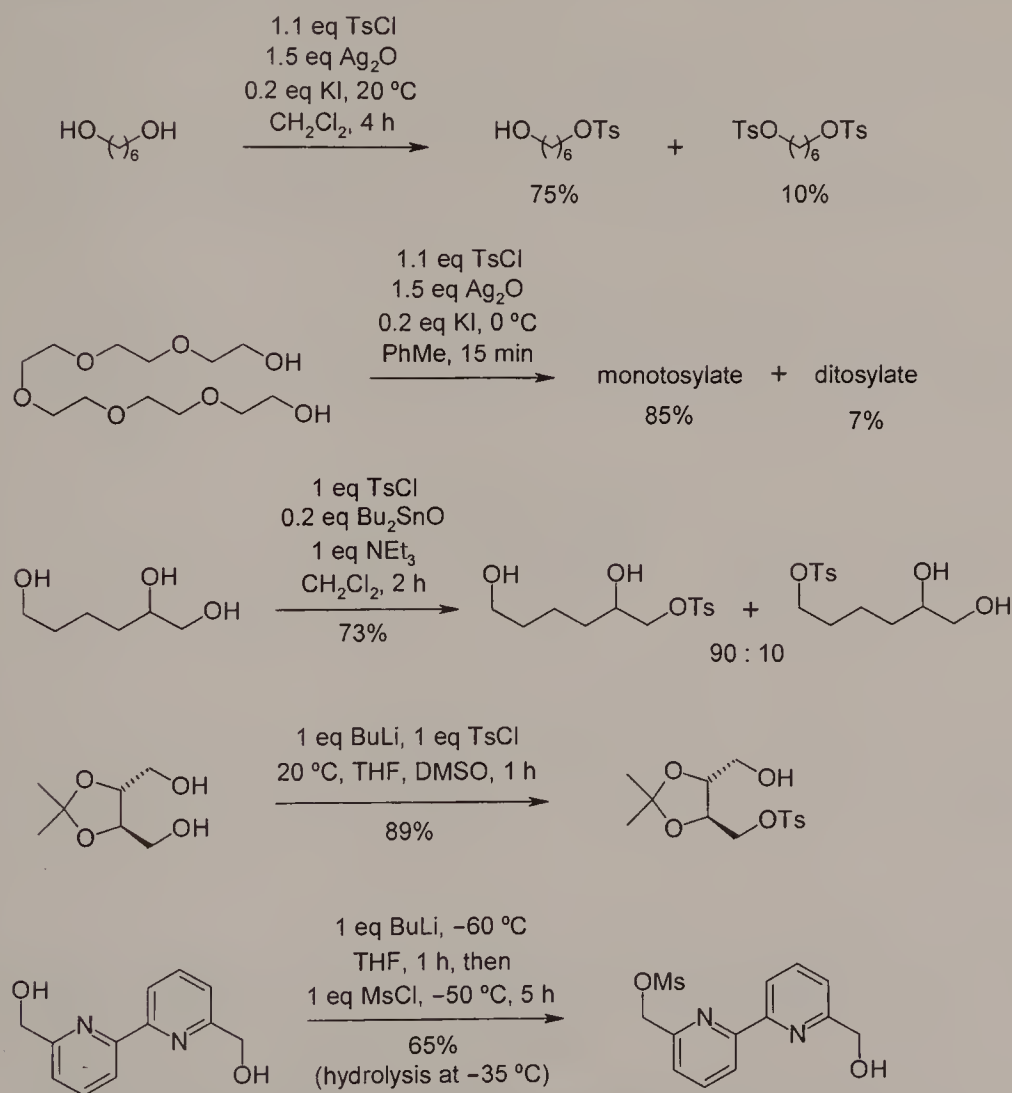
Diols can also be selectively monoacylated by treatment with an acylating agent of low reactivity (vinyl, 2,2,2-trifluoroethyl, phenyl, or ethyl esters) in the presence of catalytic amounts of an esterase (Scheme 10.8) [27]. Surprisingly, these enzymatic



Scheme 10.8. Enzymatic acetylation of diols and deacetylation of diacetates [30–34].

acylations can be conducted in pure organic solvents, but reaction times can be quite long. The absence of water drives these reactions in a direction opposite to that of normal esterase activity. The monoacylation will usually fail if the two hydroxyl groups are too far apart (e.g. >10 carbon atoms [28]). If the two hydroxyl groups are enantiotopic, enantiomerically enriched products can result [29]. Esterases can also be used to partially saponify diesters of symmetrical diols (last reaction, Scheme 10.8).

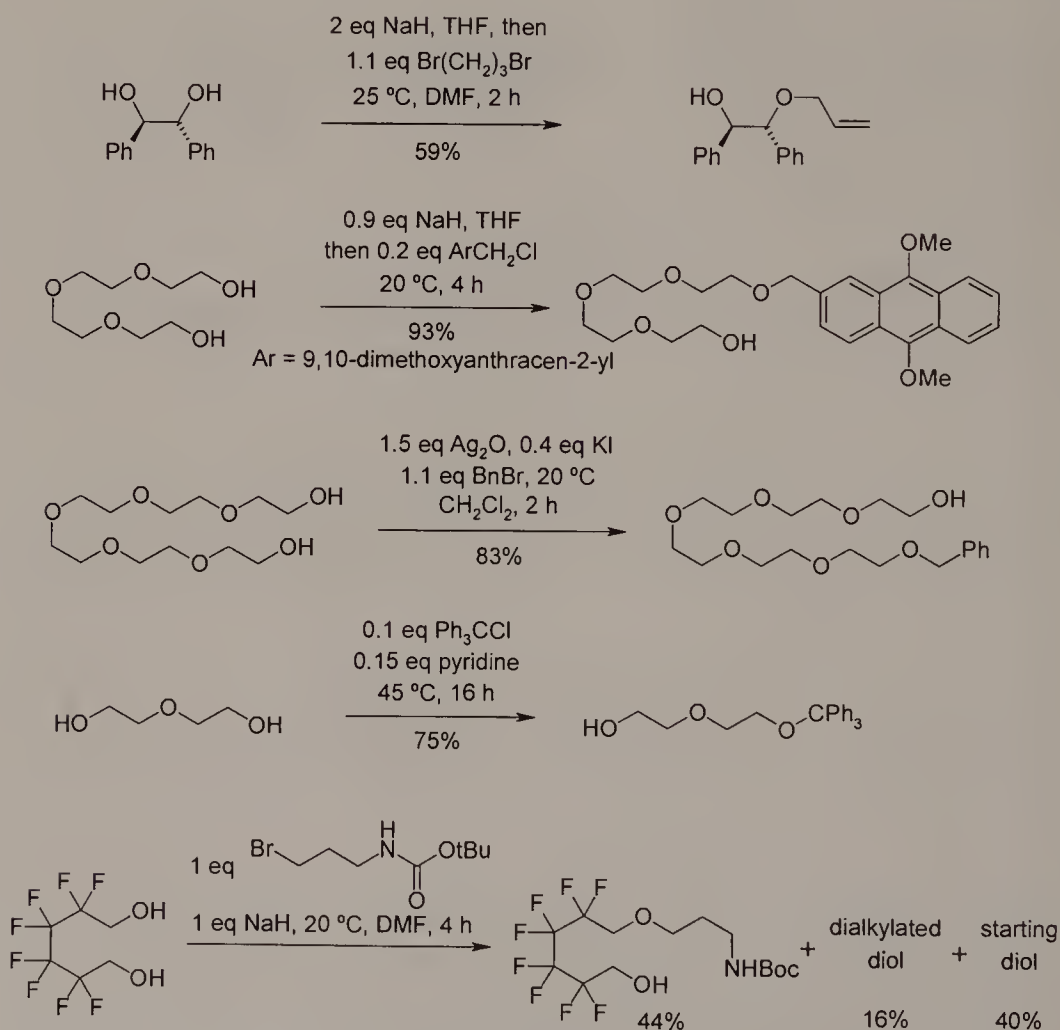
The reaction of arenesulfonyl chlorides with alcohols to yield sulfonates is relatively slow (if compared, e.g., with the formation of mesylates or sulfonamides), and treatment of diols with tosyl chloride can readily yield the statistically expected amount of monotosylated product [35, 36]. The selectivity of such reactions can sometimes be enhanced by additives such as AgO [37] or Bu₂SnO [38]. Deprotonation of the diol can be used to increase its nucleophilicity and thereby reduce the reaction time (Scheme 10.9). This strategy can, however, lead to problems, because the products are sensitive toward strong bases, and may cyclize, oligomerize, or undergo elimination.



Scheme 10.9. Monosulfonylation of diols [37–40].

The reaction of diols with alkylating agents can also be performed such that approximately the theoretical amount of monoalkylated product is obtained. Some substrates can even be monoalkylated [36, 41, 42] or monoarylated [43] with substantially higher yields than statistics would predict what must be due to the slowness of the second alkylation. This behavior, however, is not usually observed, and other strategies must usually be used to achieve clean monoalkylations. Use of excess diol will often furnish pure monoalkylated diol, but a suitable means of removal of excess diol will be required. In the examples sketched in Scheme 10.10 the products were purified by column chromatography, recrystallization, or distillation. As with acylations, the formation of monoalkylated diols can also be promoted by Ag_2O [44] or by transient protection with boron [45] or tin [46] derivatives.

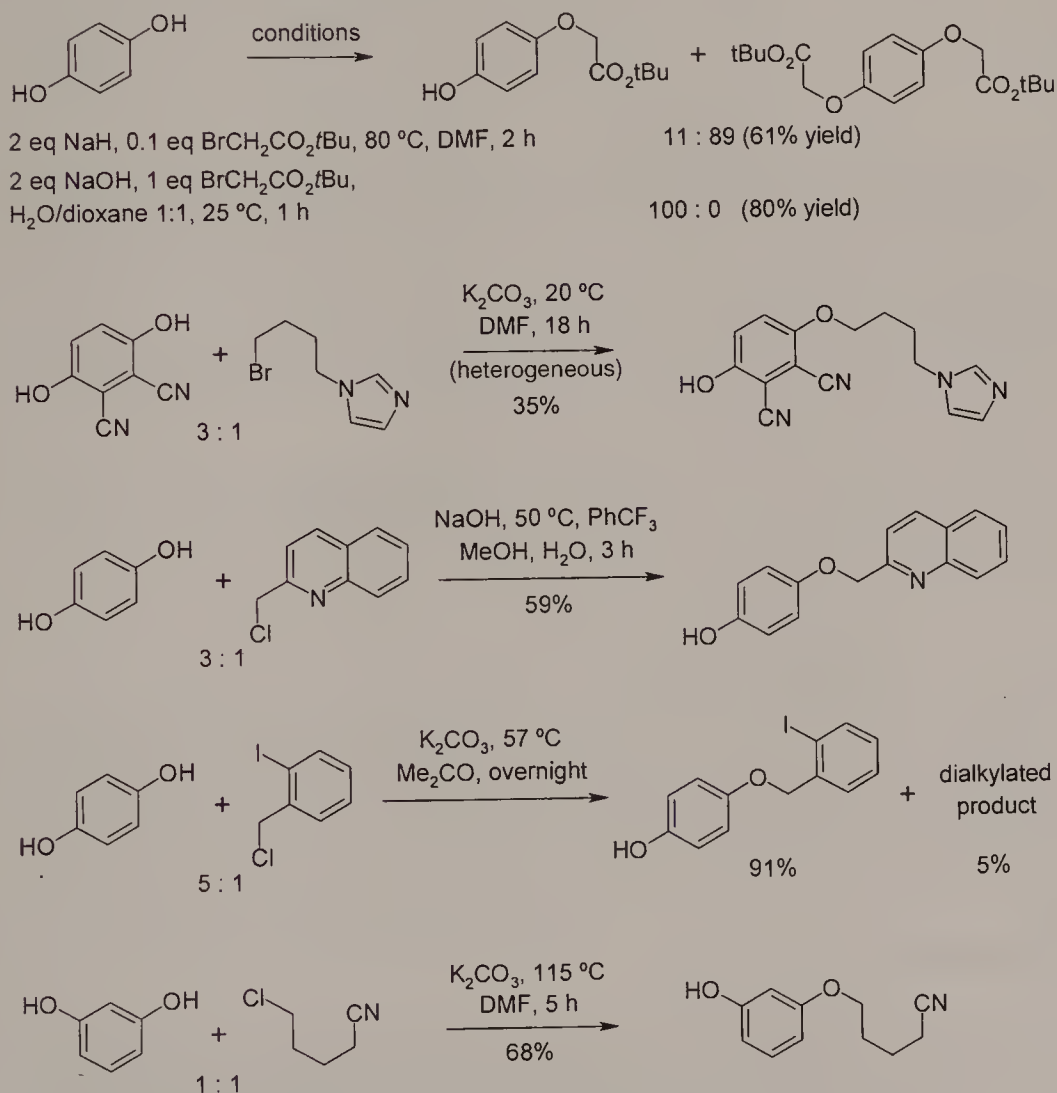
As mentioned above, the statistically predicted amount of monofunctionalized product can only be obtained if both reactants are thoroughly mixed. If the difunctional reagent is poorly soluble under the reaction conditions chosen, its concentration might be lower than that of the monofunctional reagent. This can lead to large



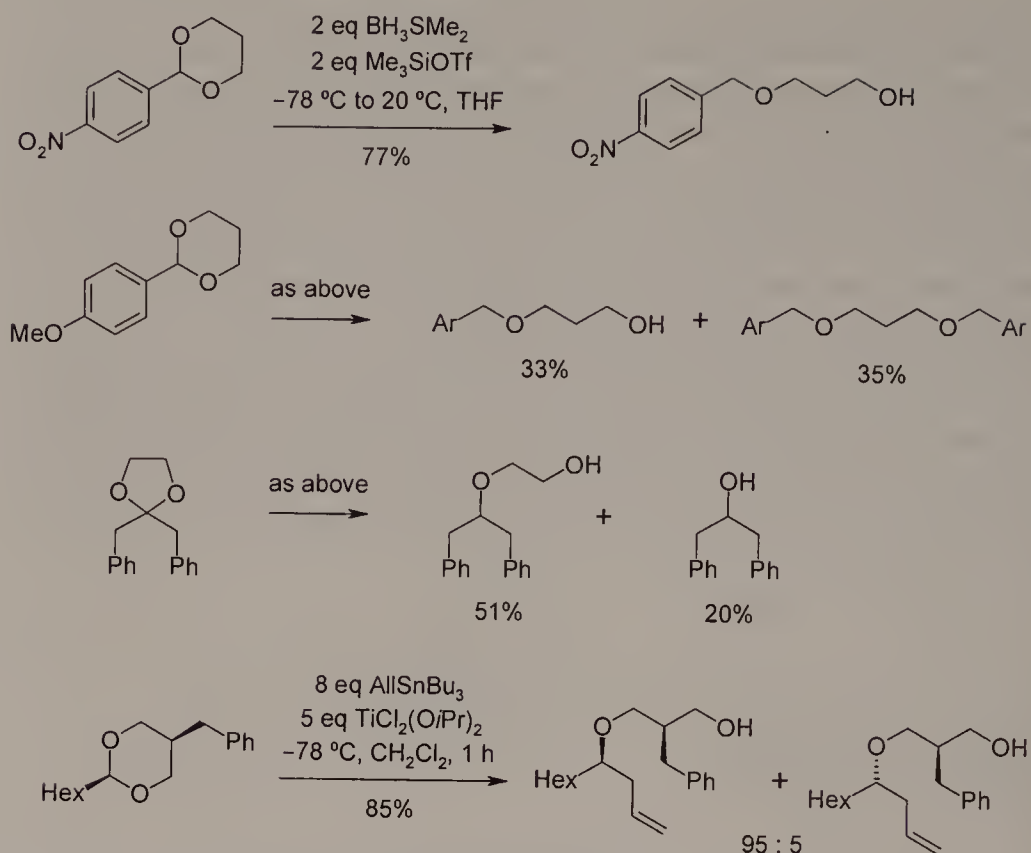
Scheme 10.10. Monoalkylation of diols [36, 42, 47–50].

amounts of difunctionalized product, even if a large excess of difunctional reagent has been used. This can happen readily during the monofunctionalization of polyhydroxybenzenes, because the salts of these compounds are often poorly soluble in organic solvents. Thus, the monoalkylation of hydroquinone is complicated by the low solubility of the dianion in organic solvents, which leads to heterogeneous reaction mixtures and large amounts of dialkylated products, even if a large excess of hydroquinone is used. This problem can be solved for certain electrophiles by using an aqueous solvent in which the dianion of hydroquinone is soluble (Scheme 10.11) [50]. Alternatively, partially alkylated polyhydroxybenzenes can also be prepared by partial dealkylation of polyalkoxybenzenes [51].

An elegant strategy for the preparation of monoalkylated 1,2- and 1,3-diols is the nucleophilic ring-opening of cyclic acetals by hydride or by other nucleophiles (Scheme 10.12) [46, 56]. Not all acetals undergo these reactions cleanly, and careful



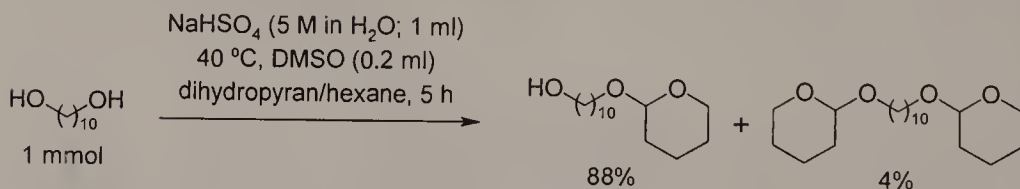
Scheme 10.11. Partial alkylation of polyhydroxybenzenes [50, 52–55].



Scheme 10.12. Nucleophilic ring-opening of acetals [57, 58]. Ar = 4-MeOC₆H₄.

optimization might be required for some substrates. Six-membered acetals are usually more reactive than five-membered acetals [57].

Diols can be protected as monotetrahydropyranyl ethers, and good yields have even been reported for substrates in which the two hydroxyl groups are far away from each other [59] (Scheme 10.13). The reasons for the higher reaction rate of the diol compared with the monoethers is unclear.



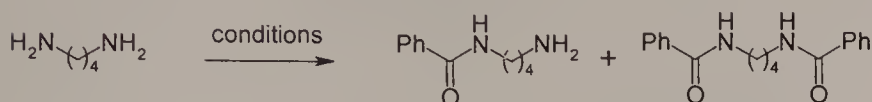
Scheme 10.13. Monotetrahydropyranylation of diols [60].

10.4

Monofunctionalization of Diamines

If diamines are treated with strong acylating or sulfonylating reagents, high yields of bis-derivatized products are usually obtained, even if a large excess of diamine is used [61] (Scheme 10.14). Because the derivatization reaction is very fast, it goes to

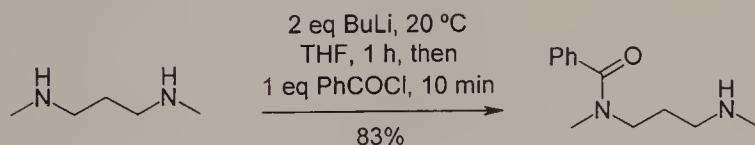
completion after each added droplet, before the monoacylated product can diffuse away from the added portion of acylating agent. The statistically expected yields of monoacylated diamines can, however, be obtained if less reactive acylating agents are used (e.g. benzyl esters in the presence of a lipase [62], *N*-hydroxysuccinimidyl esters [61, 63], methyl esters [64], ethyl esters [65], or amides [66]) or if the reagents are mixed at low temperatures, to prevent extensive reaction before complete mixing of the reacting partners has occurred. The reactivity of amines can be reduced by complexation with Lewis acids [67].



0.95 eq PhCOCl, THF	< 5 : 95 (95% yield)
0.2 eq PhCOCl, -78 °C, CH ₂ Cl ₂ , overnight	35 : 65
0.2 eq (PhCO) ₂ O, -78 °C, CH ₂ Cl ₂ , overnight	84 : 16
1 eq 9-BBN, THF, then 0.95 eq PhCOCl	90 : 10 (88% yield)

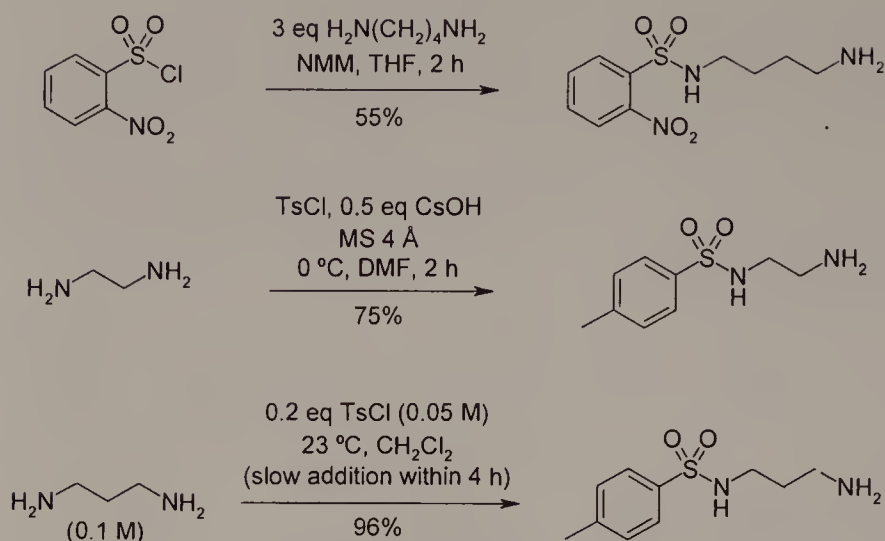
Scheme 10.14. Mono- and diacylation of putrescine [61, 67].

A further strategy for the monoacylation of symmetric diamines consists in deprotonating the diamine twice and treating the resulting dianion with one equivalent of acylating reagent (Scheme 10.15). In 1,2- and 1,3-diaminoalkanes the dianion will be significantly more reactive than the product, and high yields of monoacylated diamines can be obtained. This strategy is particularly suitable for monoacylation of piperazine and related diamines, but will not be suitable for diamines with a large distance between the two amino groups.



Scheme 10.15. Twofold deprotonation and monoacylation of diamines [68].

As for acylations with reactive acylating agents, the reaction of diamines with sulfonyl chlorides usually leads to large amounts of bis-sulfonylated diamine. Notable exceptions are shown in Scheme 10.16. The last example in Scheme 10.16, in which the electrophile was added slowly with a syringe pump, indicates that monosulfonylations can be successfully performed if the reagents are mixed efficiently. Lower reaction temperatures or less reactive sulfonylating reagents should further facilitate the formation of monosulfonylated diamines.

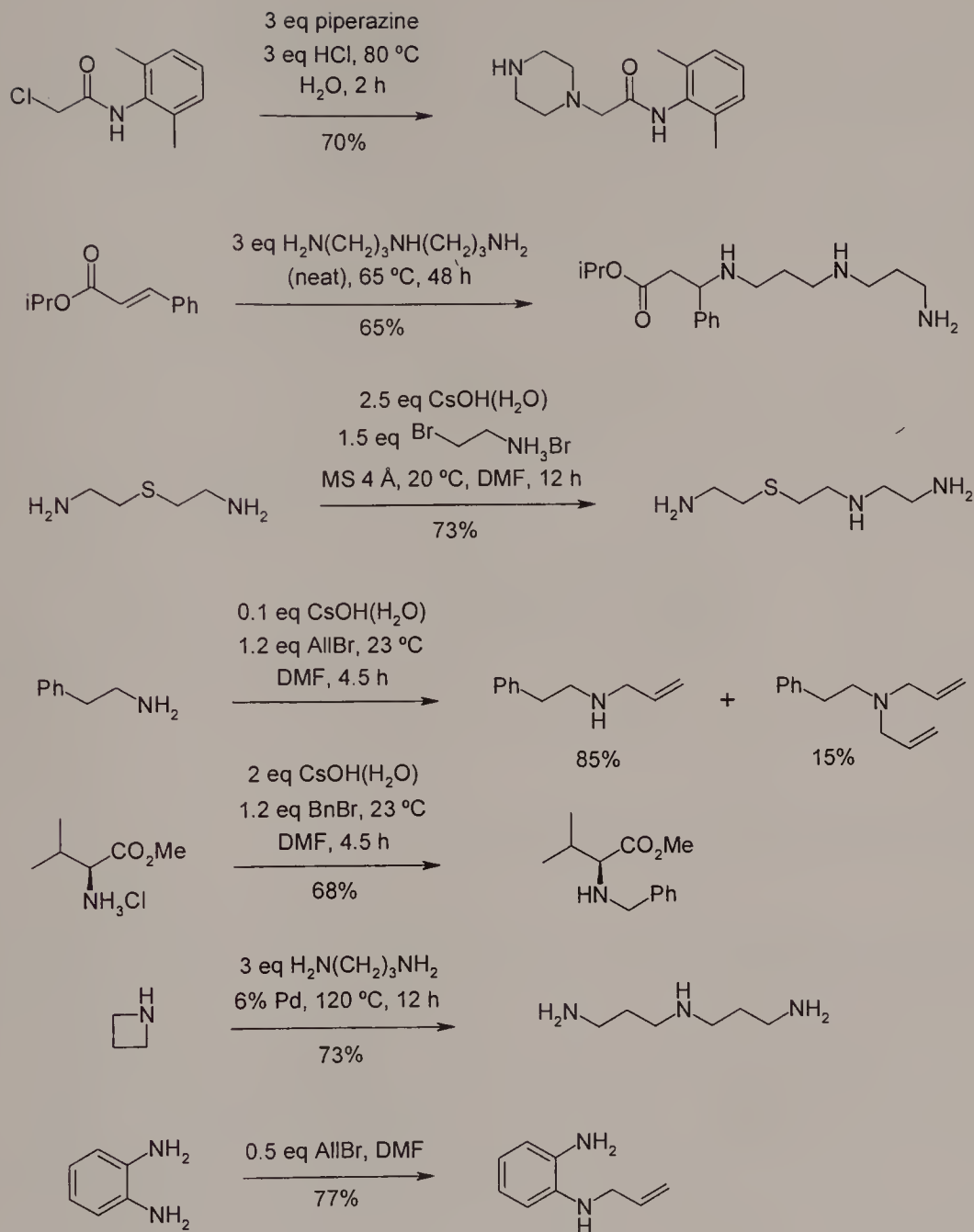


Scheme 10.16. Monosulfonylation of diamines [69–71].

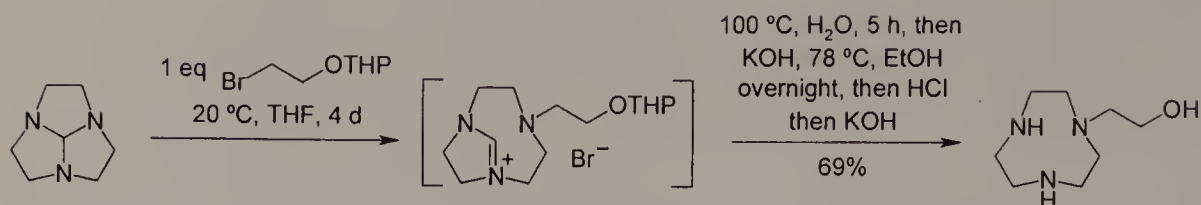
Alkylation of amines usually proceeds more slowly than acylations, and alkylating reagents can usually be thoroughly mixed with an amine before reaction is complete. Diamines or polyamines can therefore be transformed into mixtures of the statistically expected amounts of alkylated derivatives (Scheme 10.17). The use of CsOH as base has been found to be particularly conducive to the formation of monoalkylated products [72]. Some polyamines have also been monoalkylated selectively after complexation with Zn(II) [73].

The selectivity of acylations or alkylations of polyamines can also be modulated by protonation [78] or by conversion to cyclic aminals [71, 79, 80]. The latter strategy has, for instance, been used successfully for the preparation of monofunctionalized 1,4,7-triazacyclononanes (Scheme 10.18). In this reaction the first alkylation leads to the formation of an amidinium salt, which is more difficult to alkylate than a tertiary amine. Thus, the use of only one equivalent of alkylating agent leads to a clean monoalkylation.

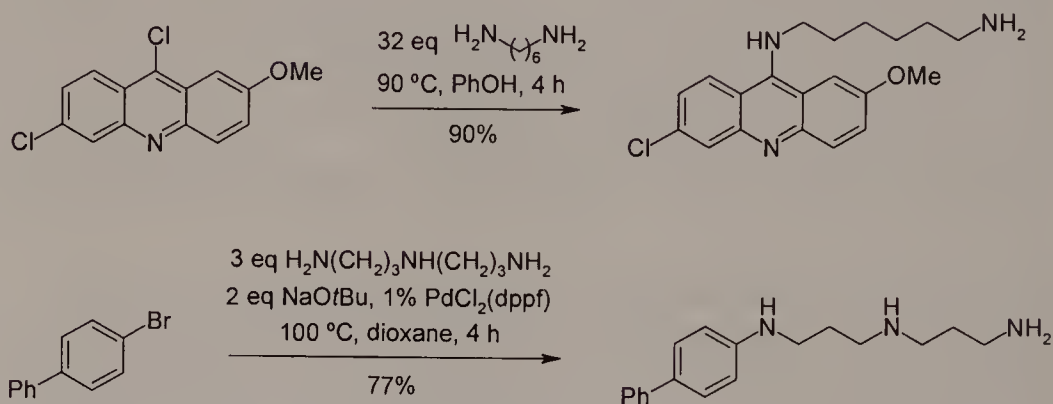
Monoarylation of diamines has been achieved by treatment of excess diamine with an arylating reagent (Scheme 10.19) [82–84]. If the arylation is slow the statistically expected amounts of mono- and diarylated product will usually result. An effective means removing excess diamine will, however, be required the purification of the products.



Scheme 10.17. Monoalkylation of amines [70, 72, 74–77].



Scheme 10.18. Monoalkylation of a tricyclic orthoamide derived from 1,4,7-triazacyclononane [81].



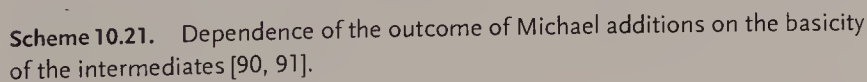
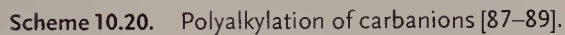
Scheme 10.19. Monoarylation of polyamines [85, 86].

10.5

Monoalkylation of C,H-Acidic Compounds

The alkylation of carbanions can sometimes lead to the formation of di- and trialkylated products (Scheme 10.20). Such polyalkylations occur more readily if alkylation is slow compared with the rate of proton exchange between the carbanion and the product. Because the acidity of organic compounds usually decreases on alkylation, the nucleophilicity of the monoalkylated carbanion will often be substantially higher than that of the starting carbanion, and will therefore be able to compete efficiently with the latter, despite its low concentration. Polyalkylations such as those shown in Scheme 10.20 can be suppressed by increasing the reactivity of the carbanion, for instance by choosing a different counter-ion (K^+ or R_4N^+ instead of Li^+ [87]) or by adding HMPA or similar cosolvents to the reaction mixture, which enhances the rate of S_N2 reactions. Alternatively, protective groups can be used to avoid multiple alkylation of carbanions [88].

The multiple alkylation of carbanions with electron-deficient alkenes (Michael addition) only yields the expected products if the carbanion is less basic than the initial product of Michael addition. If the attacking carbanion and the carbanion resulting from Michael addition have similar basicity, oligomerization of the Michael acceptor can occur instead of multiple alkylations of the same carbon atom (Scheme 10.21).

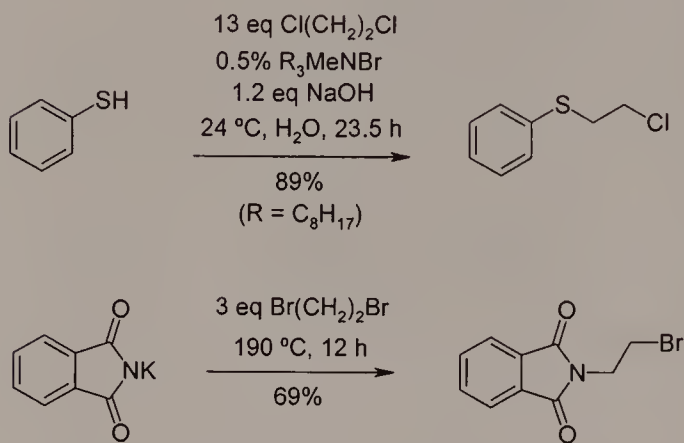


10.6

Monoderivatization of Dihalides

α,ω -Dichloro- and dibromoalkanes are cheap, readily available reagents. Their low boiling points and low heats of evaporation enable their facile separation from product mixtures, and thus their use as reactants in excess or even as solvents. Numerous successful monoderivatizations of α,ω -dihaloalkanes have been reported.

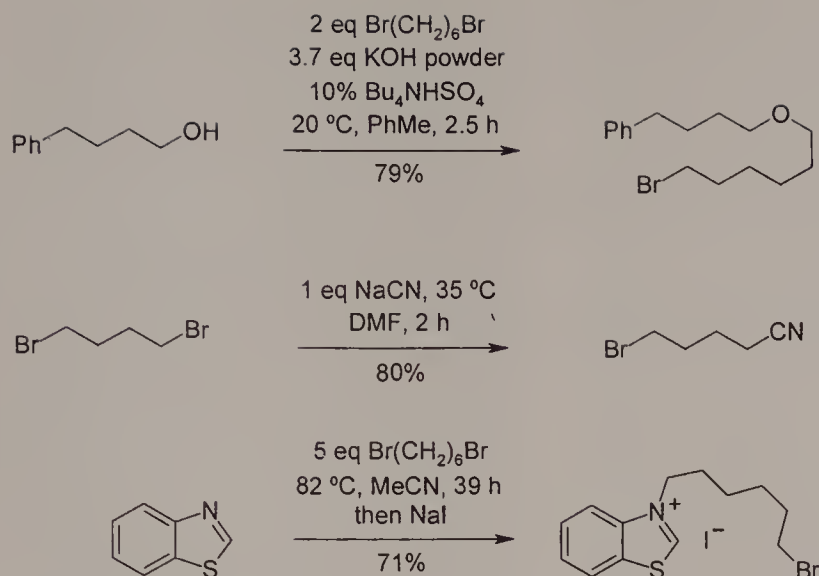
As mentioned in Section 4.3.4, 1,2-dihaloethanes undergo nucleophilic substitutions less readily than *n*-alkyl halides. Nevertheless, under optimum conditions high-yielding monosubstitutions can be performed with these reagents (Scheme 10.22) [92].



Scheme 10.22. Nucleophilic substitutions at symmetric 1,2-dihaloethanes [93, 94].

Longer α,ω -dihaloalkanes undergo nucleophilic substitutions readily, and a slight excess of dihalide can lead to acceptable yields of haloalkylated nucleophile (Scheme 10.23). Yields are sometimes higher than those predicted theoretically. Further examples are given in Schemes 4.39 and 6.23.

Halogen–metal exchange at polyhalogenated arenes significantly reduces the ability of the remaining halogen atoms to be displaced by the metal. Hence, the conversion of symmetric 1,2- and 1,3-dibromoarenes and heteroarenes into mono-Grignard reagents proceeds without problems [98–100]. Dihaloalkanes are, however, more difficult to convert into haloalkyl Grignard reagents – vicinal dihalides are usually converted into alkenes on treatment with a metalating reagent (Section 5.4.3) whereas longer dihaloalkanes can undergo cyclization upon metalation (Section 5.4.4).



Scheme 10.23. Monoderivatization of α,ω -dibromoalkanes [95–97].

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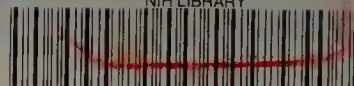
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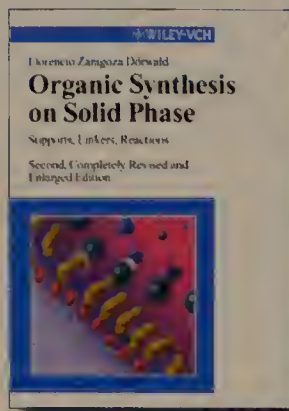
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